OSONG PUBLIC HEALTH
AND RESEARCH PERSPECTIVES
https://ophrp.org

phrp OSONG PUBLIC HEALTH AND RESEARCH PERSPECTIVES

Vol. 17, No. 1, February 2026

Pages 1-93

phrp
OSONG PUBLIC HEALTH
AND RESEARCH PERSPECTIVES

pISSN 2210-9099
eISSN 2233-6052

# Vol. 17, No. 1, February 2026

Vol. 17, No. 1, February 2026

Korea Disease Control and
Prevention Agency

https://ophrp.org

phrp
OSONG PUBLIC HEALTH AND RESEARCH PERSPECTIVES

https://ophrp.org

pISSN 2210-9099
eISSN 2233-6052

Vol. 17, No. 1, February 2026

Published on 28 February 2026

## Aims & Scope

Osong Public Health and Research Perspectives (PHRP) is the international bimonthly (published at the end of February, April, June, August, October, and December) journal founded in 2010 by the Korea Disease Control and Prevention Agency (KDCA). With the mission of the KDCA, to create a disease-free world, PHRP encourages sharing medical information and knowledge in the areas of public health.
PHRP publishes original articles, review articles, guidelines, data profiles (including cohort profiles), special articles, short communications, viewpoints, editorials, commentaries, and correspondence, and book reviews, with a focus on the following areas of expertise: emerging infectious diseases, vaccinology, zoonotic diseases, non-communicable diseases, intractable and rare diseases, and human genomics.

## Abstracting and Indexing Services

A part of articles, metadata, or full text is available from CrossRef metadata (2010–), PubMed Central (2010–), PubMed (2010–), Scopus (2010–), Embase (2010–), EBSCO Host (2010–), Directory of Open Access Journals (2018–), Korea Citation Index (2011–), and Emerging Sources Citation Index (2020–).

## Open Access

PHRP is an open access journal. All contents of the journal are available immediately upon publication without embargo period (https://ophrp.org). All articles are distributed under the terms of the Creative Commons Attribution Non-Commercial License (https://creativecommons.org/licenses/by-nc/4.0/) which permits unrestricted non-commercial use, distribution, and reproduction in any medium, provided the original work is properly cited.

---

**Publisher:** The Korea Disease Control and Prevention Agency

**Editor-in-Chief:** Jong-Koo Lee, MD, PhD

**Editorial Office:**

- **Korea Disease Control and Prevention Agency**
  National Center for Medical Information and Knowledge, 202 Osongsengmyung 2nd street, Osong-eup, Heungdeok-gu, Cheongju 28159, Republic of Korea. E-mail: ophrp@korea.kr

- **Infolumi**
  #245, 10 Jangmi-ro 48beon-gil, Bundang-gu, Seongnam 13496, Republic of Korea
  Tel: +82-31-709-0918, E-mail: osong.editorialoffice@gmail.com

© 2026 Korea Disease Control and Prevention Agency
This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).
This paper meets the requirements of KS X ISO 9706, ISO 9706-1994 & ANSI/NISO Z39.48-1992 (Permanence of Paper).

phrp
OSONG PUBLIC HEALTH AND RESEARCH PERSPECTIVES

https://ophrp.org
pISSN 2210-9099 eISSN 2233-6052

## Editorial Board

### Editor-in-Chief

Jong-Koo Lee, MD, PhD
National Academy of Medicine of Korea, Seoul, Korea

## Editors

Curie Ahn, MD, PhD National Medical Center, Korea
Shilpa Buch, PhD University of Nebraska, USA
Young June Choe, MD, PhD Korea University, Korea
Thomas Grischott, MD University of Zurich, Switzerland
Sun Huh, MD, PhD Hallym University, Korea
Sun Ha Jee, PhD Yonsei University, Korea
Yong Seok Jeong, PhD Kyung Hee University, Korea
Joseph Kamgno, MD, PhD CRFilMT, Cameroon
Jae-Heon Kang, MD, PhD Sungkyunkwan University, Korea
Dong-Hyun Kim, MD, PhD Hallym University, Korea
Dong-Su Kim, PhD Ajou University, Korea
Jinhyun Kim, PhD Seoul National University, Korea
Kyehun Kim, MD, PhD Chonnam National University, Korea
Yongkuk Kim, PhD Kyungpook National University, Korea
Moo-Song Lee, MD, PhD University of Ulsan, Korea
Martin Meltzer, PhD CDC, USA
Hiroshi Nishiura, MD, PhD Kyoto University, Japan
Hyun Joo Pai, MD, PhD Hanyang University, Korea
Kholoud Porter, PhD Medical Research Council, UK
Tomoya Saito, MD, PhD National Institute of Infectious Diseases, Japan
Gabriel Sanfélix-Gimeno, PharmD Foundation for the Promotion of Health and Biomedical Research of Valencia Region (FISABIO), Spain
James Sneyd, PhD The University of Auckland, New Zealand
Aeree Sohn, PhD Sahmyook University, Korea
Byoung-Joon Song, PhD National Institutes of Health, USA
Kiyosu Taniguchi, MD, PhD National Institute of Infectious Diseases, Japan

## Statistical Editors

Eunok Jung, PhD Konkuk University, Korea
Ho Kim, PhD Seoul National University, Korea
Nam-Kyoo Lim, PhD Korea Disease Control and Prevention Agency, Korea

## Journal Management Team

### Director

Hee Youl Chai, PhD Korea Disease Control and Prevention Agency, Korea

### Managing Editors

Se Hee Hwang, MS Korea Disease Control and Prevention Agency, Korea
Chaeshin Chu, PhD Korea Disease Control and Prevention Agency, Korea

### Editorial Coordinator

Hye-Min Cho, MA Infolumi, Korea
Jisoo Yoon, MS Infolumi, Korea

### Manuscript Editors

Sue Yeon Chung Infolumi, Korea
Yoon Joo Seo, ELS Infolumi, Korea

© 2026 Korea Disease Control and Prevention Agency

phrp
OSONG PUBLIC HEALTH AND RESEARCH PERSPECTIVES

https://ophrp.org
pISSN 2210-9099 eISSN 2233-6052

Vol. 17, No. 1, February 2026

## Editorial

1 From pandemic experience to institutional reform: building sustainable financing for infectious disease preparedness
*Jong-Koo Lee*

## Review Articles

4 Applying biotechnology to overcome cancer drug resistance and improve public health outcomes
*Franklin Akwasi Adjei, Bernard Kwame Frempong, Augustine Afriyie*

17 The role of artificial intelligence in managing COVID-19 and long COVID: a narrative review
*Bikash Kanti Sarkar, Ambuj Kumar*

## Original Articles

33 Crisis-driven innovation in the Republic of Korea's *in vitro* diagnostics industry: a pandemic case study
*Minjoon Kim, Harry Jeong, Kwangsoo Shin*

50 Time-series decomposition and modeling of dengue cases in Malaysia, 2022–2024: a nationwide observational study
*Mohamad Afiq Amsyar Hamedin, Kamarul Imran Musa, Mohd Rahim Sulong*

61 A multi-city outbreak of *Salmonella* Enteritidis infections linked to bakery products, Republic of Korea
*Da Seul Kim, Soon-Young Seo, Dong Hwi Kim, Yeon Hee Woo, Deborah Lee, Se Jeong Yang, Junyoung Kim, Eunkyung Shin, Byungsun Jung, Eunmi Lee, Min Jung Lee, Young-Joon Park*

72 Reciprocal associations between smartphone overdependence and anxiety in adolescents: evidence from a nationally representative survey in the Republic of Korea
*Eunok Park*

83 Correlates and co-occurrence of risk factors for non-communicable diseases among adolescents in schools in Karnataka, India: a cross-sectional study
*Tejaswini Bangalore Darukaradhya, Krishnamurthy Jayanna, Shivaraj Nallur Somanna, Sony Sequeira, Shalini Chandrashekar Nooyi*

© 2026 Korea Disease Control and Prevention Agency

phrp
OSONG PUBLIC HEALTH AND RESEARCH PERSPECTIVES

pISSN 2210-9099 eISSN 2233-6052
https://doi.org/10.24171/j.phrp.2026.0184
Osong Public Health Res Perspect 2026;17(1):1-3

**Editorial**

# From pandemic experience to institutional reform: building sustainable financing for infectious disease preparedness

**Jong-Koo Lee**

National Academy of Medicine of Korea, Seoul, Republic of Korea

The acute phase of coronavirus disease 2019 (COVID-19) has receded, but the risk of future pandemics has not. Emerging infectious threats—whether from zoonotic spillover, antimicrobial resistance, or climate-driven vector expansion—are no longer exceptional events; they represent recurring risks in an increasingly interconnected society. The central question is no longer whether another pandemic will occur, but whether preparedness will have been institutionalized before it does.

In late January, the Korea Disease Control and Prevention Agency (KCDA) and the National Academy of Medicine of Korea (NAMOK) convened a joint public–private forum to examine strategies for sustainable and effective pandemic response [1]. The discussion extended beyond retrospective evaluation to focus on long-term system strengthening, including research on priority pathogens and Disease X, public health measures and human rights, accelerated vaccine platforms, strengthened research and development governance, and enhanced international cooperation. Recognition of the gap between ambition and implementation must translate into durable institutional reform and financing.

The 8 articles in this issue reinforce a consistent lesson: preparedness is systemic rather than episodic. A system dynamics analysis of the Republic of Korea's *in vitro* diagnostics sector during COVID-19 demonstrates how research investment, regulatory agility, and public–private coordination shape epidemic trajectories. A nationwide dengue modelling study underscores regional heterogeneity and the need for locally adaptive predictive systems. A multi-city investigation of *Salmonella* enteritidis linked to widely distributed food products highlights the importance of integrated surveillance and genomic epidemiology. Two studies focusing on adolescents remind us that vulnerability accumulates long before infectious crises emerge. One identifies reciprocal associations between smartphone overdependence and anxiety among Korean youth, illustrating the interaction between digital exposure and mental health. Another demonstrates that clustering of non-communicable disease risk factors among adolescents in India is socially patterned and cumulative rather than individually isolated. Reviews addressing biotechnology approaches to overcoming cancer drug resistance and artificial intelligence applications in COVID-19 and long COVID management further indicate that technological innovation must be accompanied by advances in regulatory science, equity, and public trust. Taken together, these contributions reaffirm that preparedness extends

**Received:** February 18, 2026
**Accepted:** February 22, 2026

Corresponding author:
Jong-Koo Lee
National Academy of Medicine of Korea, 51 Seochojungang-ro, Seocho-gu, Seoul 06654, Republic of Korea
E-mail: docmohw@snu.ac.kr

The opinions expressed by authors contributing to this journal do not necessarily reflect the opinions of the Korea Disease Control and Prevention Agency and Korea National Institute of Health.

© 2026 Korea Disease Control and Prevention Agency.
This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

beyond pathogen detection to encompass surveillance systems, regulatory science, innovation capacity, and the social determinants of health.

Financing remains decisive. Recent amendments to the International Health Regulations introduce a financial coordination mechanism intended to mobilize new and additional resources and to promote predictable and sustainable financing [2]. The draft World Health Organization Pandemic Agreement similarly emphasizes sustainable financing arrangements to support preparedness, capacity building, and equitable access to health products [3]. These developments converge on a shared conclusion: preparedness requires stable funding structures. However, international agreements do not automatically secure resources. Implementation ultimately depends on national legislation and budgetary decisions.

At a critical moment during the ongoing pandemic, the bereaved family of a private entrepreneur made a philanthropic contribution of 700 billion Korean won to support infectious disease research, infrastructure, and clinical facilities. The scale of this donation accelerated the expansion of national capacity. However, it also underscores a structural policy reality: essential preparedness functions should not depend on exceptional acts of philanthropy.

Although philanthropic funding can facilitate capital investment, long-term preparedness requires stable and predictable public financing. The construction of facilities represents only the first step. Sustainable operation—including workforce support, surveillance systems, research platforms, and deployment of medical countermeasures (MCMs)—depends on sustained annual governmental budget commitments. Without secure public financing, even newly established capacity may face structural financial pressures over time.

This reality calls for innovation in domestic financing mechanisms. The Republic of Korea previously operated outbound travel–associated contributions [1]; however, expansion of their statutory purpose diluted their original public health focus. The lesson is clear: financing mechanisms must have clearly defined objectives and be dedicated exclusively to preparedness functions. A preparedness contribution specifically earmarked for the prevention and management of imported infectious diseases—including surveillance, border health measures, and MCMs—would align funding with actual risk pathways. Infectious disease risks cross borders through mobility, and financing structures should reflect this transnational exposure. When transparently governed and reserved solely for preparedness purposes, such an approach could provide stable, long-term public financing insulated from annual budget volatility.

Future pandemics will require layered responses. Public health measures—including community mitigation strategies, distancing policies, and risk communication—remain foundational. MCMs must be supported by resilient health-care systems capable of surge response. Social policies that protect vulnerable populations and sustain public trust are equally essential. Preparedness therefore requires integration of public health, medical, and social strategies within coherent governance structures.

Implementation gaps persist not because knowledge is lacking, but because political attention fluctuates. Surveillance systems weaken as urgency fades. Research activity slows when budgets contract. Ambition recedes as collective memory of the crisis diminishes. The greatest threat after a pandemic may not be viral mutation but institutional complacency [4]. Preparedness is not a temporary programme activated during a crisis; it is a permanent national responsibility. International norms now recognize the necessity of sustainable financing. The remaining task is domestic institutionalization.

The recent joint forum convened by the KCDA and the NAMOK was therefore both timely and consequential. It reflected broad agreement that preparedness must extend beyond emergency response toward institutional reform. Yet agreement alone is insufficient. The decisive test lies in translating deliberation into legislation, dialogue into enforceable financing mechanisms, and policy discussion into sustained budgetary commitment. The opportunity created by timely discussion will narrow unless it is converted into concrete institutional action. Ultimately, preparedness will be secured not through debate, but through implementation.

## Notes

**Ethics Approval**
Not applicable.

**Conflicts of Interest**
Jong-Koo Lee has been the editor-in-chief of *Osong Public Health and Research Perspectives* since October 2021.

**Funding**
None.

## References

1. Korea Disease Control and Prevention Agency (KDCA) (KR). January 21, 2026 news briefing. A joint public–private forum on sustainable and efficient pandemic response strategies [Internet]. KDCA; 2026 [cited 2026 Feb 19]. Available from: https://www.kdca.go.kr/kdca/2848/subview.do?enc=Zm5jdDF8QEB8JTJGYmJzJTJGa2RjYSUyRjQyJTJGMzA5ODM1JTJGYXJ0Y2xWaWV3LmRvJTNG. Korean.


https://doi.org/10.24171/j.phrp.2026.0184

2. World Health Organization (WHO) (CH). International Health Regulations (2005) As amended in 2014, 2022 and 2024 [Internet]. WHO; 2024 [cited 2026 Feb 19]. Available from: https://apps.who.int/gb/bd/pdf_files/IHR_2014-2022-2024-en.pdf.
3. World Health Organization (WHO) (CH). WHO Pandemic Agreement [Internet]. WHO; 2025 [cited 2026 Feb 19]. Available from: https://apps.who.int/gb/ebwha/pdf_files/WHA78/A78_R1-en.pdf.
4. Castro KG, LoBue PA. Bridging implementation, knowledge, and ambition gaps to eliminate tuberculosis in the United States and globally. Emerg Infect Dis 2011;17:337–42.

phrp
OSONG PUBLIC HEALTH AND RESEARCH PERSPECTIVES

pISSN 2210-9099 eISSN 2233-6052
https://doi.org/10.24171/j.phrp.2025.0336
Osong Public Health Res Perspect 2026;17(1):4-16

Review Article

# Applying biotechnology to overcome cancer drug resistance and improve public health outcomes

**Franklin Akwasi Adjei**[1], **Bernard Kwame Frempong**[2], **Augustine Afriyie**[3]

[1]Division of Kinesiology and Health, College of Health Sciences, University of Wyoming, Laramie, WY, USA
[2]Department of Biomedical Sciences, School of Medicine & Health Sciences, University of North Dakota, Grand Forks, ND, USA
[3]College of Basic and Applied Sciences, Middle Tennessee State University, Murfreesboro, TN, USA

## ABSTRACT

This review examines how biotechnology advances (CRISPR/Cas9, next-generation targeted therapies, nanotechnology-based drug delivery, and immunotherapies) can be applied to address cancer drug resistance worldwide. It also considers the economic burden of resistance, inequities in access to biotechnology solutions, and ethical concerns surrounding rapid innovation, particularly in low-resource settings. A narrative review synthesized evidence from basic science studies, clinical trials, translational research, and policy analyses. Evidence was prioritized for 2015–2025 publications. The synthesis highlights resistance biology and evaluates how precision medicine, biomarker-guided treatment, and high-throughput drug screening can inform individualized regimens and rational combinations. Breakthroughs in gene editing, targeted inhibitors, nanocarriers, and immune engineering can counter key resistance mechanisms, including resistance-conferring mutations, altered drug transport, immune evasion, and tumor microenvironment–mediated protection. Despite progress, implementation barriers remain substantial: high drug and development costs, limited molecular diagnostics and manufacturing capacity, and regulatory and governance challenges that can delay adoption and widen disparities, particularly in low- and middle-income countries. Integrating biotechnology innovations within precision medicine frameworks may improve treatment selection and patient outcomes. Maximizing public health impact requires affordability and financing strategies, robust ethical oversight, timely regulatory pathways, and coordinated global collaboration to ensure access to effective therapies across health systems worldwide.

**Keywords:** Artificial intelligence; Biotechnology; Drug resistance; Immunotherapy; Global health; Neoplasms

**Received:** August 24, 2025
**Revised:** December 10, 2025
**Accepted:** December 14, 2025

Corresponding author:
Franklin Akwasi Adjei
Division of Kinesiology and Health, College of Health Sciences, University of Wyoming, 1000 E. University Avenue, Laramie, WY 82071, USA
E-mail: franklinadjei509@gmail.com

The opinions expressed by authors contributing to this journal do not necessarily reflect the opinions of the Korea Disease Control and Prevention Agency and Korea National Institute of Health.

© 2026 Korea Disease Control and Prevention Agency.
This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

## Introduction

### Overview of Cancer and Drug Resistance

Cancer is associated with substantial morbidity and mortality worldwide [1]. It is the second leading cause of death globally, and its overall burden is projected to increase over the next 20 years [2]. Approximately 20 million new cancer cases were reported in 2022 [3]. In addition to being a major barrier to increasing life expectancy, cancer imposes significant societal and macroeconomic costs that vary according to cancer type, geographic region, and gender [4]. Despite advances in cancer treatment, including chemotherapy, radiation therapy, and targeted therapies, cancer remains a major global health burden. Conventional treatment approaches such as surgery, chemotherapy, and radiation have improved survival rates for many patients, but their effectiveness is frequently limited by the ability of cancer cells to develop resistance to these interventions [5]. As a result, treatments may fail, leading to poor survival outcomes [6].

Cancer drug resistance occurs when cancer cells fail to respond to a drug that was initially effective in treating the disease [7]. This resistance can be intrinsic, meaning that tumor cells are inherently resistant to therapy from the outset, or acquired, meaning that cancer cells develop resistance following an initial response to treatment [8]. Drug resistance is particularly relevant in the context of chemotherapy, where the emergence of resistance frequently leads to tumor recurrence, disease progression, and a poor prognosis for patients [9].

The mechanisms underlying cancer drug resistance are complex and include genetic mutations, alterations in drug transport systems, changes in intracellular signaling pathways, and evasion of immune surveillance [10,11]. As cancer cells evolve, they adapt to sustained therapeutic pressures, progressively reducing the effectiveness of standard treatments [12]. Consequently, overcoming cancer drug resistance remains a major and persistent challenge in oncology.

Biotechnology plays a vital role in the development of innovative therapeutic strategies to overcome cancer drug resistance. Substantial advances in genetic engineering, molecular biology, nanotechnology, and related biotechnological fields have generated new tools to target resistance mechanisms and enhance the efficacy of cancer treatments [12].

This paper aims to explore recent biotechnological approaches to cancer drug resistance by examining the mechanisms that drive resistance, emerging therapeutic innovations, and the public health challenges associated with implementing these solutions globally. In addition, it examines the role of biotechnology in improving cancer treatment outcomes while emphasizing the importance of ensuring equitable access to advanced therapies across populations, regardless of socioeconomic status.

**HIGHLIGHTS**

- Emerging technologies such as synthetic biology, artificial intelligence, and advanced imaging have become increasingly necessary to overcome cancer drug resistance and to personalize treatment strategies.
- The growing economic burden of drug resistance underscores the need for more affordable therapies and improved access in low-resource settings. Global research collaboration and efficient regulatory pathways are essential to ensure equitable access to innovative treatments.

### Research Methodology

The study employed a narrative review approach to examine the role of biotechnology in overcoming cancer drug resistance. This approach was selected because it allows for a flexible and integrative synthesis of heterogeneous evidence, including basic science studies, clinical trials, translational research, and policy analyses, thereby facilitating the development of a coherent account of technological advances, biological mechanisms, and public health implications. The review design emphasized breadth and interpretive depth rather than formal meta-analytic aggregation, which was appropriate given the rapidly evolving and multidisciplinary nature of the topic.

### Search Terms and Strategy

Data for the review were gathered through an iterative literature search of peer-reviewed journals, clinical reports, and relevant gray literature. Major bibliographic databases, including PubMed, Scopus, Web of Science, and Google Scholar, were searched using combinations of terms such as “cancer drug resistance,” “biotechnology,” “CRISPR,” “nanomedicine,” “epigenetic modulators,” “immunotherapy,” and “AI in oncology.” The search strategy prioritized recent publications (2015–2025) to capture contemporary biotechnological innovations, while also incorporating seminal earlier studies that elucidated foundational mechanisms. Inclusion criteria required that sources be peer-reviewed and address mechanisms of resistance, biotechnological interventions, clinical applications, or

issues related to implementation and equity; editorials and commentaries were included selectively when they provided relevant conceptual or policy insight. Research articles that did not engage with drug-resistance mechanisms or biotechnological solutions, as well as items lacking sufficient methodological or evidentiary detail, were excluded.

### Data Synthesis and Analysis

The extracted material described mechanistic features such as intrinsic and acquired resistance, multidrug resistance (MDR), and contributions from the tumor microenvironment (TME). It also encompassed biotechnological strategies, including gene-editing approaches, targeted therapies, immunotherapies, nanotechnology-based delivery systems, and epigenetic modulators. The review further incorporated reports of clinical applications and examined implementation challenges, including cost, access, regulatory barriers, and ethical considerations. Information was systematically recorded in a study log documenting bibliographic details, study objectives, methods, key findings, limitations, and relevance to the review question. The collected literature was coded for recurring concepts and patterns related to mechanisms of resistance, technological strategies to counter resistance, therapeutic combinations and sequencing, biomarkers, precision medicine approaches, and system-level barriers to adoption. These codes were subsequently organized into higher-order themes that structured the narrative: (1) biological bases of resistance, (2) molecular and delivery-focused biotechnological solutions, (3) clinical and translational evidence for efficacy, and (4) public-health, ethical, and regulatory implications.

The study maintained ethical and methodological rigor by applying transparent inclusion criteria, documenting search processes and analytical decisions in a review log, and critically evaluating the strength of evidence when drawing conclusions. Because the review relied exclusively on secondary, publicly available sources, no formal institutional review board approval was required; nevertheless, the work adhered to established academic standards for appropriate attribution, balanced interpretation, and clear discussion of ethical issues.

## Mechanisms of Cancer Drug Resistance

### Intrinsic Drug Resistance

Intrinsic resistance refers to the inherent ability of certain cancer cells to resist the effects of chemotherapy or targeted therapies from the outset of treatment [13]. This form of resistance can be attributed to several factors, including the underlying genetic and molecular characteristics of tumor cells [14]. Tumor heterogeneity, in which distinct cell populations within the same tumor harbor different genetic mutations, can contribute to intrinsic resistance [15]. Cancer cells may already possess mutations that reduce their susceptibility to chemotherapeutic agents [16]. In some cases, these cells exhibit enhanced drug-metabolizing pathways that allow them to inactivate or neutralize therapeutic agents before the drugs can exert their intended effects. Additionally, tumor cells frequently display altered drug uptake and efflux mechanisms [17]. The expression of drug transporters, such as P-glycoprotein, can actively pump chemotherapeutic agents out of the cell, thereby preventing adequate intracellular drug accumulation [17]. This represents another important mechanism by which intrinsic drug resistance can arise.

Apoptosis is a form of programmed cell death that enables the orderly elimination of damaged or unnecessary cells, including those affected by DNA damage or developmental cues [18]. Alterations in the apoptotic machinery can allow cancer cells to evade destruction, even in the presence of drugs that would normally induce cell death in non-malignant cells [19].

### Acquired Drug Resistance

Acquired resistance occurs when cancer cells that are initially sensitive to therapy gradually become resistant over time. This form of resistance develops through a combination of genetic mutations and adaptive cellular changes that enable tumor cells to evade the effects of anticancer drugs. Acquired resistance can arise through multiple mechanisms, including mutations in drug target proteins, activation of alternative signaling pathways, and enhanced DNA repair capacity [5]. One example involves tyrosine kinase inhibitors, which are used in cancers such as chronic myelogenous leukemia. Acquired mutations in the *BCR-ABL* gene can render these drugs ineffective [20]. Similarly, mutations in the epidermal growth factor receptor (EGFR) can lead to resistance to EGFR inhibitors in non-small cell lung cancer [21].

Acquired resistance poses a major challenge in cancer treatment because it frequently leads to therapeutic failure, and patients who initially respond to therapy may later experience tumor recurrence [22]. The emergence of acquired resistance in clinical settings underscores the need for continuous monitoring and the ongoing development of new therapeutic strategies to address this evolving problem [23].

### Multidrug Resistance

MDR is a complex form of resistance in which cancer cells


https://doi.org/10.24171/j.phrp.2025.0336

become resistant to multiple chemotherapy agents, thereby reducing the effectiveness of standard treatment regimens [24]. MDR primarily arises from the overexpression of drug efflux pumps, such as P-glycoprotein and MDR–associated protein [25]. These transporters actively expel a wide range of chemotherapeutic agents from cancer cells, rendering treatments less effective [26]. This form of resistance is frequently observed in cancers that have undergone repeated cycles of chemotherapy, during which tumor cells are exposed to multiple drugs over time. As a result, MDR substantially limits the number of viable treatment options available to patients. Overcoming this form of resistance therefore requires the development of strategies that either inhibit drug efflux pumps or employ alternative mechanisms of drug delivery [24].

## Impact of the Tumor Microenvironment

The TME plays a critical role in the development and persistence of cancer drug resistance [26]. The TME comprises multiple components, including cancer-associated fibroblasts, immune cells, blood vessels, and extracellular matrix elements [27]. Together, these components create a protective niche that shields cancer cells from therapeutic agents. For example, hypoxic conditions within solid tumors can promote resistance by inducing the expression of genes that protect cancer cells from chemotherapy-induced damage [28]. Tumors characterized by low oxygen tension frequently exhibit enhanced DNA repair capacity, increased drug resistance, and reduced susceptibility to apoptosis [28]. In addition, the immunosuppressive nature of the TME contributes to resistance by limiting effective immune surveillance and immune-mediated elimination of cancer cells [29]. Certain populations of tumor-associated macrophages can further protect cancer cells from drug-induced cytotoxicity by secreting a range of bioactive factors [30]. These factors may include enzymes, exosomes, interleukins, and chemokines, all of which can contribute to the development and maintenance of drug resistance [31].

Moreover, the extracellular matrix and stromal cells can form physical barriers that impede drug penetration into tumor tissue [26]. This results in an environment in which cancer cells are less likely to encounter therapeutically effective drug concentrations, thereby further promoting resistance. Understanding the dynamic interactions between tumor cells and their microenvironment is therefore essential for the development of therapeutic strategies capable of overcoming this form of resistance (Figure 1).

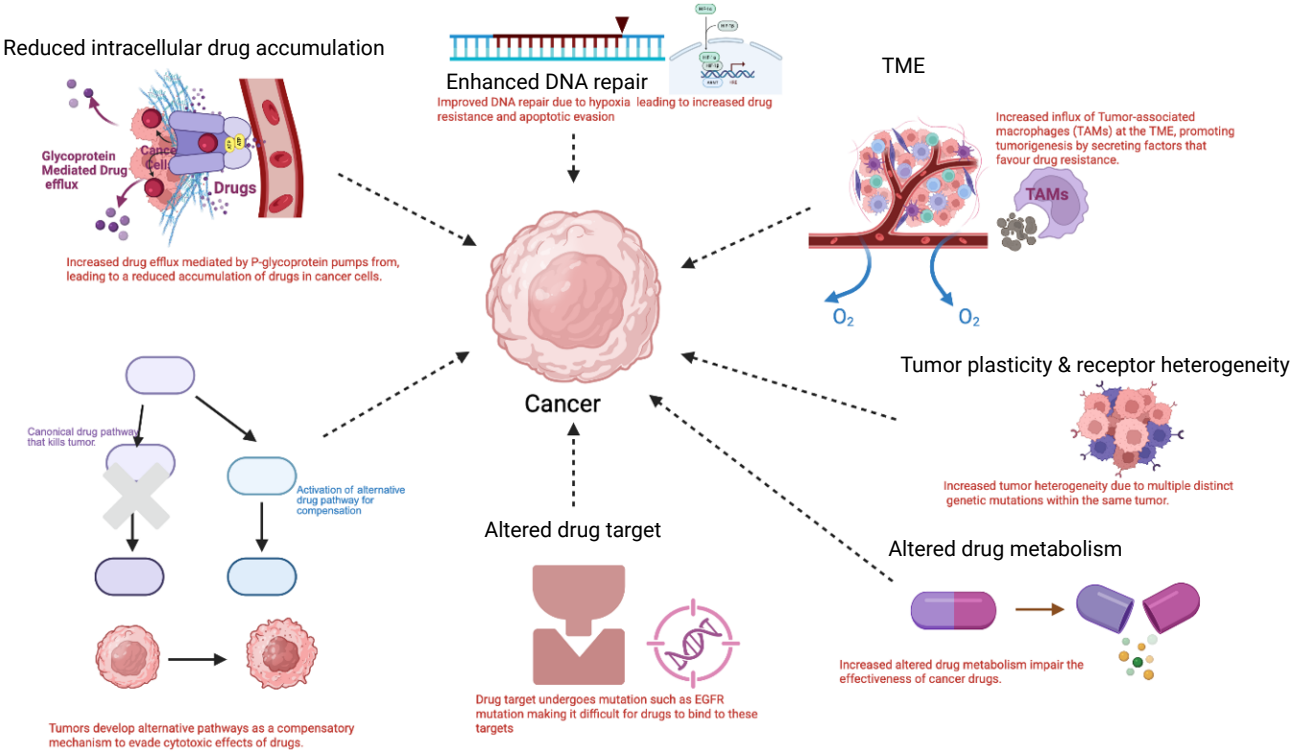



**Figure 1.** Cancer resistance mechanisms.
TME, tumor microenvironment; TAM, tumor-associated macrophages.

## Biotechnological Solutions to Overcome Cancer Drug Resistance

### Genetic Engineering and CRISPR Technology

Genetic engineering using CRISPR/Cas9 technology offers promising opportunities to overcome cancer drug resistance. CRISPR/Cas9 enables precise genome editing, allowing targeted modification of specific genes that contribute to resistance mechanisms [32]. This technology can be used to knock out genes responsible for cancer drug efflux, such as P-glycoprotein, thereby increasing tumor cell susceptibility to chemotherapy [33]. In addition, CRISPR can be applied to correct mutations that drive resistance to targeted therapies, restoring the effectiveness of drugs that were previously ineffective [34,35]. Beyond direct targeting of resistance-related genes, CRISPR technology can also be used to engineer immune cells, such as T cells, to enhance their capacity to recognize and eliminate cancer cells [36].

Gene-editing platforms such as CRISPR/Cas9 provide a highly precise approach to counteracting the genetic determinants of drug resistance. Resistance frequently arises from mutations that alter drug-binding sites, upregulate efflux transporters, or disrupt apoptotic pathways [5]. CRISPR-mediated knockout of efflux pump genes, such as ABCB1 encoding P-glycoprotein, and correction of resistance-associated driver mutations have demonstrated potential to restore chemosensitivity [37]. Furthermore, CRISPR-based approaches can reprogram immune cells, thereby enhancing T-cell recognition of tumor antigens and reducing immune evasion [38]. Although CRISPR-based therapeutics have advanced into early-phase clinical trials for hematologic disorders, their application to cancer drug resistance remains largely preclinical [34]. Ongoing clinical studies are evaluating CRISPR-edited T cells in solid tumors, with preliminary safety and efficacy data suggesting feasibility [39]. However, regulatory approval remains constrained by concerns related to off-target effects, delivery efficiency, and long-term genomic stability [40]. At present, genetic engineering and CRISPR-based technologies are largely confined to high-income settings with well-developed genomic and regulatory infrastructure [41]. In low- and middle-income countries (LMICs), limited sequencing capacity, insufficient ethical oversight, and substantial cost barriers restrict clinical translation [42]. Broad implementation will require targeted capacity-building initiatives, subsidized gene-editing platforms, and harmonized regulatory frameworks to ensure safety and equitable access.

### Targeted Therapy and Next-Generation Drug Development

Biotechnology has enabled the development of next-generation targeted therapies that directly address the molecular drivers of cancer drug resistance. These therapies are designed to inhibit specific proteins or signaling pathways altered in cancer cells, thereby reducing reliance on conventional cytotoxic chemotherapy. Novel inhibitors targeting mutant forms of proteins such as EGFR or BRAF have demonstrated promise in overcoming resistance in selected cancer types [43]. These agents are engineered to bind more effectively to mutated targets, thereby counteracting resistance-conferring alterations that would otherwise reduce drug efficacy [44]. In addition to single-agent approaches, combination therapies incorporating multiple targeted drugs are being developed to address the complex and multifactorial nature of resistance [43]. By simultaneously targeting distinct pathways or resistance mechanisms, combination strategies may overcome adaptive cellular responses that emerge during treatment [45]. Combining targeted therapies with immunotherapies or epigenetic drugs may provide a more comprehensive approach to overcoming resistance. Next-generation targeted therapies specifically address molecular events underlying acquired resistance to first-line inhibitors. Key mechanisms include mutations within kinase domains and activation of alternative signaling pathways that compensate for inhibited targets [46]. Newer inhibitors are designed to exhibit higher binding affinity and broader mutation coverage, while combination regimens aim to suppress compensatory signaling networks [5]. Several next-generation inhibitors have received regulatory approval from agencies such as the US Food and Drug Administration and European Medicines Agency for the treatment of resistant malignancies. In parallel, numerous phase II and III clinical trials are evaluating dual- or multi-targeted regimens, including combination strategies that integrate immunotherapies [47]. The effectiveness of targeted therapy is also influenced by regional patterns of genomic variation. For instance, EGFR mutations occur at higher frequencies in East Asian populations, shaping treatment selection and adoption [48]. However, in regions lacking access to molecular diagnostic testing, the benefits of precision-targeted therapy remain limited. High drug costs, inadequate reimbursement mechanisms, and insufficient diagnostic infrastructure in LMICs continue to pose major barriers to equitable implementation [49].

### Computational Aspects in Drug Development

Computational technologies are becoming increasingly


https://doi.org/10.24171/j.phrp.2025.0336

essential for the development of therapies aimed at overcoming cancer drug resistance, effectively bridging the gap between laboratory research and clinical application. Approaches such as molecular dynamics simulations, machine learning algorithms, and structure-based drug design are transforming how next-generation therapies are identified and optimized [50,51]. These computational methods enable prediction of how mutations in key cancer-related proteins influence drug binding and activity, thereby facilitating the design of more effective and selective inhibitors [52,53]. Virtual screening tools, which assess interactions between thousands of small molecules and mutated protein targets, further accelerate the identification of candidate compounds capable of bypassing known resistance mechanisms [54]. Beyond drug design, computational approaches also support the development of combination therapies. By integrating genomic, proteomic, and transcriptomic datasets, computational models assist in identifying synergistic drug combinations that simultaneously target multiple resistance pathways [55,56]. These models additionally enable personalized selection of combination regimens tailored to an individual patient's molecular profile. Furthermore, artificial intelligence (AI) and machine learning techniques are increasingly applied to large-scale datasets to predict patterns of drug resistance, treatment responses, and the emergence of novel mutations [57,58]. This predictive capacity is particularly important for designing adaptive treatment strategies and improving clinical outcomes. As computational tools continue to advance, they are expected not only to accelerate drug discovery but also to enhance treatment precision by enabling timely identification of effective therapies and supporting long-term survival in cancer patients.

## Nanotechnology in Drug Delivery

Nanotechnology offers a novel strategy for overcoming drug resistance by enhancing the delivery and effectiveness of chemotherapeutic and targeted agents. Nanoparticles, including liposomes and polymer-based carriers, can encapsulate drugs and deliver them directly to tumor sites, thereby overcoming barriers that limit effective drug penetration [59]. This targeted delivery approach increases the local concentration of therapeutic agents within tumors while reducing systemic toxicity. In addition to improving delivery efficiency, nanoparticles can be engineered to respond to specific conditions within the TME [60]. For example, nanoparticles may be designed to release their drug payloads in response to stimuli such as pH or temperature changes, which are commonly observed in tumor tissues [61,62]. Nanomedicine can also address MDR by co-encapsulating multiple agents within a single nanoparticle, enabling combination therapy while reducing the likelihood of drug efflux from cancer cells [63].

Nanocarrier-based delivery systems help mitigate pharmacokinetic barriers that contribute to drug resistance. Encapsulation within nanoparticles can bypass efflux pumps, enhance tumor accumulation through the enhanced permeability and retention effect, and enable localized drug release in response to tumor-specific stimuli [64]. These mechanisms collectively increase intracellular drug concentrations while limiting systemic toxicity. Several nanomedicines, including liposomal doxorubicin and albumin-bound paclitaxel, have received clinical approval [65]. At the same time, newer multifunctional nanoparticle platforms are progressing through early-stage clinical trials. Despite their promising therapeutic potential, challenges related to scalability, manufacturing reproducibility, and long-term toxicity continue to present significant regulatory hurdles [66].

Translation of nanotechnology-based therapies into routine clinical practice depends on the availability of advanced manufacturing processes and robust quality-control systems. High production costs and limited regulatory expertise in nanomedicine oversight restrict accessibility, particularly in LMICs [67]. Regional collaborations and technology-transfer initiatives are therefore critical for supporting local manufacturing capacity and reducing reliance on imported nanomedicine formulations [68].

## Immunotherapy and Biotechnology

Immunotherapy has emerged as one of the most promising treatment strategies for cancer, and biotechnology plays a critical role in developing and optimizing these therapies. Immune checkpoint inhibitors, such as pembrolizumab and nivolumab, have revolutionized the treatment of cancers like melanoma and non-small cell lung cancer by blocking the immune checkpoints that cancer cells use to evade immune detection [69]. This enhances the immune system's ability to fight cancer cells. In addition to checkpoint inhibitors, chimeric antigen receptor T-cell (CAR-T) therapy is another breakthrough immunotherapy that has shown promise in treating certain hematologic cancers [70]. CAR-T cells are genetically engineered to target specific antigens on cancer cells, allowing for a more targeted and potent immune response [71].

Immunotherapeutic strategies specifically address resistance driven by immune escape mechanisms, including checkpoint activation, antigen loss, and an immunosuppressive TME [72]. Advances in biotechnology have optimized immune checkpoint inhibitors and enabled

the development of genetically modified immune cells, such as CAR-T and T-cell receptor–engineered T cells, which enhance immune recognition and persistence [73]. Immune checkpoint inhibitors are now considered standard of care for melanoma, lung, and renal cancers, and numerous ongoing clinical trials are evaluating combination regimens to overcome acquired resistance [74]. CAR-T therapies have received regulatory approval for refractory hematologic malignancies; however, their efficacy in solid tumors remains an active area of investigation [75]. Biotechnology-driven innovations, including armored and logic-gated CAR-T constructs, are currently entering early-phase clinical trials [76].

The uptake of immunotherapy varies substantially due to differences in cost, infrastructure requirements, and availability of specialized clinical expertise [77]. CAR-T therapy remains largely inaccessible outside highly specialized centers in high-income settings, while LMICs face additional challenges related to limited cell-manufacturing facilities, inadequate reimbursement mechanisms, and underdeveloped ethical governance frameworks for advanced biologic therapies [78]. Expanding global access will depend on the development of decentralized manufacturing strategies and lower-cost biosimilar products (Figure 2; Table 1) [79–85].

## Public Health Challenges and Implications

### Economic Costs of Drug Resistance

The economic burden associated with cancer drug resistance is substantial. The development of new therapies, particularly biologics and personalized treatments, is highly costly, and these therapies are often inaccessible to many patients because of their price. The reported cost to develop a cancer drug is approximately 648.0 million United States dollars (USD), which is significantly lower than some prior estimates but remains considerable [86]. Cancer drugs are frequently priced at more than 100,000 USD per year of treatment, with some approaching or exceeding 200,000 USD annually [86,87]. In addition, patients who develop resistance to an

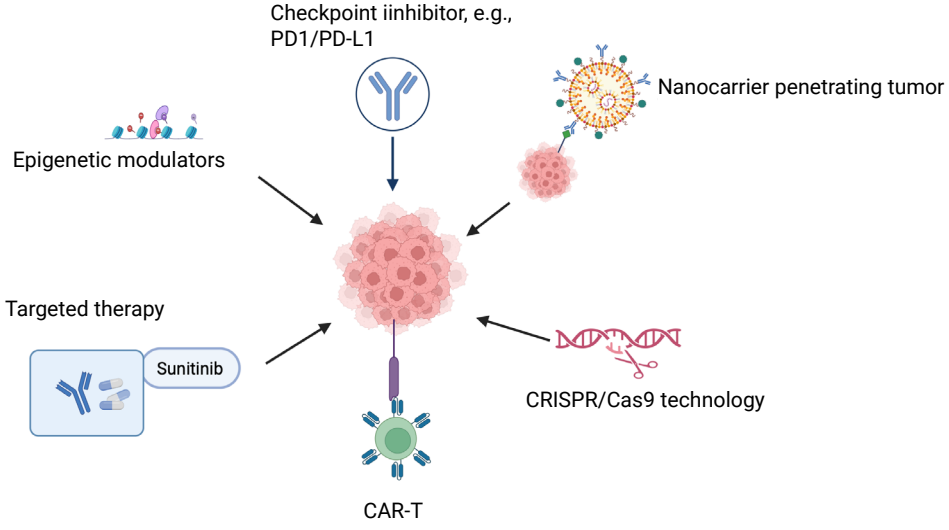



**Figure 2.** Immunotherapy & biotechnology platforms.
PD1, programmed cell death protein 1; PD-L1, programmed cell death ligand 1; CAR-T, chimeric antigen receptor T-cell.

**Table 1.** Biotechnology platforms, clinical trial information, and key resistance mechanisms targeted in cancer treatment

| Biotechnology platform | Clinical trial IDs | Tumor types | Key resistance mechanisms targeted |
|---|---|---|---|
| CRISPR/Cas9 | NCT03745326, NCT02349633 | Leukemia, solid tumors | Mutant EGFR, BCR-ABL, P-glycoprotein, apoptosis evasion [80] |
| CAR-T cell therapy | NCT02228096, NCT05253495 | Leukemia, lymphomas, solid tumors | CD19+ resistance, immune checkpoint evasion, antigen loss [81,82] |
| Checkpoint Blockade (e.g., PD-1/PD-L1) | NCT02759783, NCT02819337 | Melanoma, NSCLC, RCC | PD-L1 upregulation, immune evasion, tumor-associated macrophages [83,84] |
| Epigenetic modulators | NCT03522361 | Solid tumors | DNA methylation, histone modifications, drug resistance gene reprogramming [85] |

EGFR, epidermal growth factor receptor; CAR-T, chimeric antigen receptor T-cell; PD-1, programmed cell death protein 1; PD-L1, programmed cell death ligand 1; NSCLC, non-small cell lung cancer; RCC, renal cell carcinoma.


https://doi.org/10.24171/j.phrp.2025.0336

initial therapy may be required to transition to more expensive second- or later-line treatments, further increasing overall healthcare expenditures. These financial burdens are borne not only by healthcare systems but also by patients and their families, who may face substantial out-of-pocket costs for advanced therapies. The escalating economic impact of drug resistance underscores the need for more effective strategies to prevent and manage resistance, including the development of affordable treatment options and improved access to innovative therapies in low-resource settings.

### Access to Biotechnology Solutions

Access represents one of the most significant challenges associated with biotechnology-based approaches to cancer drug resistance. Advanced interventions, including gene editing, nanomedicine, and immunotherapy, are frequently costly, limiting their availability primarily to well-resourced healthcare systems in high-income countries [86,87]. In low- and middle-income settings, constraints such as limited healthcare infrastructure, regulatory complexity, and financial barriers further exacerbate inequities in access to life-saving cancer treatments. Addressing these disparities will require coordinated efforts to ensure that biotechnological innovations are accessible across diverse populations, particularly in underserved regions. Public–private partnerships, sustained government investment, and international collaborations will be critical for reducing access gaps and promoting equitable distribution of advanced cancer therapies (Figure 3).

### Health Equity and Ethical Concerns

The rapid advancement of biotechnology raises important ethical questions related to equity, fairness, and access to emerging cancer treatments. As biotechnological innovation accelerates, concerns regarding unequal access to potentially life-saving therapies have intensified. Ethical considerations surrounding gene editing and personalized medicine, including issues related to safety and long-term consequences, require careful and ongoing evaluation. The use of CRISPR-Cas9 to genetically modify human germline cells and embryos, referred to as germline genome editing, remains particularly controversial. Germline genome editing presents multiple bioethical challenges, including the risk of unintended genetic alterations, uncertainty regarding informed consent, and the potential for eugenic practices through human selection [88]. Ensuring that technological advances benefit all populations necessitates the development of clear ethical guidelines, robust regulatory frameworks, and public policies that explicitly prioritize health equity (Table 2) [89–103].

## Discussion

The future of biotechnology in cancer treatment depends on the continued development and integration of novel technologies capable of overcoming drug resistance. Emerging tools, including synthetic biology, AI-driven drug discovery, and advanced imaging techniques, are expected to further enhance the identification of new therapies and improve the precision of cancer treatment. With increasing computational power, these technologies can propose optimized drug combinations or personalized treatment strategies designed to overcome resistance and improve patient outcomes. For example, AI has been shown to optimize chemotherapy by integrating genetic mutation profiles, drug metabolism data, and drug sensitivity patterns to predict which patients are most likely to develop resistance, thereby enabling earlier and more targeted interventions [104]. Deep learning frameworks have also demonstrated the ability to process real-time imaging and biomarker data to identify early indicators of emerging resistance [104]. Similarly, AI has played an important role in advancing immunotherapy by analyzing tumor immune-evasion mechanisms to identify patients most likely to benefit from immune-based treatments, supporting the development of more targeted and effective personalized

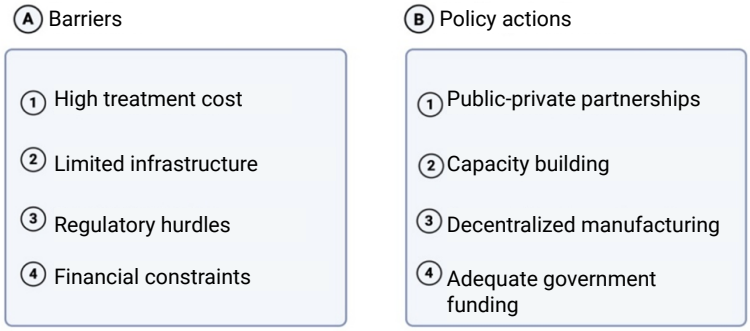



**Figure 3.** Barriers and policy actions to expand access to biotechnological solutions for drug-resistant cancers.

immunotherapies [104].

Despite their considerable promise, AI-driven approaches to drug discovery and treatment optimization raise important concerns related to health equity. The computational infrastructure and large, high-quality datasets required to train robust AI models are disproportionately concentrated in high-income countries [105–107]. As a result, the early benefits of AI-enabled drug development may accrue primarily to well-resourced settings. This creates a short-term paradox in which AI has the potential to reduce future drug development costs while simultaneously widening global access gaps in the near term (Figure 4).

**Table 2.** Geographic trends in cancer drug resistance, access barriers, and feasibility of biotechnology implementation by region

| Region | Geographic trends in cancer drug resistance | Access barriers | Feasibility of biotechnology implementation |
|---|---|---|---|
| Africa | Resistance in cancers such as cervical, breast, and prostate cancers. Multidrug resistance is commonly seen in chemotherapy for various cancers [89]. | Severe healthcare infrastructure deficits, cost barriers, and a lack of specialized cancer care centers [90]. | Low feasibility due to significant gaps in healthcare infrastructure, limited access to modern cancer treatments, and regulatory challenges [91]. |
| Europe | Increasing resistance in breast cancer, colorectal cancer, and non-small cell lung cancer [92] | High costs of advanced therapies, with disparities in healthcare access between Western and Eastern Europe [93]. | High feasibility in Western Europe with advanced healthcare systems, although cost and access disparities remain in Eastern Europe [94] |
| Asia | High prevalence of mutations in the epidermal growth factor receptor in lung cancer, particularly in East Asia. Resistance is also rising in gastrointestinal cancers and breast cancers [95]. | Limited diagnostic capacity, affordability issues, and regulatory variability between countries [96]. | Growing biotechnology sector in countries like China, Japan, and South Korea; significant access challenges in rural areas and for low-income populations [97]. |
| North America | Resistance to common cancer therapies, such as epidermal growth factor receptor inhibitors in non-small cell lung cancer, and chemotherapy resistance in breast and prostate cancers [98]. | High costs for biologic therapies, disparities in insurance coverage, and regulatory delays [99]. | High feasibility due to strong biotechnology infrastructure and access to cutting-edge therapies, although high costs limit equitable access for certain populations [99,100]. |
| South America | Increasing resistance in lung cancers [101]. | Disparities in healthcare access between urban and rural areas, with high costs for advanced cancer treatments [102]. | Moderate feasibility; adoption of biotechnology is increasing in urban centers, but rural and low-income areas face significant barriers to access [102,103]. |

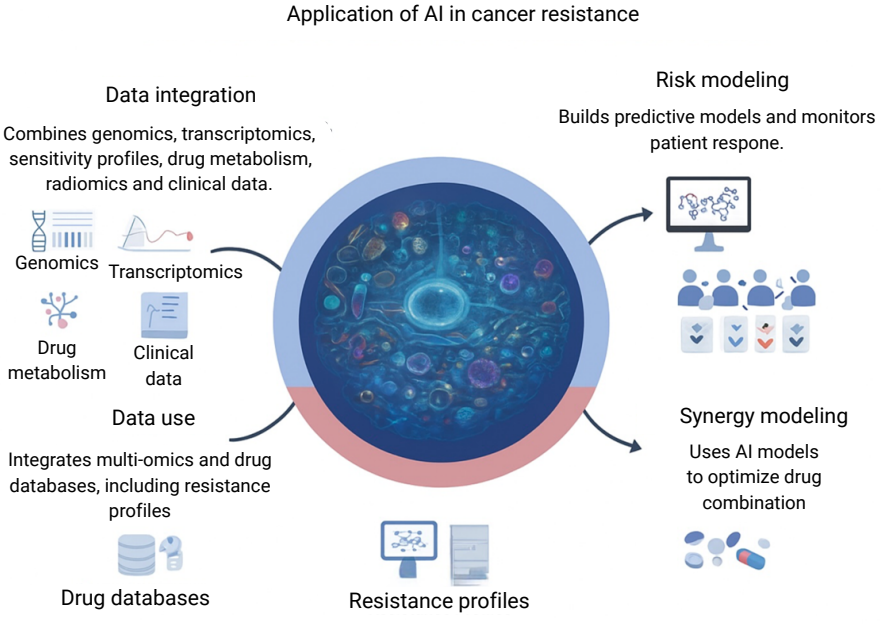



**Figure 4.** Applications of artificial intelligence (AI) in cancer drug resistance.


https://doi.org/10.24171/j.phrp.2025.0336

International collaboration will be essential for advancing biotechnology and addressing cancer drug resistance on a global scale. Multi-institutional partnerships, international clinical trial networks, and open-source data-sharing initiatives can accelerate the development of new therapies and help ensure that their benefits extend to patients worldwide. Global cooperation is also critical for addressing disparities in access to advanced treatments, particularly in low-resource settings that bear a disproportionate burden of drug-resistant cancers. At the same time, the rapid pace of biotechnological innovation requires regulatory agencies to adapt to novel scientific and clinical challenges. Clear, efficient, and harmonized regulatory pathways will be necessary to facilitate timely approval of new therapies. Governments and international organizations must therefore collaborate to address the ethical, legal, and financial complexities associated with implementing biotechnology-based cancer treatments.

## Conclusion

Cancer drug resistance remains one of the most significant challenges in oncology; however, as demonstrated in this review, biotechnology offers promising strategies to address this persistent problem. Through the development of novel therapeutics, personalized medicine approaches, and advanced drug-delivery systems, biotechnology has the potential to fundamentally transform cancer treatment. Nonetheless, effectively addressing public health challenges related to high treatment costs, limited access, and ethical considerations is essential to ensure that the benefits of these innovations reach all populations, particularly those in low-resource settings. Continued research, international collaboration, and policy innovation will be critical to realizing the full potential of biotechnology in combating cancer drug resistance and improving global public health outcomes. Ensuring affordability and accessibility remains central to reducing disparities in cancer care. Moreover, targeted efforts to expand access in underserved regions are necessary to prevent the widening of existing health inequities. Without deliberate policy interventions and sustained global cooperation, biotechnological advances risk reinforcing disparities in cancer treatment and limiting their overall public health impact.

## Notes

### Ethics Approval
Not applicable.

### Conflicts of Interest
The authors have no conflicts of interest to declare.

### Funding
None.

### Availability of Data
All data generated or analyzed during this study are included in this published article. For other data, these may be requested through the corresponding author.

### Authors' Contributions
Conceptualization: FAA; Data curation: FAA; Formal analysis: FAA; Methodology: FAA; Project administration: FAA; Resources: AA; Software: BKF; Supervision: FAA; Validation: BKF; Visualization: BKF; Writing–original draft: FAA; Writing–review & editing: all authors. All authors read and approved the final manuscript.

## References

1. Hammad R, Aglan RB, Mohammed SA, et al. Cytotoxic T cell expression of leukocyte-associated immunoglobulin-like receptor-1 (LAIR-1) in viral hepatitis C-mediated hepatocellular carcinoma. Int J Mol Sci 2022;23:12541.
2. Nwosu N. Cancer: a disease of modern times? Cureus 2024;16:e74666.
3. Wu Z, Xia F, Lin R. Global burden of cancer and associated risk factors in 204 countries and territories, 1980-2021: a systematic analysis for the GBD 2021. J Hematol Oncol 2024;17:119.
4. Chen S, Cao Z, Prettner K, et al. Estimates and projections of the global economic cost of 29 cancers in 204 countries and territories from 2020 to 2050. JAMA Oncol 2023;9:465–72.
5. Lei ZN, Tian Q, Teng QX, et al. Understanding and targeting resistance mechanisms in cancer. MedComm (2020) 2023;4:e265.
6. Wagle NS, Nogueira L, Devasia TP, et al. Cancer treatment and survivorship statistics, 2025. CA Cancer J Clin 2025;75:308–40.
7. Gautam S, Maurya R, Vikal A, et al. Understanding drug resistance in breast cancer: Mechanisms and emerging therapeutic strategies. Med Drug Discov 2025;26:100210.
8. Hamdy NM, Basalious EB, El-Sisi MG, et al. Advancements in current one-size-fits-all therapies compared to future treatment innovations for better improved chemotherapeutic outcomes: a step-toward personalized medicine. Curr Med Res Opin 2024;40:1943–61.
9. Ramos A, Sadeghi S, Tabatabaeian H. Battling chemoresistance in cancer: root causes and strategies to uproot them. Int J Mol Sci 2021;22:9451.
10. Hu X, Zhang Z. Understanding the genetic mechanisms of cancer drug resistance using genomic approaches. Trends Genet 2016;32:127–37.
11. Kara A, Ozgur A, Nalbantoglu S, et al. Dna repair pathways and their roles in drug resistance for lung adenocarcinoma. Mol Biol Rep 2021;48:3813–25.
12. Atta H, Alzahaby N, Hamdy NM, et al. New trends in synthetic drugs and natural products targeting 20S proteasomes in cancers. Bioorg Chem 2023;133:106427.
13. Song J, Yang P, Chen C, et al. Targeting epigenetic regulators as a

promising avenue to overcome cancer therapy resistance. Signal Transduct Target Ther 2025;10:219.
14. Tufail M, Hu JJ, Liang J, et al. Hallmarks of cancer resistance. iScience 2024;27:109979.
15. Lovly CM, Salama AK, Salgia R. Tumor heterogeneity and therapeutic resistance. Am Soc Clin Oncol Educ Book 2016;35:e585–93.
16. Tilsed CM, Fisher SA, Nowak AK, et al. Cancer chemotherapy: insights into cellular and tumor microenvironmental mechanisms of action. Front Oncol 2022;12:960317.
17. Mansoori B, Mohammadi A, Davudian S, et al. The different mechanisms of cancer drug resistance: a brief review. Adv Pharm Bull 2017;7:339–48.
18. Mustafa M, Ahmad R, Tantry IQ, et al. Apoptosis: a comprehensive overview of signaling pathways, morphological changes, and physiological significance and therapeutic implications. Cells 2024; 13:1838.
19. Strasser A, Vaux DL. Cell death in the origin and treatment of cancer. Mol Cell 2020;78:1045–54.
20. Alves R, Goncalves AC, Rutella S, et al. Resistance to tyrosine kinase inhibitors in chronic myeloid leukemia-from molecular mechanisms to clinical relevance. Cancers (Basel) 2021;13:4820.
21. Jorge SE, Kobayashi SS, Costa DB. Epidermal growth factor receptor (EGFR) mutations in lung cancer: preclinical and clinical data. Braz J Med Biol Res 2014;47:929–39.
22. Soragni A, Knudsen ES, O'Connor TN, et al. Acquired resistance in cancer: towards targeted therapeutic strategies. Nat Rev Cancer 2025; 25:613–33.
23. Chinemerem Nwobodo D, Ugwu MC, Oliseloke Anie C, et al. Antibiotic resistance: the challenges and some emerging strategies for tackling a global menace. J Clin Lab Anal 2022;36:e24655.
24. Emran TB, Shahriar A, Mahmud AR, et al. Multidrug resistance in cancer: understanding molecular mechanisms, immunoprevention and therapeutic approaches. Front Oncol 2022;12:891652.
25. Nishino K, Yamasaki S, Nakashima R, et al. Function and inhibitory mechanisms of multidrug efflux pumps. Front Microbiol 2021;12: 737288.
26. Senthebane DA, Rowe A, Thomford NE, et al. The role of tumor microenvironment in chemoresistance: to survive, keep your enemies closer. Int J Mol Sci 2017;18:1586.
27. Anderson NM, Simon MC. The tumor microenvironment. Curr Biol 2020;30:R921–5.
28. Chen Z, Han F, Du Y, et al. Hypoxic microenvironment in cancer: molecular mechanisms and therapeutic interventions. Signal Transduct Target Ther 2023;8:70.
29. Tie Y, Tang F, Wei YQ, et al. Immunosuppressive cells in cancer: mechanisms and potential therapeutic targets. J Hematol Oncol 2022;15:61.
30. Bai B, Xie S, Wang Y, et al. Development of anti-cancer drugs for tumor-associated macrophages: a comprehensive review and mechanistic insights. Front Mol Biosci 2024;11:1463061.
31. Salemme V, Centonze G, Avalle L, et al. The role of tumor microenvironment in drug resistance: emerging technologies to unravel breast cancer heterogeneity. Front Oncol 2023;13:1170264.
32. Rabaan AA, AlSaihati H, Bukhamsin R, et al. Application of CRISPR/ Cas9 technology in cancer treatment: a future direction. Curr Oncol 2023;30:1954–76.
33. Vaghari-Tabari M, Hassanpour P, Sadeghsoltani F, et al. Crispr/Cas9 gene editing: a new approach for overcoming drug resistance in cancer. Cell Mol Biol Lett 2022;27:49.
34. Chehelgerdi M, Chehelgerdi M, Khorramian-Ghahfarokhi M, et al. Comprehensive review of CRISPR-based gene editing: mechanisms, challenges, and applications in cancer therapy. Mol Cancer 2024;23:9.
35. Hussen BM, Abdullah SR, Hidayat HJ, et al. Crispr/cas as a tool to overcome drug resistance in cancer: from challenge to opportunity. Mol Cell Probes 2025;84:102052.
36. Feng X, Li Z, Liu Y, et al. Crispr/Cas9 technology for advancements in cancer immunotherapy: from uncovering regulatory mechanisms to therapeutic applications. Exp Hematol Oncol 2024;13:102.
37. Di Carlo E, Sorrentino C. State of the art CRISPR-based strategies for cancer diagnostics and treatment. Biomark Res 2024;12:156.
38. Lei T, Wang Y, Zhang Y, et al. Leveraging CRISPR gene editing technology to optimize the efficacy, safety and accessibility of CAR T-cell therapy. Leukemia 2024;38:2517–43.
39. Raigani M, Eftekhari Z, Adeli A, et al. Advancing gene editing therapeutics: clinical trials and innovative delivery systems across diverse diseases. Mol Ther Nucleic Acids 2025;36:102666.
40. Rosell R, Filipska M, Chaib I, et al. Commentary: safety and feasibility of CRISPR-edited T cells in patients with refractory non-small-cell lung cancer. Front Oncol 2020;10:1726.
41. Wang JY, Doudna JA. Crispr technology: a decade of genome editing is only the beginning. Science 2023;379:eadd8643.
42. Boakye Serebour T, Cribbs AP, Baldwin MJ, et al. Overcoming barriers to single-cell RNA sequencing adoption in low- and middle-income countries. Eur J Hum Genet 2024;32:1206–13.
43. Garg P, Malhotra J, Kulkarni P, et al. Emerging therapeutic strategies to overcome drug resistance in cancer cells. Cancers (Basel) 2024;16: 2478.
44. Haynes J, Manogaran P. Mechanisms and strategies to overcome drug resistance in colorectal cancer. Int J Mol Sci 2025;26:1988.
45. Koirala M, DiPaola M. Overcoming cancer resistance: strategies and modalities for effective treatment. Biomedicines 2024;12:1801.
46. Ou X, Gao G, Habaz IA, et al. Mechanisms of resistance to tyrosine kinase inhibitor-targeted therapy and overcoming strategies. MedComm (2020) 2024;5:e694.
47. Garg P, Pareek S, Kulkarni P, et al. Next-generation immunotherapy: advancing clinical applications in cancer treatment. J Clin Med 2024;13:6537.
48. Noronha V, Budukh A, Chaturvedi P, et al. Uniqueness of lung cancer in Southeast Asia. Lancet Reg Health Southeast Asia 2024;27:100430.
49. Barragan-Carillo R, Asirwa FC, Dienstmann R, et al. Global oncology:



https://doi.org/10.24171/j.phrp.2025.0336

tackling disparities and promoting innovations in low- and middle-income countries. Am Soc Clin Oncol Educ Book 2025;45:e473930.

50. Patil PA, Kumbhar BV. Structure based drug design and machine learning approaches for identifying natural inhibitors against the human αβIII tubulin isotype. Sci Rep 2025;15:32716.
51. Salo-Ahen OM, Alanko I, Bhadane R, et al. Molecular dynamics simulations in drug discovery and pharmaceutical development. Processes 2021;9:71.
52. Pei J, Zhang J, Cong Q. Computational analysis of protein-protein interactions of cancer drivers in renal cell carcinoma. FEBS Open Bio 2024;14:112–26.
53. Okereke M, David KB, Adedeji OJ. Computational approaches to targeting protein-protein interactions in cancer: a pathway to drug discovery. Future Drug Discov 2023;5:FDD80.
54. Qiao L, Huo X, Huang W, et al. Advances in high-throughput drug screening based on pharmacotranscriptomics. J Adv Res 2025 Sep 11 [Epub]. https://doi.org/10.1016/j.jare.2025.09.006.
55. Chen J, Lin A, Jiang A, et al. Computational frameworks transform antagonism to synergy in optimizing combination therapies. NPJ Digit Med 2025;8:44.
56. Boonyarit B, Kositchutima M, Phattalung TN, et al. SynProtX: a large-scale proteomics-based deep learning model for predicting synergistic anticancer drug combinations. Gigascience 2025;14:giaf080.
57. Elalouf A, Elalouf H, Rosenfeld A, et al. Artificial intelligence in drug resistance management. 3 Biotech 2025;15:126.
58. Bilal H, Khan MN, Khan S, et al. The role of artificial intelligence and machine learning in predicting and combating antimicrobial resistance. Comput Struct Biotechnol J 2025;27:423–39.
59. Siddiqui IA, Adhami VM, Chamcheu JC, et al. Impact of nanotechnology in cancer: emphasis on nanochemoprevention. Int J Nanomedicine 2012;7:591–605.
60. Li J, Burgess DJ. Nanomedicine-based drug delivery towards tumor biological and immunological microenvironment. Acta Pharm Sin B 2020;10:2110–24.
61. Zhu J, Lee H, Huang R, et al. Harnessing nanotechnology for cancer treatment. Front Bioeng Biotechnol 2024;12:1514890.
62. Elumalai K, Srinivasan S, Shanmugam A. Review of the efficacy of nanoparticle-based drug delivery systems for cancer treatment. Biomed Technol 2024;5:109–22.
63. Bhattacharjee S. Craft of co-encapsulation in nanomedicine: a struggle to achieve synergy through reciprocity. ACS Pharmacol Transl Sci 2022;5:278–98.
64. Jarmila P, Veronika M, Peter M. Advances in the delivery of anticancer drugs by nanoparticles and chitosan-based nanoparticles. Int J Pharm X 2024;8:100281.
65. Melo MN, Amaral RG, Melo de Andrade LR, et al. An overview of randomized phase III clinical trials of cancer nanomedicines. Cancer Pathog Ther 2025;3:322–36.
66. Desai N, Rana D, Patel M, et al. Nanoparticle therapeutics in clinical perspective: classification, marketed products, and regulatory landscape. Small 2025;21:e2502315.
67. Fortune A, Aime A, Raymond D, et al. Nanotechnology in medicine: a double-edged sword for health outcomes. Health Nanotechnol 2025;1:9.
68. Mahumud RA. Optimising cancer medicine in clinical practices: are neoadjuvant and adjuvant immunotherapies affordable for cancer patients in low- and middle-income countries? Cancers (Basel) 2025;17:1722.
69. Alturki NA. Review of the immune checkpoint inhibitors in the context of cancer treatment. J Clin Med 2023;12:4301.
70. Jogalekar MP, Rajendran RL, Khan F, et al. Car T-cell-based gene therapy for cancers: new perspectives, challenges, and clinical developments. Front Immunol 2022;13:925985.
71. Uscanga-Palomeque AC, Chavez-Escamilla AK, Alvizo-Baez CA, et al. Car-T cell therapy: from the shop to cancer therapy. Int J Mol Sci 2023;24:15688.
72. Seliger B, Massa C. Immune therapy resistance and immune escape of tumors. Cancers (Basel) 2021;13:551.
73. Sanomachi T, Katsuya Y, Nakatsura T, et al. Next-generation CAR-T and TCR-T cell therapies for solid tumors: innovations, challenges, and global development trends. Cancers (Basel) 2025;17:1945.
74. Favier S, Xiong W, Chalabi-Dchar M, et al. Exploring and bypassing resistance to targeted therapies in colorectal cancer. Biomed Pharmacother 2025;193:118741.
75. Vo MC, Tran VD, Nguyen VT, et al. Challenges and limitations of chimeric antigen receptor T-cell therapies in solid tumors: why are approvals restricted to hematologic malignancies? J Hematol Oncol 2025;18:91.
76. Zhu J, Zhou J, Tang Y, et al. Advancements and challenges in CAR-T cell therapy for solid tumors: a comprehensive review of antigen targets, strategies, and future directions. Cancer Cell Int 2025;25:313.
77. Dent J, Jorge M, Sobrevilla N, et al. Cancer immunotherapy clinical trials to support urgently needed access in low- and middle-income countries: a report from the SITC global access and impact committee. J Immunother Cancer 2025;13:e011258.
78. Medina-Olivares FJ, Gomez-De Leon A, Ghosh N. Obstacles to global implementation of CAR T cell therapy in myeloma and lymphoma. Front Oncol 2024;14:1397613.
79. Tu SS, Goode R, Turner M, et al. Accelerating biosimilar market access: the case for allowing earlier standing. J Law Biosci 2025;12:lsae030.
80. National Cancer Institute (NCI) (US). Administering peripheral blood lymphocytes transduced with a murine T-cell receptor recognizing the G12D variant of mutated RAS in HLA-A*11:01 patients [Internet]. ClinicalTrials.gov; 2025 [cited 2025 Nov 15]. Available from: https://clinicaltrials.gov/study/NCT03745326.
81. Novartis Pharmaceuticals (US). Study of efficacy and safety of CTL019 in pediatric ALL patients (ENSIGN) [Internet]. ClinicalTrials.gov; 2020 [cited 2025 Nov 15]. Available from: https://clinicaltrials.gov/study/NCT02228096.

82. New York Medical College (US). Chemoradiotherapy with targeted immunotherapy in pediatric lymphoma (radical) [Internet]. ClinicalTrials.gov; 2025 [cited 2025 Nov 15]. Available from: https://clinicaltrials.gov/study/NCT05253495.
83. Royal Marsden NHS Foundation Trust (US). Conventional care versus radioablation (stereotactic body radiotherapy) for extracranial oligometastases (core) [Internet]. ClinicalTrials.gov; 2019 [cited 2025 Nov 15]. Available from: https://clinicaltrials.gov/study/NCT02759783.
84. Bernicker E. Trial of radiation and gene therapy before nivolumab for metastatic non-small cell lung carcinoma and uveal melanoma (ENSIGN) [Internet]. ClinicalTrials.gov; 2023 [cited 2025 Nov 15]. Available from: https://clinicaltrials.gov/study/NCT02831933.
85. Berghoff A. Personalized targeted glioblastoma therapies by ex vivo drug screening (attract) [Internet]. ClinicalTrials.gov; 2024 [cited 2025 Nov 15]. Available from: https://clinicaltrials.gov/study/NCT06512311.
86. Prasad V, Mailankody S. Research and development spending to bring a single cancer drug to market and revenues after approval. JAMA Intern Med 2017;177:1569–75.
87. Mailankody S, Prasad V. Five years of cancer drug approvals: innovation, efficacy, and costs. JAMA Oncol 2015;1:539–40.
88. Ayanoglu FB, Elcin AE, Elcin YM. Bioethical issues in genome editing by CRISPR-Cas9 technology. Turk J Biol 2020;44:110–20.
89. Musekiwa A, Moyo M, Mohammed M, et al. Mapping evidence on the burden of breast, cervical, and prostate cancers in Sub-Saharan Africa: a scoping review. Front Public Health 2022;10:908302.
90. Ramutumbu NJ, Ramathuba DU, Maputle MS. Barriers to accessing oncology services for effective cancer care in the public health institutions in Limpopo Province, South Africa: a qualitative study. Nurs Rep 2023;13:956–68.
91. Matthew KA, Opia FN, Matthew A, et al. Achieving personalized oncology care: insights and challenges in sub-Saharan Africa. IJMRGE 2022;3:775–83.
92. Ingham J, Ruan JL, Coelho MA. Breaking barriers: we need a multidisciplinary approach to tackle cancer drug resistance. BJC Rep 2025;3:11.
93. Akodad S, Goldman M, Stevens H. Early access disparities in innovative therapies across the US, EU, China, and Japan. Front Med (Lausanne) 2025;12:1642882.
94. Lawler M, Bhatti S, Przewiezlikowski P, et al. Central and Eastern Europe: a crucible for clinical cancer innovation? J Cancer Policy 2025;46:100647.
95. Zhang YL, Yuan JQ, Wang KF, et al. The prevalence of EGFR mutation in patients with non-small cell lung cancer: a systematic review and meta-analysis. Oncotarget 2016;7:78985–93.
96. Julian GS, Shau WY, Chou HW, et al. Bridging real-world data gaps: connecting dots across 10 Asian countries. JMIR Med Inform 2024;12:e58548.
97. Zhang K, Liu W. The current status, trend, and development strategies of chinese biopharmaceutical industry with a challenging perspective. Sage Open 2020;10:215824402090152.
98. Wang X, Zhang H, Chen X. Drug resistance and combating drug resistance in cancer. Cancer Drug Resist 2019;2:141–60.
99. Feng K, Russo M, Maini L, et al. Patient out-of-pocket costs for biologic drugs after biosimilar competition. JAMA Health Forum 2024;5:e235429.
100. Rueda J, de Miguel Beriain I, Montoliu L. Affordable pricing of CRISPR treatments is a pressing ethical imperative. CRISPR J 2024;7:220–6.
101. Castaneda-Gonzalez JP, Parra-Medina R, Riess JW, et al. Genetic ancestry and lung cancer in Latin American patients: a crucial step for understanding a diverse population. Clin Lung Cancer 2025;26:e342–52.
102. Gomez-Abuin G, Mando P, Curigliano G, et al. Main challenges to cancer care in Latin America: an analysis through breast cancer lenses. Lancet Reg Health Am 2025;48:101147.
103. Nunes Filho PR, Brandalise P, Kannan GS, et al. Latin America and cancer clinical trials: underrepresented region with significant growth potential. J Clin Oncol 2024;42:e23038.
104. Gu J, Zhang J, Zeng S, et al. Artificial intelligence in tumor drug resistance: mechanisms and treatment prospects. Intell Oncol 2025;1:73–88.
105. Yang J, Dung NT, Thach PN, et al. Generalizability assessment of AI models across hospitals in a low-middle and high income country. Nat Commun 2024;15:8270.
106. Zuhair V, Babar A, Ali R, et al. Exploring the impact of artificial intelligence on global health and enhancing healthcare in developing nations. J Prim Care Community Health 2024;15:21501319241245847.
107. Rashid AB, Kausik MA. AI revolutionizing industries worldwide: a comprehensive overview of its diverse applications. Hybrid Adv 2024;7:100277.



https://doi.org/10.24171/j.phrp.2025.0336

phrp
OSONG PUBLIC HEALTH AND RESEARCH PERSPECTIVES

pISSN 2210-9099 eISSN 2233-6052
https://doi.org/10.24171/j.phrp.2025.0347
Osong Public Health Res Perspect 2026;17(1):17-32

Review Article

# The role of artificial intelligence in managing COVID-19 and long COVID: a narrative review

**Bikash Kanti Sarkar, Ambuj Kumar**

Department of Computer Science and Engineering, Birla Institute of Technology, Ranchi, India

## ABSTRACT

The coronavirus disease 2019 (COVID-19) pandemic had an unprecedented global impact, resulting in both positive and negative consequences. The virus not only affected millions of lives worldwide but also caused long-term harm to multiple organ systems in many survivors, thereby substantially impairing quality of life. This persistent condition is now referred to as long COVID (LC). The aim of this study is to raise awareness of LC-related organ system impacts and to highlight the key role of artificial intelligence (AI) in mitigating these effects. The present research conducts a narrative review focusing on LC-related impacts. In this context, unstructured searches were conducted to identify a total of 69 relevant studies indexed in Embase, PubMed, Web of Science, or Scopus, each of which was reviewed by at least 2 experts with sufficient domain knowledge in health sciences. Based on the authors' perspectives and insights, the review narratively examines damage to human organ systems attributable to LC and explores the role of AI in addressing LC-related challenges. Significant ethical, practical, and societal concerns arising from the extensive use of AI, particularly major issues such as data privacy and algorithmic bias, are also discussed. LC has caused lasting impacts on human organ systems, while AI is offering substantial potential for LC-related care.

**Keywords:** Artificial-intelligence-role; Concerns; Damage; Human-organ-systems; Long-COVID

**Received:** September 8, 2025
**Revised:** November 15, 2025
**Accepted:** December 10, 2025

Corresponding author:
Bikash Kanti Sarkar
Department of Computer Science and Engineering, Birla Institute of Technology, Mesra, Ranchi-835215, Jharkhand, India
E-mail: bksarkar@bitmesra.ac.in

## Introduction

Coronavirus disease 2019 (COVID-19), caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) virus, triggered a global health emergency of unprecedented scale, claiming millions of lives and profoundly disrupting societies worldwide [1]. Importantly, prior to the development of COVID-19 vaccines and effective treatments, lockdown measures were the primary strategy available to limit disease transmission. According to reports from the World Health Organization (WHO), COVID-19 vaccination began in August 2020 to reduce viral spread and associated mortality, and approximately 11,811,627,599 vaccine doses had

The opinions expressed by authors contributing to this journal do not necessarily reflect the opinions of the Korea Disease Control and Prevention Agency and Korea National Institute of Health.

© 2026 Korea Disease Control and Prevention Agency.
This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

been administered globally as of May 23, 2022. Of these, 5,193,581,059 individuals had received at least 1 dose, while 4,710,246,957 were fully vaccinated [2]. Owing to mass vaccination efforts, the global situation gradually normalized toward the end of 2023. Assuming that most survivors are vaccinated, millions are now experiencing a range of post-COVID-19 conditions collectively referred to as long COVID (LC). LC is known by several terms, including post-COVID-19 conditions, long-haul COVID, and post-acute COVID-19 syndrome. LC is essentially a chronic condition arising as an after-effect of SARS-CoV-2 infection and/or vaccine administration, persisting for at least 3 months after acute infection, and gradually affecting 1 or more organ systems in survivors. One study reported that approximately 10% to 12% of vaccinated individuals experienced LC [3]. More than 200 post-COVID-19 symptoms have been documented. Previous studies have identified key LC symptoms, including brain fog, fatigue, fever, insomnia, dyspnea, musculoskeletal pain, diabetes, headaches, skin rashes, neurological disturbances, gastrointestinal issues, and emotional symptoms such as sadness and anxiety, all of which reflect underlying organ system involvement [4–6]. In addition, some researchers have raised concerns that COVID-19 may act similarly to environmental stressors—such as air and water pollution, temperature variation, radiation exposure, pesticide exposure, and lifestyle factors including tobacco use, alcohol consumption, and fast-food intake—that increase long-term disease risks, including cancer.

At present, there is no definitive statistical evidence demonstrating an increased post-COVID-19 mortality rate; however, reports of deaths appear more frequent than during the pre-COVID-19 era. This observation highlights the need for further investigation. Encouragingly, ongoing research is actively exploring the causes of post-COVID-19 symptoms and leveraging artificial intelligence (AI)-based approaches to mitigate these impacts. Although numerous studies addressing AI applications in COVID-19 and LC exist in the literature, relatively few have focused on the ethical, practical, and societal concerns associated with the extensive use of AI.

This narrative review aims to provide a broad overview of current understanding of LC, with particular emphasis on its multiorgan system effects and underlying pathophysiological mechanisms. Drawing on the authors' perspectives and insights, this review incorporates emerging AI applications—including machine learning (ML), deep learning (DL), and natural language processing (NLP)—to address complexities in LC diagnosis, prognosis, symptom monitoring, and therapeutic development. Furthermore, the study examines key ethical, practical, and societal challenges associated with widespread AI deployment in LC care, emphasizing issues such as data privacy, algorithmic bias, and the necessity of human oversight. Through this approach, the study seeks to raise awareness of the complex, multisystemic nature of LC-induced organ damage.

***HIGHLIGHTS***

- This review raises awareness about coronavirus disease 2019 (COVID-19)–induced damage to human organ systems and the global burden.
- The potential of artificial intelligence (AI) for addressing long COVID–related health challenges is explored.
- Significant ethical, practical, and societal challenges are posed by the extensive use of AI.
- More research is necessary on long COVID throughout the world.

## Research Questions

The specific review questions addressed here are: (1) What are the impacts of COVID-19 on the human body?; (2) Is AI playing important roles in mitigating the impacts? If so, how is AI doing it?; (3) What challenges arise from the extensive use of AI?

## Contributions of the Study

Raising awareness about COVID-19–induced damage to human organ systems and the global burden. Exploring the potential of AI in addressing LC-related health challenges. Highlighting significant ethical, practical, and societal concerns related to the extensive use of AI. Indicating the growing volume of global research on LC.

## Organization of the Paper

In addition to the introduction (Section 1), the materials (research articles) and search methods, including inclusion and exclusion criteria for article selection, are described in Section 2. Section 3 provides an overview of proposed pathophysiological mechanisms underlying LC. Section 4 discusses the effects of COVID-19 infection on major human organ systems in survivors. The overall global impact of LC is examined in Section 5. Section 6 addresses AI-based techniques that were applied during COVID-19 and are now being used to mitigate post-COVID-19 impacts. Ethical concerns, including data privacy and broader challenges associated with AI use, are discussed in Section 7. The limitations of the present study are outlined in Section 8, and Section 9 concludes the article. The overall discussion



https://doi.org/10.24171/j.phrp.2025.0347

framework of this study is illustrated pictorially in Figure 1.

## Materials and Methods

LC is currently a broad and evolving topic that requires deeper theoretical insight; therefore, a narrative study design is considered more appropriate. In this context, the present narrative study aims to integrate valuable information from multiple sources without adhering to a standardized methodology for literature selection and analysis, in order to provide a comprehensive understanding of LC-related scenarios. In addition, the study discusses the role of AI in mitigating the identified issues based on the authors' perspectives and insights. Although a standardized methodology for article selection was not applied, the authors nevertheless collected relevant literature from established and credible data sources using predefined search strategies to support discussion and analysis.

We searched the PubMed, ScienceDirect, Embase, Scopus, and Google Scholar databases for studies published after January 2020, using keywords such as "long COVID," "post-COVID," "human organ systems," "role of AI in mitigating post-COVID," "AI in patient monitoring," health justice," "health data privacy," and "ethical considerations in AI." The study includes relevant research articles, review papers, case studies, and materials obtained from web-based sources related to LC. In total, 69 relevant studies were included based on careful screening of titles and abstracts, with each article assessed by at least 2 reviewers possessing sufficient expertise in AI, ML, COVID-19, and data privacy and security. Importantly, reviewers initially examined the title and abstract of each article, followed by full-text evaluation to determine its relevance for inclusion in this study.

### Data Sources and Search Strategy

The sources of the included articles were indexed in PubMed, Scopus, or Web of Science (WoS) databases and were ultimately selected for inclusion in this narrative review. The inclusion and exclusion criteria applied to article selection are described below. (1) Included articles comprised research articles, review articles, or book chapters published in scientific journals or presented at standard academic conferences, irrespective of geographic location. (2) Letters to the editor, or articles with unclear or incomplete data and methods were excluded from the study. Additionally, manuscripts not written in English were excluded directly.

### Search Strategy

For retrieving articles from the PubMed database, the [tiab] (Title and Abstract) tag was used (e.g., "Long COVID"[tiab] AND "Human Body Impact"[tiab] AND "Role of AI"[tiab]). For searching Scopus-indexed manuscripts, the Scopus platform was accessed directly and the TITLE-ABS-KEY tag was applied (e.g., TITLE-ABS-KEY(("Long COVID" OR "Post-COVID") AND "Human Organ Impact")). For articles indexed in the WoS database, searches were conducted using the topic search (TS) function, such as TS = ("Long COVID" OR "Post-COVID") AND TS = ("Human Organ Impact") AND TS = ("Role of AI"). The Medical Subject Headings (MeSH) terms applied in the search process included "Long COVID," "Human body," "Immune system," "SARS-CoV-2," and "pathophysiological mechanisms," among others.

## Proposed Pathophysiological Mechanisms

Pathophysiological mechanisms refer to the complex biological processes within the body that are responsible for the development of disease symptoms and the progression of disease states. These mechanisms disrupt normal physiological functioning and contribute to sustained morbidity. Well-accepted pathophysiological mechanisms relevant to LC are summarized in Table 1. AI-based approaches assist in exploring these mechanisms by identifying patterns associated with symptom development and disease progression.

## Long COVID and Its Impact on Human Organs

This section discusses the impact of LC on various human organ systems.

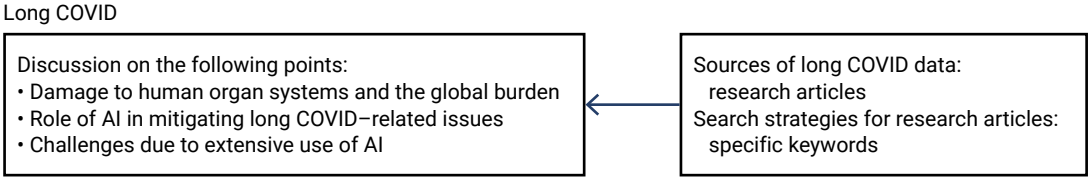



**Figure 1.** Conceptual diagram of the present study.
COVID, coronavirus disease; AI, artificial intelligence.

**Table 1.** Proposed pathophysiological mechanisms

| Organ system | Functional and biochemical changes in the body and the mechanisms thereof |
|---|---|
| Nervous system | Immune dysregulation: This occurs due to breakdown or maladaptive changes in molecular immune-control processes, which may lead to autoimmune diseases and some cancers. COVID-19 can cause long-lasting alterations in immune system function. Some patients show persistent inflammation, whereas others exhibit reduced or ineffective immune responses. This imbalance can affect multiple organs and may contribute to fatigue, reduced exercise tolerance, and difficulties with concentration or memory. Prolonged immune activation may also impair the body's ability to heal and return to baseline health. |
| | Autoimmune diseases: These occur when the immune system attacks the body's own tissues instead of protecting them. Emerging evidence suggests that COVID-19 may trigger autoimmune processes in certain individuals, potentially contributing to symptoms affecting the nervous system, circulation, or other organs. |
| | Viral persistence: This refers to the long-term presence of viral components within the body, potentially causing chronic infection and diminished metabolic function. In some individuals, fragments of the virus appear to persist for months after the initial infection. |
| | Microvascular inflammation: Inflammation resulting from immune dysregulation or infection may activate the microcirculation and affect blood pressure regulation. Small-vessel inflammation, clotting abnormalities, and impaired circulation may persist after the acute illness. |
| | Neuroinflammation: This refers to inflammation of nervous tissue, often involving microglial activation. It may contribute to memory impairment and disruption of daily functioning. |
| Cardiovascular system | Endothelial dysfunction condition: This condition arises when the inner lining of blood vessels fails to function properly, contributing to cardiovascular complications such as microvascular inflammation or thrombo-inflammation. |
| | Direct viral impact on cardiac tissue: SARS-CoV-2 may directly damage cardiac tissue, potentially leading to long-term or permanent cardiac injury. |
| Respiratory system | Viral damage: Direct viral injury to lung tissue can impair healing and recovery. |
| | Pulmonary infiltrates: Accumulation of substances denser than air in the lungs can lead to infections such as pneumonia or tuberculosis. |
| | Inflammation: Chronic inflammation may affect energy metabolism, digestion, cognition, and overall physiological balance. |
| | Fibrosis: Excessive accumulation of fibrous connective tissue causes scarring and impaired lung function and may also affect the heart, liver, skin, and other organs. |
| Renal system | Viral illness of kidney cells: Viral infection may hijack renal cellular pathways, disrupting normal kidney function. Inflammation and reduced renal blood flow can contribute to conditions such as atherosclerosis, diabetes, and obesity. |
| | Sepsis: Systemic infection may lead to widespread inflammation and multiorgan dysfunction. |
| Immune system | Immune dysregulation and viral persistence: Persistent immune imbalance and viral remnants may impair immune responses. |
| | Oxidative stress: Infection may reduce host immune defense capacity. |
| | Autoantibody production: Breakdown of immune self-tolerance may trigger B-cell-mediated autoantibody generation. |
| GI system | Viral infection of GI epithelial cells, intestinal microbiota dysbiosis (associated with bacterial infections such as *Helicobacter* pylori and *Clostridioides difficile*), and inflammation involving the liver. |
| Dermatological system | Immune responses play a critical role in neutralizing pathogens. Impaired immune responses may result in frequent infections, delayed wound healing, and skin inflammation. |
| | Direct viral effects on skin cells may cause lesions and inflammatory skin manifestations. |

COVID-19, coronavirus disease 2019; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; GI, gastrointestinal.

## Long COVID and Its Impact on the Major Human Organ Systems

LC is characterized by a wide spectrum of symptoms that often persist for several months or even years following the initial SARS-CoV-2 infection. The major human organ systems affected, along with the associated damage attributable to COVID-19, are reviewed below.

### The nervous system

The nervous system includes the brain, vertebral structures, and an intricate network of nerves, and it plays a central role in regulating bodily functions. It coordinates voluntary actions and sensory input throughout the body by transmitting electrical signals. Commonly reported neurological and neuropsychiatric manifestations include cognitive difficulties (often described as brain fog), memory loss, diminished sense of taste (ageusia), loss of smell (anosmia), headaches, sleep disorders, panic, and anxiety [7–10]. According to the WHO clinical definition of LC, these symptoms are more prevalent among individuals who were hospitalized, with 53% of hospitalized individuals reporting symptoms compared with 35% of non-hospitalized individuals. In



https://doi.org/10.24171/j.phrp.2025.0347

addition, a higher incidence was reported among women (approximately 49%) than men (37%). Brain fog was identified as the most frequently reported neuropsychiatric symptom, affecting 74% of individuals. Other commonly reported symptoms included memory problems (65%), disturbed sleep (62%), altered sense of smell or taste—referred to as hyposmia and hypogeusia, respectively (57%)—headaches (56%), and depression (50%) [11].

Brain fog, also referred to as mental fog, describes a cognitive state characterized by confusion, difficulty concentrating, learning challenges, and impaired recall of past events. Research indicates that approximately 20% to 35% of individuals experience brain fog following COVID-19 infection [12]. Sleep disturbances represent another prevalent neurological complaint in LC, affecting approximately 26% of patients, and are closely associated with mental health conditions [13–15]. These disturbances may include insomnia as well as vivid dreams or nightmares [16]. Recently, Hermans et al. [17] reported a prevalent symptom cluster—including sleep disorders, joint pain, fatigue, and headaches—among individuals with LC in lower-middle-income countries.

Overall, mental health conditions such as psychological strain, anxiety, and depression significantly affected daily life during the COVID-19 pandemic, and these effects persist in the post-pandemic period. These ongoing issues have placed additional pressure on global healthcare systems due to the increasing number of individuals experiencing mental health challenges. AI-driven monitoring and decision-support systems offer potential tools for managing and mitigating these long-term neurological and psychological consequences of the pandemic.

### The cardiovascular system

The cardiovascular system consists of the heart, blood, and an extensive network of vessels, including arteries, veins, and capillaries. Its primary function is to circulate blood throughout the body, deliver oxygen and essential nutrients to all cells, and remove metabolic waste products such as carbon dioxide. Research indicates that approximately 7% to 40% of individuals develop some form of cardiovascular disorder following COVID-19 infection. Common symptoms that may indicate cardiovascular impairment include chest discomfort, palpitations or irregular heartbeats, dizziness, and an elevated resting heart rate [18].

According to a study by Barman et al. [19], approximately 20% to 30% of patients hospitalized due to COVID-19 exhibit elevated troponin levels. Troponin is a biochemical marker associated with type 2 myocardial infarction, which occurs when an imbalance develops between myocardial oxygen supply and oxygen demand. In individuals with COVID-19, troponin levels exceeding the 99th percentile are associated with a 3- to 6-fold increased risk of developing coronary artery disease (CAD) [20]. Additional findings suggest that individuals infected with COVID-19 may continue to face an increased risk of myocardial infarction and stroke for up to 3 years following the initial infection [21].

### The respiratory system

The respiratory system regulates the process of breathing, which is essential for sustaining life. It enables the body to absorb oxygen and eliminate carbon dioxide. This system comprises the lungs, airways (including the trachea, bronchi, and bronchioles), diaphragm, larynx (voice box), throat, nose, and mouth, all of which work together to facilitate gas exchange. Its primary function is to ensure adequate oxygen delivery to body tissues while removing carbon dioxide as a metabolic waste product.

COVID-19 is known to severely affect the respiratory system, producing symptoms such as chest pain, choking sensations, persistent coughing, chest discomfort, dyspnea, and various pulmonary complications. Evidence indicates that approximately 80% of infections remain confined to the upper respiratory tract, whereas around 20% progress to the lower respiratory system, reaching the alveoli and resulting in lung infiltrates [22].

A study conducted by Long et al. [23], which analyzed data from 4,478 participants across 16 cohort studies, reported that 20% of individuals infected with COVID-19 experienced some degree of lung function impairment. Reduced diffusion capacity was the most frequently observed abnormality, followed by restrictive ventilatory patterns.

### The renal system

The renal system comprises the kidneys, ureters, and urethra, and it plays a crucial role in removing liquid toxins and excess ions from the human body. By filtering approximately 200 L of fluid from the blood each day, the renal system helps maintain internal homeostasis and physiological balance.

Following COVID-19 infection, renal function may be adversely affected, leading to complications such as reduced renal perfusion, hypotension, ischemia, increased salt excretion (salt diuresis), sympathetic nervous system overactivation, and enhanced salt and water retention. Both direct and indirect effects of SARS-CoV-2 may persist after recovery from the acute phase, potentially resulting in long-term outcomes such as sepsis, recurrent episodes of acute kidney injury, and progression toward chronic kidney disease.

In a notable study, Ramamoorthy et al. [24] were the first

to propose that renal fibrosis may represent a long-term consequence of viral infection. Their findings, derived from experimental studies involving mice infected with mouse hepatitis virus-1 following acute infection, provide supporting evidence for this hypothesis.

### The immune system

The immune system consists of the thymus, bone marrow, spleen, lymph nodes, tonsils, and liver, and its primary function is to protect the body against harmful bacteria and viruses. When immune function is impaired, 3 major categories of health conditions may arise: allergies, autoimmune disorders, and immunodeficiencies. Diseases such as type 1 diabetes, lupus, and rheumatoid arthritis exemplify disorders associated with immune system dysfunction.

COVID-19 has also been shown to affect immune system integrity. A 2024 study by Kratzer et al. [25], published in the journal Allergy and conducted by a research group in Vienna, reported that SARS-CoV-2 infection may induce long-lasting immune alterations, even among individuals who experienced only mild illness. These findings enhance current understanding of the prolonged immune consequences associated with COVID-19.

### The gastrointestinal system

The gastrointestinal tract consists of the mouth, pharynx, esophagus, stomach, small and large intestines, rectum, and anus, and is commonly referred to as the digestive system. Its primary function is to break down ingested food to facilitate nutrient absorption and eliminate waste products from the body.

Gastrointestinal complications associated with illness may present as diarrhea, nausea, vomiting, abdominal pain, loss of appetite, and altered taste perception. These manifestations may arise from various underlying conditions, including acid-related disorders, impaired gastrointestinal motility, belching, hepatobiliary disease, functional bowel disorders, rectal bleeding, and liver injury. A study by Ma et al. [26] reported that individuals with severe COVID-19 infections tend to experience more pronounced gastrointestinal symptoms.

There is substantial evidence that SARS-CoV-2 negatively affects multiple components of the digestive system [27,28]. Furthermore, Choudhury et al. [29] reported that 12% of individuals in the post-COVID-19 phase and 22% of those with LC exhibited symptoms indicative of gastrointestinal tract damage. Additional research suggests that individuals with LC may face an increased risk of developing chronic digestive system disorders [30].

### Dermatological complications

Dermatological disorders primarily affect the skin surface and may present as rashes, inflammation, itching, or other visible alterations in skin appearance. Research has established associations between SARS-CoV-2 infection and a range of dermatological manifestations that may emerge during recovery or in the post-infection period [31,32]. To date, more than 30 distinct types of COVID-19–related skin eruptions have been documented [33], with substantial interindividual variability in clinical presentation [31,32]. A study conducted by McMahon et al. [34] analyzed dermatological manifestations in patients from 41 countries, including individuals with laboratory-confirmed or suspected COVID-19, as well as cases in which skin findings were the primary or sole indicator of infection.

Table 2 summarizes the affected organ systems, key symptoms, prevalence, associated functional and biological changes, and the potential underlying mechanisms [11,18,22,23,29,31,32,35].

## Prevalence, Risk Factors, and Functional Impact of Long COVID

Understanding the global burden of LC, including its variable prevalence, associated risk factors, diagnostic challenges, and profound functional impact, is essential for both public health planning and individual patient care. These dimensions are briefly described below.

### Global and Regional Prevalence Estimates

LC affects millions of individuals worldwide. According to global estimates, approximately 65 million people are currently living with LC. In this context, a study by Lovaglio et al. [36] provides the following relevant information: (1) In 2022, approximately 2.7% of the adult population in the United Kingdom was affected by LC (Islam et al. *Mymensingh Med J* 2024;33:1250–7). In the United States, a report published in *MMWR Morbidity and Mortality Weekly Report* (Ford et al. *MMWR Morb Mortal Wkly Rep* 2024;73:135–6) estimated that around 6.9% of the adult population was affected by LC in 2022. Globally, it is estimated that 10% to 20% of individuals infected with COVID-19 during the first 2 years of the pandemic developed LC (https://www.who.int/europe/news-room/fact-sheets/item/post-covid-19-condition). (2) Reported LC prevalence among individuals infected with COVID-19 varies considerably across studies and regions, ranging from approximately 10% to 50% (https://www.sciencealert.com/long-covid-rate-in-africa-is-almost-50-of-cases-researchers-warn). (3) The median proportion of patients reporting at least 1 persistent symptom within 60



https://doi.org/10.24171/j.phrp.2025.0347

**Table 2.** Summary of long COVID symptoms and the affected human organ systems

| Organ system | Key symptoms | Prevalence/severity notes |
|---|---|---|
| Nervous system | Brain fog, memory loss, anosmia/ageusia, headaches, sleep disorders, anxiety, depression | Higher in hospitalized patients (53%) and women (49%); brain fog (74%), memory problems (65%), disturbed sleep (62%); impaired work/school for 6 months–2+ years [11] |
| Cardiovascular system | Chest pain/pressure, irregular heartbeat (palpitations), light-headedness, increased resting heart rate, increased risk of heart attacks | 7%–40% experience condition; 20%–30% hospitalized exhibit elevated troponin; risk of heart attacks/strokes persists up to 3 years [18] |
| Respiratory system | Chest pain, shortness of breath, persistent coughing, lung dysfunction (diffusion impairment, restrictive defects) | 20% lung function abnormalities; potential for pulmonary fibrosis [22] |
| Renal system | Reduced renal perfusion, hypotension, ischemia, increased salt excretion, recurrent AKI, onset of CKD | Renal fibrosis as long-term consequence [23] |
| Immune system | Lasting alterations to immune system, chronic fatigue, autoimmunity, reactivation of latent viruses (EBV, HHV-6, CMV), bacterial diseases (TB) | Affects even mild cases; linked to fatigue, POTS, neurocognitive dysfunction [35] |
| GI system | Diarrhea, nausea, vomiting, abdominal pain, loss of appetite, altered taste perception, liver damage, motility problems | Increased likelihood in long COVID patients; 12%–22% exhibit GI tract damage [29] |
| Dermatological system | Rashes, inflammation, itching, over 30 types of skin rashes | Varies widely among individuals [31,32] |

COVID, coronavirus disease; AKI, acute kidney injury; CKD, chronic kidney disease; EBV, Epstein-Barr virus; HHV-6, human herpesvirus 6; CMV, cytomegalovirus; TB, tuberculosis; POTS, postural orthostatic tachycardia syndrome; GI, gastrointestinal.

days of COVID-19 onset was estimated to be 72.5% [37]. (4) One study estimated the prevalence of post-acute sequelae of COVID-19 at 22.8%, which closely aligns with regional national estimates. However, a recently developed AI-based tool by researchers at Mass General Brigham suggests a higher prevalence of 22.8% of LC in the general population (Harvard University source: SciTechDaily.com, Nov. 17, 2024).

The following factors may explain the marked variation in prevalence estimates reported above. (1) Natural immunity varies across populations, communities, and geographic regions; consequently, countries experienced differing proportions of COVID-19–affected individuals. (2) No vaccine provides complete protection against infection, particularly as new viral variants emerge. However, vaccination substantially reduces the risk of developing severe disease and LC compared with remaining unvaccinated. (3) Differences in standards of living, healthcare infrastructure, and vaccination coverage further contribute to observed variability in prevalence estimates.

## Identified Risk Factors

Several factors have been identified that increase an individual's risk of developing LC.

### Demographic factors

Female sex has been consistently associated with higher LC prevalence. LC predominantly affects adults younger than 65 years, and risk increases with greater severity of acute COVID-19 illness. Certain racial and ethnic populations, including American Indian communities and some multicultural societies, have demonstrated higher reported prevalence.

### Vaccination status

Individuals who are unvaccinated or inadequately vaccinated against COVID-19 exhibit a higher risk of developing LC compared with fully vaccinated adults [36].

### Pre-existing health conditions

Prior disability and coexisting medical conditions significantly elevate LC risk, including cardiovascular disease, diabetes, obesity, respiratory disorders, and depression. Smoking status is also associated with increased likelihood of LC symptoms.

### Severity of acute infection

LC risk increases with the severity of the initial COVID-19 illness. Individuals who required hospitalization due to COVID-19 are approximately 2 to 3 times more likely to develop LC than those who were not hospitalized.

## Functional Impairment and Impact on Quality of Life

The persistent and heterogeneous symptom profile of LC results in substantial functional impairment and diminished quality of life among affected individuals [38]. This study reports that symptoms such as chronic fatigue, post-exertional malaise (worsening of symptoms following physical or mental exertion), cognitive impairment (commonly referred to as brain fog), and autonomic dysfunction can severely compromise an individual's

capacity to work. These symptoms also interfere with academic engagement, sustained concentration, and the performance of routine daily activities for prolonged durations, often ranging from 6 months to 2 years or longer. A greater number or increased severity of LC symptoms is directly associated with poorer quality of life and reduced physical functioning (https://www.nationalacademies.org/news/2024/06/new-report-reviews-evidence-on-long-covid-diagnosis-risk-symptoms-and-functional-impact-for-patients). These realities underscore the need for fundamental shifts in public health strategies, including the development of comprehensive long-term care and support systems. Furthermore, disparities in access to healthcare services—including COVID-19 testing, vaccination, therapeutics, and specialized rehabilitation clinics—have been documented across socioeconomic strata, geographic regions, health literacy levels, and racial and ethnic groups [39]. These disparities were amplified during the pandemic and have since evolved into a critical health equity challenge.

Fortunately, AI is increasingly playing a valuable role in addressing many of the challenges discussed above that have emerged in the context of COVID-19 and LC.

## Role of AI in Long COVID Management

AI is a field of computer science focused on enabling machines to perform intelligent behaviors analogous to human cognitive functions, including visual perception, speech recognition, image analysis, decision-making, language translation, and reasoning. AI-based models progressively improve their performance in tasks such as classification, regression, and clustering as additional data are incorporated, a process conceptually similar to human learning through experience. AI represents a broad framework encompassing subfields such as ML, DL, and generative AI. Importantly, AI played a significant role during the COVID-19 pandemic and continues to contribute to LC management by offering data-driven solutions—ranging from early screening and contact tracing to post-infection monitoring—to address major challenges in pandemic response and recovery [40].

As evidence, advanced ML and DL techniques are increasingly used to extract actionable insights from large-scale datasets across multiple domains. The key roles of AI are outlined below. (1) Role 1: Data collection using AI-based techniques; (2) Role 2: Forecasting the spread of COVID-19 and its variants, early detection and prediction of disease progression, identification of organ systems affected by LC, and assessment of disease severity; (3) Role 3: Risk analysis and policymaking to combat COVID-19; and (4) Role 4: Drug and vaccine discovery for COVID-19.

### Role 1: Data Collection Using AI-Based Techniques

To understand the dynamic and fluctuating nature of LC symptoms, extensive and continuous data collection is required. AI tools leverage electronic health records (EHRs) to gather large volumes of de-identified patient data across multiple healthcare systems. This approach supports a more comprehensive understanding of LC at the population level. A review study [41] discusses how AI algorithms can analyze data collected from wearable devices to enable continuous patient monitoring. AI demonstrates particular strengths in this domain, as outlined below.

Miao et al. [42] developed an NLP framework to track LC symptoms across demographic groups, geographic regions, and time. They also created an online dashboard that integrates LC symptom text with NLP algorithms, including recurrent neural networks (RNNs) and convolutional neural networks (CNNs), to support symptom analysis. NLP-based AI algorithms are also capable of analyzing data collected from wearable devices for continuous patient monitoring, as reported in this study [43]. By tracking patient information in real time, clinicians can tailor treatment strategies to individual symptom profiles, while patients can use these insights to better manage their health based on changes in symptoms and physical condition. As a result, wearable devices offer substantial potential for continuous patient monitoring. Collectively, these technologies represent a transition toward more comprehensive and real-time patient data collection, which is essential for understanding the fluctuating and evolving nature of LC symptoms. The review study provides a broad discussion demonstrating that NLP algorithms are highly effective at extracting valuable symptom information from unstructured text in electronic medical records, including clinical notes [44]. This capability enables the identification of a wide range of symptoms, such as fever, cough, headache, fatigue, and dyspnea, which may not be captured through structured data sources alone [44].

### Role 2: Forecasting the Spread of COVID-19 and Its Variants, Early Detection and Prediction of Disease Progression, Identification of Organ Systems Affected by Long COVID, and Assessment of Disease Severity

Using dynamically expanding COVID-19 datasets, researchers have sought to control emerging cases through predictive modeling. De Araujo Morais and da Silva Gomes [45] introduced an effective forecasting model that combines



https://doi.org/10.24171/j.phrp.2025.0347

autoregressive integrated moving average methods with neural network approaches to predict daily COVID-19 case counts worldwide. This hybrid model was able to capture both linear and nonlinear patterns within the data. New variants of SARS-CoV-2 emerged rapidly earlier in the pandemic and continue to arise, making effective variant prediction critically important. To address this challenge, Ullah et al. [46] developed a CNN-based model. This approach integrates a variational autoencoder–decoder network with the Basic Local Alignment Search Tool to determine whether a detected variant originates from existing viral strains or represents a novel mutation.

Recent advancements in AI have covered various applications to understand the progression and outcomes in patients with COVID-19. Specifically, DL-based models, taking chest computed tomography (CT) images and clinical data, have been developed to predict progression of COVID-19 disease [47]. Researchers have also developed early warning systems using DL algorithms with collected clinical data and patient CT scans to predict deterioration processes in patients with COVID-19 [43,48]. For early detection and diagnosis of the disease, crucial tools based on chest X-ray have been developed [49].

AI-based models have also been introduced to detect LC in affected individuals. Ensemble learning approaches, such as XGBoost, have been applied in recent studies to identify LC cases [50–52]. Patel et al. [53] proposed a random forest–based model that utilizes blood protein levels to distinguish affected individuals. Similarly, Sengupta et al. [54] introduced a hybrid architecture combining bidirectional long short-term memory networks with 1-dimensional CNNs to classify LC patients. In contrast, a model developed by Subramanian et al. [55] using VGG-16, ResNet-50, and U-Net architectures demonstrated superior predictive accuracy.

### Role 3: Risk Analysis and Policymaking to Combat COVID-19

AI algorithms are increasingly capable of dynamically assessing COVID-19 transmission and infection risk to support healthcare professionals. Cloud- and fog-computing-based models have proven particularly useful for large-scale data collection, real-time risk assessment, and efficient monitoring and control of disease spread [56,57]. Furthermore, AI has emerged as a powerful tool for pandemic response by enabling data-driven policy decision-making. Bhatia et al. [56] developed a decision tree–based model to assess infection severity and classify individuals according to symptom profiles, achieving a reported accuracy of 96.68% and supporting timely monitoring and intervention.

### Role 4: Drug and Vaccine Discovery for COVID-19

In the absence of definitive curative treatments and virus-specific medications for COVID-19, and given the urgent need for rapid solutions due to high transmissibility and fatality rates compared with other viral infections, researchers increasingly turned to AI-based approaches. As traditional self-care measures became insufficient, technology-driven alternatives gained prominence. By analyzing large-scale biological and clinical datasets, AI has demonstrated the capacity to identify potential drug targets, predict drug efficacy, and optimize formulation parameters.

Conventional drug and vaccine discovery processes are widely recognized as costly and time-intensive, often requiring many years or even decades; however, the pandemic necessitated accelerated alternatives. A major challenge in drug repurposing lies in identifying robust drug–disease relationships. To overcome these limitations, drug repurposing or repositioning and AI-assisted vaccine discovery emerged as prominent strategies, with AI contributing substantially by optimizing candidate selection and formulation parameters. For example, Pfizer employed AI-driven tools during clinical trials to efficiently process large datasets and meet regulatory requirements. Using multiple network-based strategies, Zeng et al. [58] developed an integrative DL framework, COVID-19 Knowledge Graph Embeddings (CoV-KGE), to identify adaptable drugs for COVID-19.

Lv et al. [59] applied a multimodal approach to the virus–host interactome by integrating graph convolutional networks, network diffusion, and network proximity methods, achieving a reported success rate of 62% and identifying 6 drugs that reduced viral infection. The development of AI-driven vaccines for viruses such as Zika and Ebola has also been discussed in the context of pandemic preparedness [59,60].

Importantly, multiple AI algorithms significantly facilitated drug repurposing and therapeutic deployment during the COVID-19 era. In 2020, Mohanty et al. [61] provided a comprehensive review of Repurpose Drug Databases and Open Chemical/Drug Databases and developed a model using ML, RNNs, CNNs, and deep belief networks to rapidly and accurately screen candidate drugs. Gupta et al. [62] applied ML techniques to datasets derived from PubChem, achieving an approximate prediction accuracy of 73%. More recently, in 2024, Serrano et al. [63] reported that AI played a crucial role in accelerating the identification of reliable biomarkers, diagnostics, and novel therapeutic candidates for LC.

### Overall Discussion about the Uses of AI in COVID-19 and Long COVID

Thus, AI has increasingly replaced many manually managed traditional systems that are time-consuming, error-prone, and costly. More specifically, current AI-driven monitoring systems—often integrating AI with the Internet of Things (IoT), including sensors and connected devices—are capable of continuously monitoring patients' vital parameters, including early symptom changes, to generate actionable insights for both patients and healthcare providers. This capability supports earlier diagnosis and contributes to improved patient outcomes. AI algorithms are designed by researchers to collect live data for disease diagnosis, which are subsequently analyzed using statistical tools such as SPSS to identify target trends based on specific categories and geographic locations. Based on these analyses, appropriate predictive models are developed to enable accurate and rapid diagnosis, thereby assisting clinical practitioners. Recent AI-based algorithms, including CNNs, RNNs, and generative adversarial networks, aim to enhance decision quality by selecting the most relevant features for a given decision problem. This feature selection improves prediction accuracy and reduces error or misclassification rates on unseen data. Furthermore, removing irrelevant features from datasets decreases learning time and facilitates the generation of compact, informative knowledge representations, ultimately reducing decision-making time for end users and organizations.

AI-based technologies are playing a central role in redefining how modern medicine addresses the complexities of LC. In particular, AI is bridging multiple gaps in medical science by facilitating cross-organ diagnostics, uncovering latent correlations across heterogeneous symptoms, and enabling scalable population-level surveillance. Collectively, these capabilities reduce clinical workload, enhance patient engagement, and support evidence-informed policymaking.

Based on the discussion presented in Section 6, a comprehensive overview of key AI applications in LC—highlighting the techniques employed, data sources utilized, and associated clinical impacts—is provided in Table 3 [42,47,48,50,52,55,58,62].

## Concerns and Challenges in AI Deployment for Long COVID

AI has the potential to revolutionize healthcare, particularly in the management of complex conditions such as LC; however, its integration into clinical practice raises substantial ethical and practical concerns. Addressing these concerns requires the establishment of clear guidelines and robust governance frameworks [64]. Several key challenges arising from the generation of large-scale data through LC-related sources—such as patient records, medical imaging, and genomic information—and from the application of AI-based tools to these data are highlighted below.

### Data Privacy and Security Concerns

This category includes the following major concerns.

#### Confidentiality breaches

Significant risks exist to the privacy of sensitive patient information, particularly through cyberattacks, hacking incidents, or vulnerabilities in data security infrastructures. Such events can lead to serious breaches of confidentiality and unauthorized data disclosure [65].

#### Data ownership and control

Patients may not always be fully informed about who owns or controls their health data when such data are processed by algorithms or managed by external organizations. Clear and transparent policies are therefore required to define data ownership and to protect patients' rights regarding the use, sharing, and governance of their medical information.

#### Regulatory compliance

Compliance with data protection regulations—such as the Health Insurance Portability and Accountability Act in the United States and the General Data Protection Regulation in the European Union—is essential to protect patient data and maintain public trust in healthcare systems. Regulatory compliance also helps safeguard developers and users of AI-enabled systems from legal liability. Federated learning approaches can support compliance by enabling model training without direct sharing of raw patient data; however, broader legal and ethical standards are still evolving to adequately address these complex challenges.

### Algorithmic Bias and Its Implications for Health Equity

Accurate and representative data are fundamental to the development of reliable AI and ML models. When training datasets are incomplete, imbalanced, or biased, AI systems may reinforce or exacerbate existing healthcare disparities [65]. Key forms of algorithmic bias relevant to LC applications are outlined below.

#### Bias in training data

When algorithms are trained on datasets that do not adequately represent population diversity, their performance may be reduced for certain demographic groups, particularly



https://doi.org/10.24171/j.phrp.2025.0347

**Table 3.** Key AI applications for long COVID: techniques, data sources, and health consequences

| Medical issues | AI applications | AI techniques | Health consequences |
|---|---|---|---|
| Diagnosis and prognosis | Detecting long COVID ML models for risk prediction for lung CT images.<br>Detection of new variants of COVID-19 | XGBoost (accuracy, 98%; precision, 99%; sensitivity, 99%) for detecting LC [51]; methodological rigour, superior; relevance to review, superior; clarity of reporting, superior; validity of findings, superior<br>Random Forest (precision, 0.85; recall, 0.86) for detecting LC [49]; methodological rigour, superior; relevance to review, superior; clarity of reporting, superior; validity of findings, superior, CNN-based VGG-16 with LR, 0.001 (accuracy, 45.87%; precision, 45.8%; recall, 100%; F1-score, 62.8%), ResNet-50 with LR, 0.001 (accuracy, 94.24%; precision, 92.42%; recall, 95.31; F1-score, 93.85) [54]; methodological rigour, average; relevance to review, average; clarity of reporting, average; validity of findings, superior<br>Variational autoencoder-decoder networks achieves 0.72 AUC value for detection of new variants of COVID-19 [45]; methodological rigour, superior; relevance to review, superior; clarity of reporting, average; validity of findings, average | Improved diagnostic accuracy, reduced diagnostic bias, early risk warning, personalized care |
| Lung damage assessment | Imaging analysis | Deep Neural Network, U-Net (segmentation, accuracy, 97.132%) [46]; methodological rigour, average; relevance to review, average; clarity of reporting, superior; validity of findings, superior | Automated diagnosis, precise lung opacity segmentation, quantification of affected lung volume, reduced diagnostic inconsistency |
| Symptom tracking and patient monitoring | NLP, wearable data analysis | Developed interface, best accuracy, 89% for understanding of long COVID symptoms [41]; methodological rigour, superior; relevance to review, superior; clarity of reporting, superior; validity of findings, superior | Timely symptom identification, comprehensive symptom characterization, continuous patient monitoring, personalized treatment guidance |
| | Predicting COVID-19 malignant progression | AUC of 0.920 in the single-centre study and an average AUC of 0.874 in the multicentred study [47]; methodological rigour, superior; relevance to review, superior; clarity of reporting, average; validity of findings, average | |
| Treatment discovery | Drug remodeling and novel compound identification | DL-based model (accuracy, 73%) in drug prediction [61]; methodological rigour, superior; relevance to review, superior; clarity of reporting, superior, 62% success rate in drug-design [57]; methodological rigour, superior; relevance to review, superior; clarity of reporting, average; validity of findings, average | Accelerated discovery of biomarkers, diagnostics, repurposed drugs, and novel therapies; optimized formulation parameters |

AI, artificial intelligence; COVID, coronavirus disease; ML, machine learning; CT, computed tomography; COVID-19, coronavirus disease 2019; LC, long COVID; CNN, convolutional neural network; VGG-16, Visual Geometry Group-16; AUC, area under the curve; NLP, natural language processing.

those from minority or underserved communities. For example, a model developed primarily using data from Caucasian populations may yield less accurate diagnostic or prognostic results for African, Hispanic, or Asian individuals.

#### Disparities linked to healthcare access

Efforts to optimize algorithmic performance may unintentionally reinforce pre-existing inequalities in healthcare access. For instance, models that prioritize high-cost or high-frequency healthcare users may overlook individuals in rural or low-income settings, who often have limited access to healthcare services and diagnostic resources [65].

#### Ethical considerations

Algorithmic bias raises substantial ethical concerns related to fairness and equity in healthcare delivery. A key risk is that certain population groups may receive lower-quality care, thereby widening existing health disparities and producing unjust outcomes [65]. This highlights that algorithmic bias is not merely a technical issue but also a social determinant that can intensify structural health inequalities. Sustained and deliberate efforts are therefore required to ensure the development and use of inclusive, representative datasets that promote equitable healthcare outcomes. It is also critical to recognize that bias can emerge at multiple stages, including data collection, data access, preprocessing, model development, and variations in the expertise of system designers.

### Transparency, Accountability and Human Oversight

The design of advanced models (particularly DL architectures) can create a black box problem, where it becomes difficult to understand how conclusions are reached. A few key issues are outlined below:

#### Opacity of AI decisions

Limited transparency in complex AI algorithms makes their internal decision-making processes difficult to interpret. This limitation is particularly concerning in clinical contexts, where understanding the rationale behind diagnostic outputs or treatment recommendations is essential for safe and accountable care.

#### Need for explainability

Progress in explainable approaches is crucial to improve understanding of how models arrive at their outputs, thereby enhancing trust and supporting clinical adoption.

#### Maintaining human oversight

Human oversight, through human-in-the-loop or human-on-the-loop frameworks, remains essential to ensure clinical accuracy, prevent adverse outcomes, and uphold professional integrity, particularly in high-stakes healthcare environments [66]. AI systems are limited in their ability to generate novel clinical insights or integrate experiential judgment and may hallucinate or overgeneralize; therefore, expert review and intervention remain necessary.

### Implementation Challenges

Integrating AI technologies into existing healthcare systems presents substantial practical challenges, as outlined below.

#### Technical challenges

Robust architectures for handling ML models and associated data, together with high-performance computing systems, are required for the effective integration of AI technologies into healthcare settings.

#### Knowledge gaps and resistance to change

An often overlooked challenge is the natural human resistance to adopting new ways of working. Increasing awareness within the healthcare community regarding the benefits of AI integration therefore represents a significant psychological and organizational challenge.

#### Lack of standard guidelines

At present, there are few well-defined and widely accepted guidelines governing the ethical use of AI and ML in healthcare. This lack of standardization remains a significant barrier to AI adoption in the healthcare domain. Table 4 summarizes these ethical and practical challenges, along with proposed mitigation strategies [65–67].

## Limitations of the Current Review and Future Directions

This review provides an integrated overview of LC and examines the role of AI in its management. Afterall, the review studies [68,69] assisted the authors for shaping the present article. Although the analysis is based on 69 peer-reviewed publications, some relevant studies may not have been captured. In addition, heterogeneity in research designs, study populations, symptom definitions, and follow-up durations may limit the comparability of reported findings.

### Future Directions

To improve the understanding, diagnosis, and management of LC, further progress is required in the following areas.



https://doi.org/10.24171/j.phrp.2025.0347

**Table 4.** Ethical and practical challenges of AI in healthcare for long COVID

| Challenge class | Specific risk | Implication for long COVID care | Suggested mitigation strategy |
|---|---|---|---|
| Data privacy and security | Confidentiality breaches and unauthorized access to sensitive patient data [64] | Loss of patient trust, legal liability, misuse of medical information | Federated learning, robust encryption, clear data-ownership policies, strict HIPAA/GDPR compliance |
| Algorithmic bias | AI models trained on biased datasets that perpetuate healthcare disparities [64] | Inaccurate diagnoses in marginalized populations, suboptimal care, worsening health inequalities, unfair resource allocation | Diverse training datasets, bias-detection algorithms, continuous auditing, fairness-aware evaluation metrics |
| Transparency and accountability | Black-box decision-making processes that are difficult to interpret [66] | Reduced clinician trust, difficulty validating AI outputs, limited error detection | Adoption of explainable AI (XAI), transparent documentation of model logic |
| Human oversight | Over-reliance on AI with insufficient human review [65] | Misdiagnosis, adverse patient outcomes, erosion of clinician critical thinking | Human-in-the-loop and human-on-the-loop frameworks, clear review and override protocols, positioning AI as assistive |
| Implementation | Inadequate resources and unforeseen technical barriers | Delayed adoption, widening knowledge gaps, underutilization of AI potential | Robust data architecture, staff-training programs, interdisciplinary collaboration, clearly defined implementation roadmaps |

AI, artificial intelligence; COVID, coronavirus disease; HIPAA, Health Insurance Portability and Accountability Act; GDPR, General Data Protection Regulation.

### Unified data practices and system interoperability

Establishing standardized data-collection practices and improving interoperability across EHRs systems are essential. Consistent, high-quality, and interoperable datasets will support the development of reliable AI tools and help address limitations related to data variability.

### Well-designed clinical studies

Future research should prioritize prospective, controlled clinical studies evaluating AI tools for LC diagnosis, prognosis, and treatment monitoring. Strong clinical evidence is necessary to demonstrate the safety, accuracy, and real-world utility of AI-based applications.

### Biomarker identification

The identification of clear and reliable biomarkers for LC remains a major gap. AI-driven analytical approaches may play an important role in detecting biological indicators that enhance diagnostic accuracy and support personalized treatment strategies.

### Model clarity and explainability

Advancing explainable AI approaches is important for improving transparency in AI-supported clinical decision-making. Greater interpretability may increase confidence among healthcare professionals and patients and promote responsible AI use.

### Ethical and regulatory governance

As AI adoption in healthcare accelerates, there is a growing need for clear ethical standards and regulatory frameworks. Such policies should ensure fair and responsible AI deployment—particularly for complex, long-term conditions such as LC—while protecting privacy and addressing bias and accountability concerns.

## Conclusion

The long-term consequences of the COVID-19 pandemic continue to affect human health, with many survivors experiencing persistent, multiorgan complications. This review highlights LC as a multisystem condition that can substantially impair daily functioning and quality of life, underscoring the need for improved care strategies and innovative interventions.

In recent years, AI has gained increasing attention in LC research. AI techniques are being used to develop structured digital data resources that enhance analysis and knowledge sharing. When combined with IoT technologies, AI-enabled monitoring systems support real-time patient observation and earlier detection of health deterioration.

AI offers multiple applications for LC management, including support for clinical decision-making through pattern recognition, early detection, and outcome prediction. Intelligent systems also facilitate ongoing symptom tracking via wearable devices and language-based platforms, while accelerating the identification of potential therapeutic candidates. Together, these applications demonstrate the potential of AI to address the complex challenges associated with LC.

Beyond scientific and clinical benefits, this review also highlights broader implications of AI use in LC care, including data protection, mitigation of algorithmic bias, and the need to preserve human judgment in clinical decision-making. Continued global research is essential to deepen understanding of LC and to strengthen future management strategies.

## Notes

### Ethics Approval
Not applicable.

### Conflicts of Interest
The authors have no conflicts of interest to declare.

### Funding
None.

### Availability of Data
All data (published articles) analyzed during this study are included in this published article. For other relevant data, these may be requested through the corresponding author.

### Acknowledgements
The authors acknowledge the review studies [68,69] for shaping the present article. The authors acknowledge the support of an AI-generated tool to rephrase a few sentences and correct grammatical errors.

## References

1. World Health Organization (WHO) (CH). Coronavirus disease (COVID-19) [Internet]. WHO; 2022 [cited 2025 Nov 13]. Available from: https://www.who.int/news-room/fact-sheets/detail/coronavirus-disease-%28covid-19%29.
2. World Health Organization (WHO) (CH). COVID-19 cases, world [Internet]. WHO; 2025 [cited 2025 Nov 13]. Available from: https://covid19.who.int.
3. Al-Aly Z, Bowe B, Xie Y. Long COVID after breakthrough SARS-CoV-2 infection. Nat Med 2022;28:1461–7.
4. Garrigues E, Janvier P, Kherabi Y, et al. Post-discharge persistent symptoms and health-related quality of life after hospitalization for COVID-19. J Infect 2020;81:e4–6.
5. Greenhalgh T, Knight M, A'Court C, et al. Management of post-acute COVID-19 in primary care. BMJ 2020;370:m3026.
6. Peluso MJ, Deeks SG. Early clues regarding the pathogenesis of long-COVID. Trends Immunol 2022;43:268–70.
7. Nasserie T, Hittle M, Goodman SN. Assessment of the frequency and variety of persistent symptoms among patients with COVID-19: a systematic review. JAMA Netw Open 2021;4:e2111417.
8. Reiss AB, Greene C, Dayaramani C, et al. Long COVID, the brain, nerves, and cognitive function. Neurol Int 2023;15:821–41.
9. Lippi G, Sanchis-Gomar F, Henry BM. Covid-19 and its long-term sequelae: what do we know in 2023? Pol Arch Intern Med 2023; 133:16402.
10. O'Mahoney LL, Routen A, Gillies C, et al. The prevalence and long-term health effects of long COVID among hospitalised and non-hospitalised populations: a systematic review and meta-analysis. EClinicalMedicine 2023;55:101762.
11. Soriano JB, Murthy S, Marshall JC, et al. A clinical case definition of post-COVID-19 condition by a Delphi consensus. Lancet Infect Dis 2022;22:e102–7.
12. Panagea E, Messinis L, Petri MC, et al. Neurocognitive impairment in long COVID: a systematic review. Arch Clin Neuropsychol 2025;40: 125–49.
13. Huang C, Huang L, Wang Y, et al. 6-month consequences of COVID-19 in patients discharged from hospital: a cohort study. Lancet 2021;397:220–32.
14. Premraj L, Kannapadi NV, Briggs J, et al. Mid and long-term neurological and neuropsychiatric manifestations of post-COVID-19 syndrome: a meta-analysis. J Neurol Sci 2022;434:120162.
15. Efstathiou V, Stefanou MI, Demetriou M, et al. Long COVID and neuropsychiatric manifestations (review). Exp Ther Med 2022;23:363.
16. Scarpelli S, Nadorff MR, Bjorvatn B, et al. Nightmares in people with COVID-19: did coronavirus infect our dreams? Nat Sci Sleep 2022; 14:93–108.
17. Hermans LE, Wasserman S, Xu L, et al. Long COVID prevalence and risk factors in adults residing in middle- and high-income countries: secondary analysis of the multinational Anti-Coronavirus Therapies (ACT) trials. BMJ Glob Health 2025;10:e017126.
18. Dixit NM, Churchill A, Nsair A, et al. Post-acute COVID-19 syndrome and the cardiovascular system: what is known? Am Heart J Plus 2021;5:100025.
19. Barman HA, Atici A, Sahin I, et al. Prognostic significance of cardiac injury in COVID-19 patients with and without coronary artery disease. Coron Artery Dis 2021;32:359–66.
20. Nai Fovino L, Cademartiri F, Tarantini G. Subclinical coronary artery disease in COVID-19 patients. Eur Heart J Cardiovasc Imaging 2020; 21:1055–6.
21. Hilser JR, Spencer NJ, Afshari K, et al. COVID-19 is a coronary artery disease risk equivalent and exhibits a genetic interaction with ABO blood type. Arterioscler Thromb Vasc Biol 2024;44:2321–33.
22. Visco V, Vitale C, Rispoli A, et al. Post-COVID-19 syndrome: involvement and interactions between respiratory, cardiovascular and nervous systems. J Clin Med 2022;11:524.
23. Long Q, Li J, Hu X, et al. Follow-ups on persistent symptoms and pulmonary function among post-acute COVID-19 patients: a systematic review and meta-analysis. Front Med (Lausanne) 2021;8: 702635.
24. Ramamoorthy R, Hussain H, Ravelo N, et al. Kidney damage in long COVID: studies in experimental mice. Biology (Basel) 2023;12:1070.
25. Kratzer B, Gattinger P, Trapin D, et al. Differential decline of SARS-CoV-2-specific antibody levels, innate and adaptive immune cells, and shift of Th1/inflammatory to Th2 serum cytokine levels long



https://doi.org/10.24171/j.phrp.2025.0347

after first COVID-19. Allergy 2024;79:2482–501.
26. Ma Y, Zhang L, Wei R, et al. Risks of digestive diseases in long COVID: evidence from a population-based cohort study. BMC Med 2024; 22:14.
27. Rokkas T. Gastrointestinal involvement in COVID-19: a systematic review and meta-analysis. Ann Gastroenterol 2020;33:355–65.
28. Bogariu AM, Dumitrascu DL. Digestive involvement in the long-COVID syndrome. Med Pharm Rep 2022;95:5–10.
29. Choudhury A, Tariq R, Jena A, et al. Gastrointestinal manifestations of long COVID: a systematic review and meta-analysis. Therap Adv Gastroenterol 2022;15:17562848221118403.
30. Ren Z, Wang H, Cui G, et al. Alterations in the human oral and gut microbiomes and lipidomics in COVID-19. Gut 2021;70:1253–65.
31. Gottlieb M, Long B. Dermatologic manifestations and complications of COVID-19. Am J Emerg Med 2020;38:1715–21.
32. Gao JC, Huang A, Desai A, et al. "COVID toes": a true viral phenomenon or a diagnosis without a leg to stand on? JAAD Int 2022;9:1–6.
33. Singh R, Freeman EE. Viruses, variants, and vaccines: how COVID-19 has changed the way we look at skin. Curr Dermatol Rep 2022;11:289–312.
34. McMahon DE, Gallman AE, Hruza GJ, et al. Long COVID in the skin: a registry analysis of COVID-19 dermatological duration. Lancet Infect Dis 2021;21:313–4.
35. Raj V, Opie M, Arnold AC. Cognitive and psychological issues in postural tachycardia syndrome. Auton Neurosci 2018;215:46–55.
36. Lovaglio PG, Borgonovo F, Manzo Margiotta A, et al. Estimating long COVID-19 prevalence across definitions and forms of sample selection. Front Epidemiol 2025;5:1597799.
37. Davis HE, McCorkell L, Vogel JM, et al. Long COVID: major findings, mechanisms and recommendations. Nat Rev Microbiol 2023;21:133–146.
38. de Oliveira JF, de Avila RE, de Oliveira NR, et al. Persistent symptoms, quality of life, and risk factors in long COVID: a cross-sectional study of hospitalized patients in Brazil. Int J Infect Dis 2022;122:1044–51.
39. Williams AM, Clayton HB, Singleton JA. Racial and ethnic disparities in COVID-19 vaccination coverage: the contribution of socioeconomic and demographic factors. Am J Prev Med 2022;62:473–82.
40. Hassantabar S, Ahmadi M, Sharifi A. Diagnosis and detection of infected tissue of COVID-19 patients based on lung X-ray image using convolutional neural network approaches. Chaos Solitons Fractals 2020;140:110170.
41. Shajari S, Kuruvinashetti K, Komeili A, et al. The emergence of AI-based wearable sensors for digital health technology: a review. Sensors (Basel) 2023;23:9498.
42. Miao L, Last M, Litvak M. An interactive analysis of user-reported long COVID symptoms using Twitter data. In: Proceedings of the 2nd Workshop on Deriving Insights from User-Generated Text; 2022 May 27; Dublin. Association for Computational Linguistics. 2022. p. 10–9.
43. Lassau N, Ammari S, Chouzenoux E, et al. Integrating deep learning CT-scan model, biological and clinical variables to predict severity of COVID-19 patients. Nat Commun 2021;12:634.
44. Wieland-Jorna Y, van Kooten D, Verheij RA, et al. Natural language processing systems for extracting information from electronic health records about activities of daily living: a systematic review. JAMIA Open 2024;7:ooae044.
45. de Araujo Morais LR, da Silva Gomes GS. Forecasting daily COVID-19 cases in the world with a hybrid ARIMA and neural network model. Appl Soft Comput 2022;126:109315.
46. Ullah A, Malik KM, Saudagar AK, et al. COVID-19 genome sequence analysis for new variant prediction and generation. Mathematics 2022;10:4267.
47. Wang R, Jiao Z, Yang L, et al. Artificial intelligence for prediction of COVID-19 progression using CT imaging and clinical data. Eur Radiol 2022;32:205–12.
48. Fang C, Bai S, Chen Q, et al. Deep learning for predicting COVID-19 malignant progression. Med Image Anal 2021;72:102096.
49. Kumar A, Tripathi AR, Satapathy SC, et al. SARS-Net: COVID-19 detection from chest X-rays by combining graph convolutional network and convolutional neural network. Pattern Recognit 2022; 122:108255.
50. Pfaff ER, Girvin AT, Bennett TD, et al. Identifying who has long COVID in the USA: a machine learning approach using N3C data. Lancet Digit Health 2022;4:e532–41.
51. Jiang S, Loomba J, Sharma S, et al. Vital measurements of hospitalized COVID-19 patients as a predictor of long COVID: an EHR-based cohort study from the RECOVER Program in N3C. In: 2022 IEEE International Conference on Bioinformatics and Biomedicine (BIBM); 2022 Dec 6-8; Las Vegas, NV. IEEE; 2022. p. 3023–30.
52. Jha M, Gupta R, Saxena R. A precise method to detect post-COVID-19 pulmonary fibrosis through extreme gradient boosting. SN Comput Sci 2023;4:89.
53. Patel MA, Knauer MJ, Nicholson M, et al. Organ and cell-specific biomarkers of Long-COVID identified with targeted proteomics and machine learning. Mol Med 2023;29:26.
54. Sengupta S, Loomba J, Sharma S, et al. Analyzing historical diagnosis code data from NIH N3C and RECOVER Programs using deep learning to determine risk factors for long COVID. In: 2022 IEEE International Conference on Bioinformatics and Biomedicine (BIBM); 2022 Dec 6-8; Las Vegas, NV. IEEE; 2022. p. 2797–802.
55. Subramanian R, Rubi R, Dedeepya M, et al. Quantitative progression analysis of post-acute sequelae of COVID-19, pulmonary fibrosis (PASC-PF) and artificial intelligence driven CT scoring of lung involvement in COVID-19 infection using HRCT-chest images. Med Res Arch 2022;10:1–10.
56. Bhatia M, Manocha A, Ahanger TA, et al. Artificial intelligence-inspired comprehensive framework for COVID-19 outbreak control. Artif Intell Med 2022;127:102288.
57. Kaur I, Behl T, Aleya L, et al. Artificial intelligence as a fundamental tool in management of infectious diseases and its current implementation in COVID-19 pandemic. Environ Sci Pollut Res Int

2021;28:40515–32.
58. Zeng X, Song X, Ma T, et al. Repurpose open data to discover therapeutics for COVID-19 using deep learning. J Proteome Res 2020; 19:4624–36.
59. Lv H, Shi L, Berkenpas JW, et al. Application of artificial intelligence and machine learning for COVID-19 drug discovery and vaccine design. Brief Bioinform 2021;22:bbab320.
60. Black S, Bloom DE, Kaslow DC, et al. Transforming vaccine development. Semin Immunol 2020;50:101413.
61. Mohanty S, Harun Ai Rashid M, Mridul M, et al. Application of artificial intelligence in COVID-19 drug repurposing. Diabetes Metab Syndr 2020;14:1027–31.
62. Gupta R, Srivastava D, Sahu M, et al. Artificial intelligence to deep learning: machine intelligence approach for drug discovery. Mol Divers 2021;25:1315–60.
63. Serrano DR, Luciano FC, Anaya BJ, et al. Artificial intelligence (AI) applications in drug discovery and drug delivery: revolutionizing personalized medicine. Pharmaceutics 2024;16:1328.
64. Alowais SA, Alghamdi SS, Alsuhebany N, et al. Revolutionizing healthcare: the role of artificial intelligence in clinical practice. BMC Med Educ 2023;23:689.
65. Seh AH, Zarour M, Alenezi M, et al. Healthcare data breaches: insights and implications. Healthcare (Basel) 2020;8:133.
66. Frenette J. Ensuring human oversight in high-performance AI systems: a framework for control and accountability. World J Adv Res Rev 2023;20:1507–16.
67. Hassija V, Chamola V, Mahapatra A, et al. Interpreting black-box models: a review on explainable artificial intelligence. Cogn Comput 2024;16:45–74.
68. Ezazi Bojnordi T, Pourali S, Haghighat F, et al. Breast cancer detection algorithms: a comparative review of leading artificial intelligence models. InfoSci Trend 2025;2:57–77.
69. Alizade R, Safarian S, Geramifar P, et al. A systematic review of artificial intelligence for endoscopic and histologic assessment in ulcerative colitis. InfoSci Trend 2025;2:12–38.


https://doi.org/10.24171/j.phrp.2025.0347

phrp
OSONG PUBLIC HEALTH AND RESEARCH PERSPECTIVES

pISSN 2210-9099 eISSN 2233-6052
https://doi.org/10.24171/j.phrp.2025.0313
Osong Public Health Res Perspect 2026;17(1):33-49

**Original Article**

# Crisis-driven innovation in the Republic of Korea's *in vitro* diagnostics industry: a pandemic case study

**Minjoon Kim[1], Harry Jeong[2], Kwangsoo Shin[3]**

[1]Division of Laboratory Diagnosis Management, Department of Laboratory Diagnosis and analysis, Korea Disease Control and Prevention Agency, Cheongju, Republic of Korea
[2]Central Research Institute, Dr. Chung's Food Co., Ltd, Cheongju, Republic of Korea
[3]Graduate School of Public Health and Healthcare Management/Catholic Institute for Public Health and Healthcare Management, Songeui Medical Campus, The Catholic University of Korea, Seoul, Republic of Korea

## ABSTRACT

**Objectives:** This study evaluated the effectiveness of government epidemic control policies centered on diagnostic testing and examined their impact on the *in vitro* diagnostics (IVD) industry. It also analyzed the complex interplay among policy interventions, epidemic dynamics, and the IVD industry's value chain to identify key leverage points for managing future public health crises.

**Methods:** A system dynamics (SD) model calibrated using national data from the Republic of Korea simulated the interactions between epidemic progression and the IVD value chain. We conducted a scenario analysis encompassing 6 policy interventions: research and development (R&D) investment, public–private collaboration, regulatory easing, diagnostic test performance, testing intensity, and social distancing.

**Results:** Policies promoting investment, public–private collaboration, and regulatory easing accelerated the market entry of diagnostics, thereby reducing infections and deaths. However, these interventions were associated with lower overall industry revenue, attributable to increased market competition and a reduced patient population. A critical trade-off was noted: although regulatory speed is advantageous, using low-sensitivity diagnostics substantially worsened public health outcomes. Aggressive testing strategies and stringent social distancing were also confirmed to be effective in reducing both infections and mortality.

**Conclusion:** This study provides a strategic framework for understanding interactions between pandemic control policies and the IVD industry. Sustained pre-crisis investment in R&D, public–private networks, and public health infrastructure is essential for effective pandemic preparedness. During a crisis, policymakers must carefully manage the critical trade-off between regulatory speed and diagnostic quality to ensure that rapid responses do not compromise public health outcomes.

**Keywords:** Containment; Infectious disease; Innovation; *In vitro* diagnostics; Pandemics; System dynamics

**Received:** August 9, 2025
**Revised:** October 26, 2025
**Accepted:** December 11, 2025

Corresponding author:
Kwangsoo Shin
Graduate School of Public Health and Healthcare Management/Catholic Institute for Public Health and Healthcare Management, Songeui Medical Campus, The Catholic University of Korea, 222 Banpo-daero, Seocho-gu, Seoul 06691, Korea
E-mail: ksshin@catholic.ac.kr

The opinions expressed by authors contributing to this journal do not necessarily reflect the opinions of the Korea Disease Control and Prevention Agency and Korea National Institute of Health.

© 2026 Korea Disease Control and Prevention Agency.
This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

## Introduction

In response to the coronavirus disease 2019 (COVID-19) pandemic, numerous countries implemented a range of non-pharmaceutical interventions, including social distancing and lockdowns. While these containment measures successfully reduced incidence and mortality rates [1], they also generated substantial negative economic impacts [2–5]. As a result, policymakers face the ongoing challenge of deploying containment measures efficiently to control infection spread while simultaneously minimizing adverse societal consequences [6,7].

Diagnostic testing plays a pivotal role in both patient management and the control of infectious disease transmission [8–12]. Based on diagnostic test results, governments can obtain essential data for public health decision-making and effectively implement infection control measures such as contact tracing, isolation, and treatment [13,14]. Accordingly, many countries worldwide actively incorporated diagnostic testing into their COVID-19 response strategies [15–17]. The essential components required to perform such testing are *in vitro* diagnostics (IVD).

In the absence of a crisis, the IVD industry, particularly within the domain of infectious disease diagnostics, is characterized by limited innovation due to low marketability stemming from constrained demand [8,18,19]. However, a major disruptive event such as a pandemic generates an urgent, large-scale problem that stimulates problem-driven innovation [20]. Because IVD for novel infectious diseases do not preexist, governments in many countries implement policies to secure diagnostic capacity, including relaxing regulatory requirements and expediting review processes [21–23]. These policy actions create large-scale demand and provide powerful incentives for firms to enter the market, thereby establishing conditions conducive to radical innovation.

Following the COVID-19 outbreak, numerous studies have examined the effectiveness of containment measures as well as the pandemic's broader impact on various industries [24–26]. However, research that explicitly analyzes the effectiveness of containment policies centered on diagnostic testing and their subsequent impact on the IVD industry remains limited. To address this gap, the present study developed a system dynamics (SD) model based on the Republic of Korea's COVID-19 response. The model captures the dynamic interplay between epidemic progression and the IVD industry value chain. The Republic of Korea was selected as the study context because it successfully flattened the epidemic curve during the early stages of the outbreak by establishing a proactive diagnostic testing system, enabled by rapid public–private partnerships and the implementation of an emergency use authorization (EUA) for its domestic IVD industry [15,27–29].

***HIGHLIGHTS***

- Early access to accurate tests reduces pandemic spread and severity.
- Sustained investment is vital for rapid scale-up of diagnostic capacity during outbreaks.
- Rapid test deployment must be balanced with regular quality control.

This model enables a systematic analysis of epidemic control policies and their effects on innovation within the IVD industry through scenario-based modeling. The findings derived from this analysis can enhance understanding of the pandemic's impact on the IVD industry and assist policymakers in designing effective control strategies for future infectious disease crises.

The remainder of this paper is organized as follows. Section 2 outlines the research methodology. Section 3 presents the results for each modeled scenario. Section 4 discusses the key findings. Finally, Section 5 provides the conclusions of the study.

## Materials and Methods

### Sample and Data

The model was developed using both qualitative and quantitative data to parameterize, calibrate, and validate its dynamic behavior. The structure of the model, which represents causal relationships and feedback loops, was developed using qualitative data. First, based on a comprehensive review of the literature, 4 key factors central to IVD innovation, termed "innovation catalysts," were identified and used to establish the model's overall framework. In addition, interviews were conducted with government officials from the Republic of Korea involved in diagnostic testing as well as with employees from IVD manufacturers. Insights obtained from these interviews were subsequently used to refine the framework and to ensure that the final model structure accurately reflects the interactions among government infectious disease policies, regulatory processes, and the IVD industry.

The model was operationalized through parameter population, calibration, and validation using quantitative data spanning 2019 to 2021. Epidemiological data, including confirmed COVID-19 cases and polymerase chain reaction



https://doi.org/10.24171/j.phrp.2025.0313

(PCR) test volumes, were obtained from the Korea Disease Control and Prevention Agency. Regulatory data on IVD product approvals were sourced from the Ministry of Food and Drug Safety. Industry performance was assessed using sales revenue data collected for 197 firms that had received IVD approvals.

## Measures of Variables

The primary drivers of the model are 4 innovation catalysts: policy, investment, demand, and network. Policy encompasses regulatory frameworks and government interventions, where adaptive mechanisms such as EUA can spur rapid innovation [11,30,31], while more stringent regulatory requirements may act as barriers to market entry [32]. Investment, particularly in research and development (R&D), serves as a fundamental driver of new product development [33], with government funding often signaling institutional support that encourages complementary private investment [34]. Demand, especially during a public health crisis, directly increases production incentives and stimulates innovation to address unmet clinical needs [35]. Finally, network effects, operating through collaborations among firms, government agencies, and research institutions, facilitate knowledge spillovers and accelerate innovation processes [36–38].

These innovation factors were specified within the context of the medical device industry by identifying stages associated with market entry. Market entry for IVD products is influenced by a wide range of interrelated factors. Previous studies have proposed various frameworks to describe the medical device development process, frequently including stages such as regulation, R&D, manufacturing, marketing, and legal pathways [39]. A stage-gate model has been introduced that encompasses opportunity assessment, feasibility analysis, development, regulatory approval, and post-market evaluation [40,41]. These frameworks were later adapted or simplified, resulting in the identification of common stages such as concept development, validation, production, regulatory approval, and commercialization [19,42–44].

The relationships between parameters and variables, the time delays embedded in the equations, and assumptions regarding large-scale transmission events were established based on national data describing the progression of the COVID-19 pandemic in the Republic of Korea, supplemented by relevant literature. The population dynamics of the model were initialized using the Republic of Korea's total population of 51,779,203 in 2019. The daily average number of births from 2019 to 2021 ($n$=762) was added on a daily basis, while the daily average number of deaths from 2017 to 2019 ($n$=803) was subtracted. This approach was implemented to reflect baseline mortality under non-pandemic conditions and to exclude excess mortality attributable to COVID-19, thereby enhancing model accuracy. The R&D-to-sales ratio of manufacturers was set at 2% [45], and external R&D investment was modeled as 16.3% of internal investment [46]. A susceptible–infected–recovered (SIR) epidemiological model was used to generate demand dynamics [47], and transmission parameters were calibrated to match the observed pandemic trajectory in the Republic of Korea [48–50]. Market dynamics, including pricing pressure, competition, and new firm entry, were also incorporated [51–53]. The effects of vaccines were excluded from the model because of uncertainty regarding their protection levels and duration during the modeled timeframe [54–58]. Specific parameter values and the rationale for their calibration, including process-specific time delays, are provided in Tables S1–S3 [59–63].

## Models and Data Analysis Procedure

The model was developed in multiple stages. A conceptual model grounded in innovation theory and the IVD value chain was first constructed and subsequently refined through expert interviews (Figure 1). This conceptual framework was then translated into a quantitative simulation model consisting of 3 interconnected modules representing the stages of market entry in the IVD industry: R&D, regulatory approval, and marketing and pandemic progression.

The R&D module captures the dynamics of product development within the IVD value chain. It models how manufacturers develop prototype products through processes such as market analysis and target selection, which are driven by R&D investment and influenced by R&D costs. Network dynamics are incorporated as a central driver of innovation, affecting R&D costs, success rates, and development timelines. For example, patent-based disclosures are modeled as mechanisms that foster competition and facilitate knowledge spillovers, thereby reducing R&D expenses for subsequent innovators [38,64]. Investment behavior is driven by firm revenues and external funding, which in turn are influenced by demand-driven marketability and government intervention signals [34]. The detailed structure of this module is illustrated in Figure 2, and the corresponding mathematical formulations are provided in Table S1.

The regulatory approval module represents the process of obtaining market access. It models the flow of products through regulatory pathways leading to market approval and incorporates policy levers such as EUA that modify the duration and complexity of the approval process. The module also accounts for post-approval procedures specific

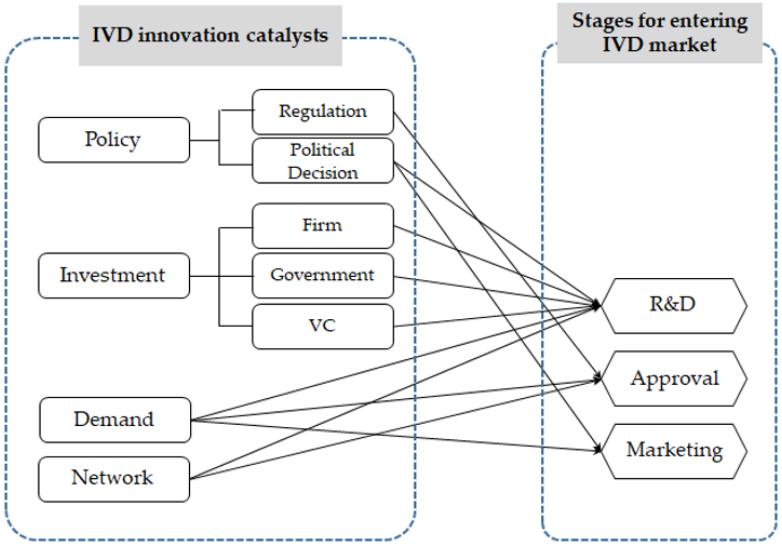



**Figure 1.** Framework for modeling the *in vitro* diagnostics (IVD) industry.
VC, venture capital; R&D, research and development.

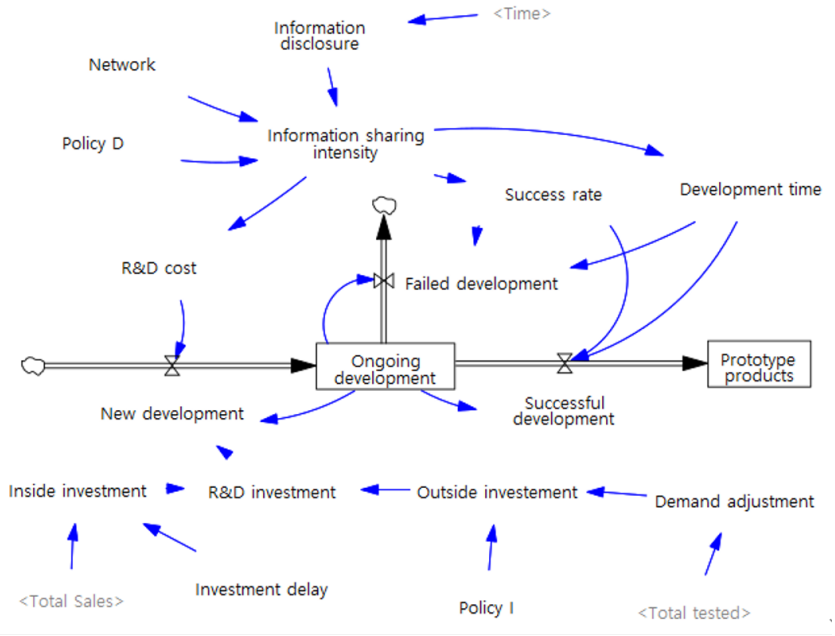



**Figure 2.** The research and development (R&D) module.

to the Republic of Korea, including new health technology assessment and insurance benefit assessment. The structure of this module is illustrated in Figure 3, and its mathematical formulations are presented in Table S2.

The marketing and pandemic progression module links the IVD market to the progression of the pandemic. The marketing process includes manufacturing, sales, and the execution of diagnostic tests. To maintain analytical focus on IVD manufacturers, the model simplifies the purchaser landscape (e.g., wholesalers) and the provider landscape (e.g., hospitals and physicians) and excludes payer-side cost flows that generate revenue for providers rather than manufacturers. Policy variables are incorporated to capture government-mandated changes in testing intensity and social distancing measures. Pandemic progression is structured using an SIR framework, linking epidemic-driven demand to the supply of diagnostic products. This structure creates a feedback loop in which the number of


https://doi.org/10.24171/j.phrp.2025.0313

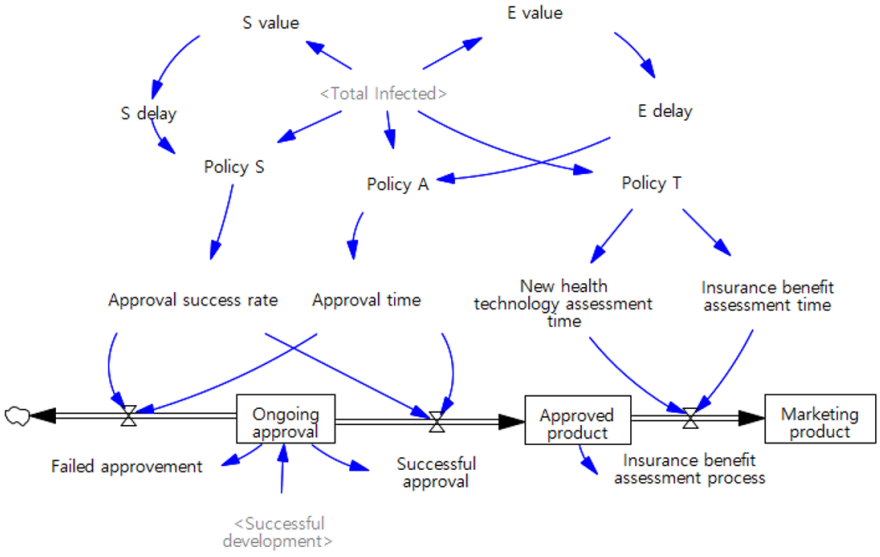



**Figure 3.** The regulatory approval module.

infected individuals influences demand, which subsequently affects industry revenue, R&D investment, and product output. The module also incorporates market dynamics such as competition and pricing pressure [51–53]. The model structure is shown in Figure 4, and mathematical formulations are provided in Table S3.

The model was validated prior to its use in scenario analysis. Validation involved comparing baseline simulation outputs with empirical data for several key indicators, including COVID-19 infections, deaths, testing volume, and industry revenue. The model was found to reproduce the overall trends observed in the empirical data (Figure S1). The close alignment between simulated and observed data indicates that the model adequately captures the fundamental dynamics of the system, supporting its suitability for scenario-based policy analysis.

To examine the effects of government diagnostic testing policies on patient incidence and mortality, as well as on the IVD industry, 6 policy scenarios were constructed. These scenarios were developed by deriving key dimensions from the innovation catalysts (policy, investment, demand, and network) and from the Republic of Korea's primary diagnostic testing measures during the COVID-19 pandemic. The first scenario evaluates the effect of varying R&D investment intensity. The second examines the impact of public–private cooperation. The third assesses the effectiveness of EUA by comparing outcomes associated with differing levels of regulatory difficulty and approval time. The fourth investigates the influence of diagnostic test performance. The fifth compares outcomes under different levels of diagnostic testing intensity, and the final scenario evaluates the effects of varying degrees of social distancing stringency.

The outcomes of these 6 scenarios were analyzed by simulating the model with systematic modifications to their respective key parameters. For each scenario, key parameters were varied across approximately 10 distinct levels, and the resulting outcomes were compared. This sensitivity analysis was designed to assess the robustness of the system's response to alternative policy interventions.

### Ethics Approval

The requirement for informed consent was waived because of the retrospective nature of this study.

## Results

Scenario 1 simulated outcomes based on the intensity of investment. Higher levels of R&D investment were associated with a faster time to market for new diagnostic products (Figure 5A, B). Conversely, as investment intensity increased, overall revenue within the IVD industry declined. This decrease was attributable to price reductions driven by intensified competition resulting from a greater number of products entering the market, as well as to a reduction in the number of patients (Figure 5C, D).

Scenario 2 simulated the effects of collaboration between the government and the private sector. As shown in Figure 6, enhanced networking between the government and the IVD industry reduced the number of infected individuals and deaths (Figure 6A, B). Stronger network linkages improved R&D success rates and shortened development timelines, thereby accelerating product market entry (Figure 6C).

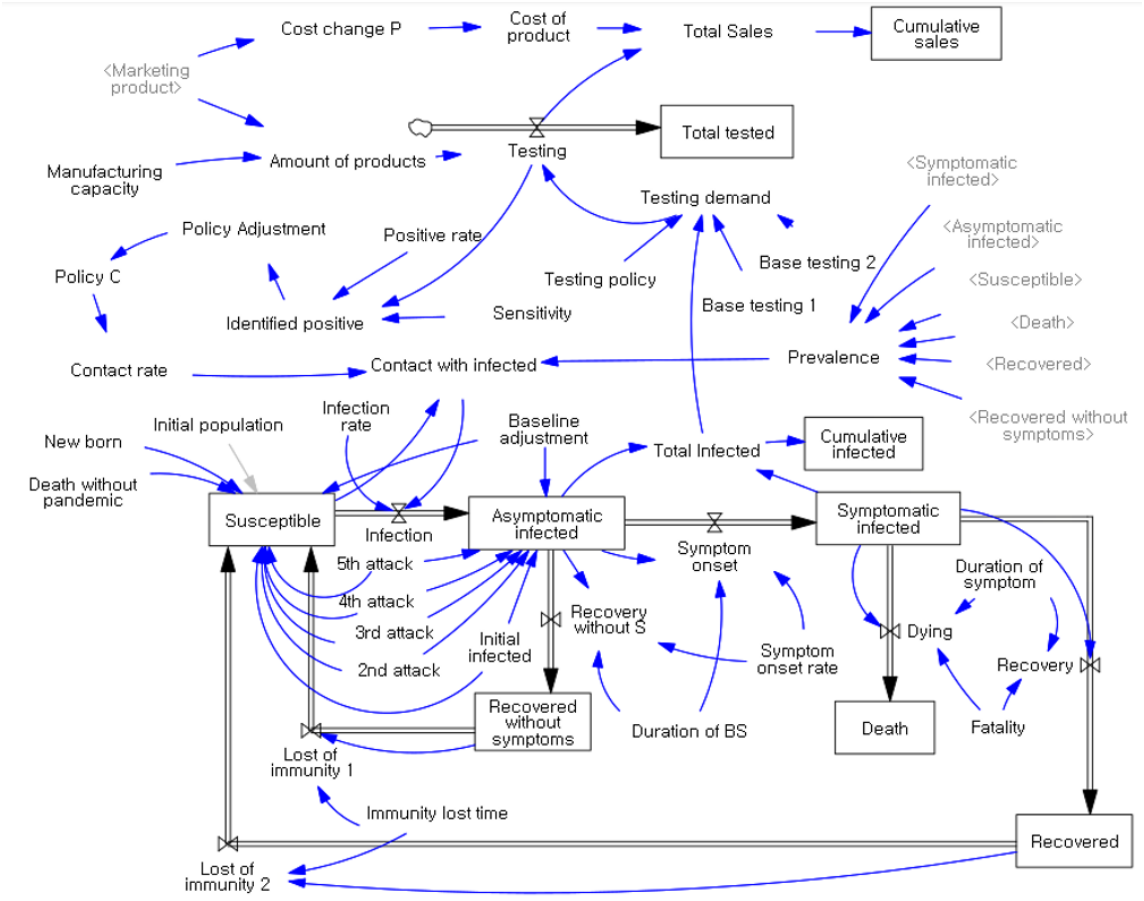



**Figure 4.** The marketing and pandemic progression module.

However, the resulting increase in competition led to a reduction in overall IVD industry revenue (Figure 6D).

In Scenario 3, the effects of regulatory difficulty and approval time on both epidemic outcomes and market dynamics were simulated. As shown in Figure 7, reductions in regulatory difficulty, achieved through easing IVD authorization requirements and shortening approval timelines, led to fewer infections. This effect was particularly pronounced during the early stages of the pandemic (Figure 7A, B). In contrast, increasing approval difficulty resulted in approximately 67,000 additional infections, while extending approval time led to roughly 61,000 additional cases. Lower regulatory difficulty also increased the number of approved products entering the market (Figure 7C, D). However, overall industry revenue declined as a result of price reductions driven by increased competition and a smaller patient population (Figure 7E, F).

Scenario 4 simulated the impact of diagnostic test performance, with a specific focus on sensitivity, defined as the ability to correctly identify infected individuals as positive. As illustrated in Figure 8, reductions in test performance led to increases in both infections and deaths. Specifically, the use of an IVD with 50% sensitivity resulted in approximately 280,000 additional infections and 3,500 additional deaths compared with the use of an IVD with 95% sensitivity (Figure 8A, B). Conversely, the use of lower-sensitivity IVD was associated with higher overall industry revenue, driven by the larger number of patients requiring testing (Figure 8C).

In Scenario 5, the impact of diagnostic testing intensity was simulated. As shown in Figure 9, more aggressive testing policies led to reductions in infections and deaths. Specifically, a 20% decrease in testing intensity relative to the current level resulted in approximately 850,000 additional infections and 10,000 additional deaths over the same period. In contrast, doubling testing intensity compared with the current level resulted in approximately 40,000 fewer infections and 500 fewer deaths.

In Scenario 6, the impact of social distancing intensity was simulated. The results indicate that higher levels of contact suppression substantially reduced infections and deaths, as shown in Figure 10. If contact suppression measures had been twice as strong as those observed in the actual situation,


https://doi.org/10.24171/j.phrp.2025.0313

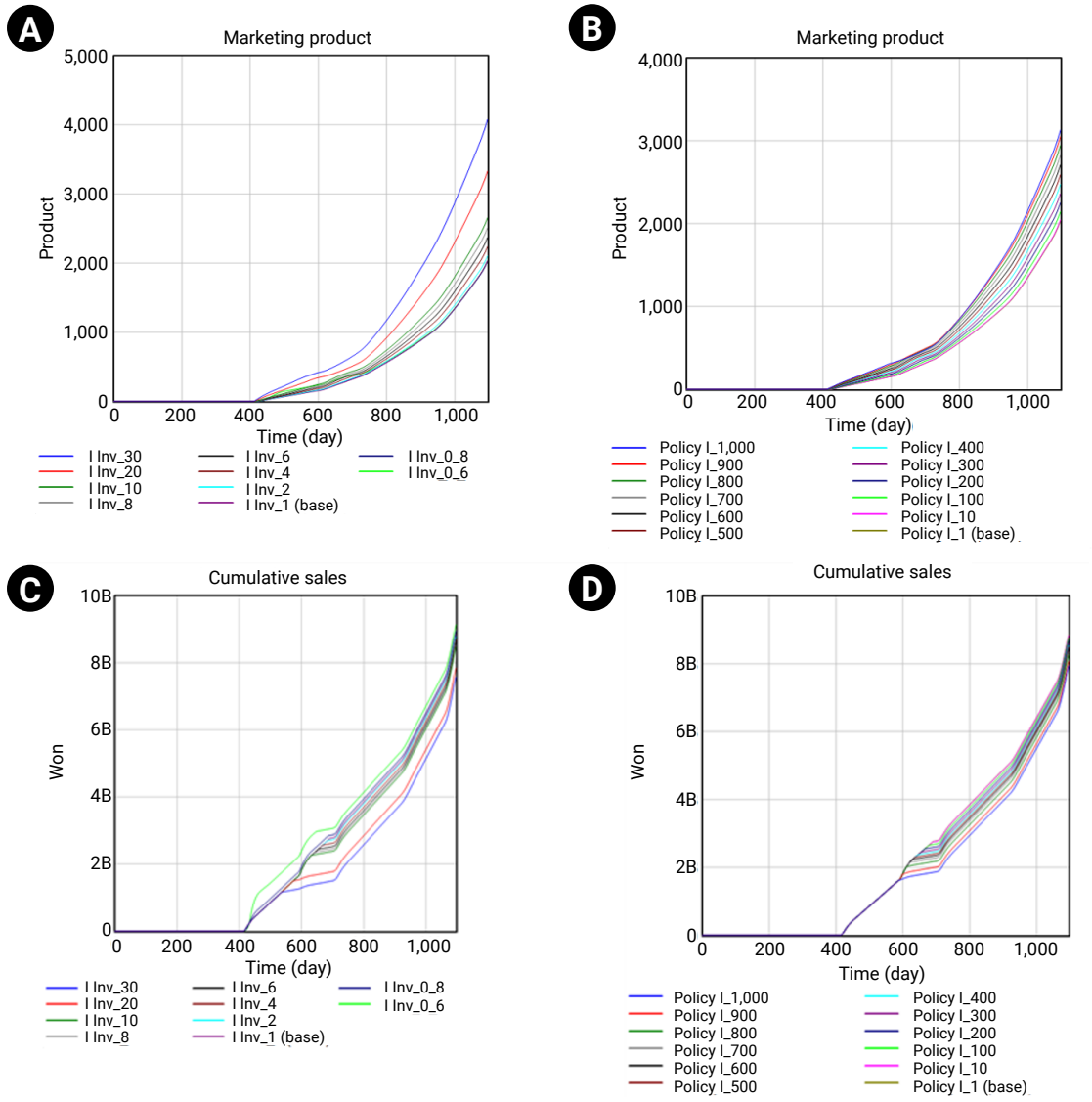



**Figure 5.** Impact of investment on the number of marketed products under company investment (A) and government investment (B), and cumulative sales under company investment (C) and government investment (D).

infections would have been reduced by approximately 60,000 and deaths by about 640. Conversely, if these measures had been implemented more weakly, reducing contact suppression effectiveness to 40% of the observed level, infections increased by approximately 700,000 and deaths by about 8,500 (Table 1).

## Discussion

Intervention policies centered on diagnostic testing were a cornerstone of the COVID-19 response in many nations. The implementation of these policies has had profound implications for both infectious disease control and the IVD industry. However, despite their widespread use, there has been limited research systematically evaluating the effectiveness of these governmental policies and their subsequent impact on the IVD industry's response. Accordingly, this study employed an SD approach to address this gap by examining the effectiveness of government pandemic control policies alongside the corresponding dynamics within the IVD industry.

The SD simulation conducted in this study underscores the critical importance of the entire IVD industry value chain, including development, market entry, and end use, in supporting an effective pandemic response. A central finding is the pivotal role of investment as a catalyst for innovation. Similar to the drug discovery industry, the IVD sector is highly technology-dependent and requires continuous R&D investment to maintain competitiveness

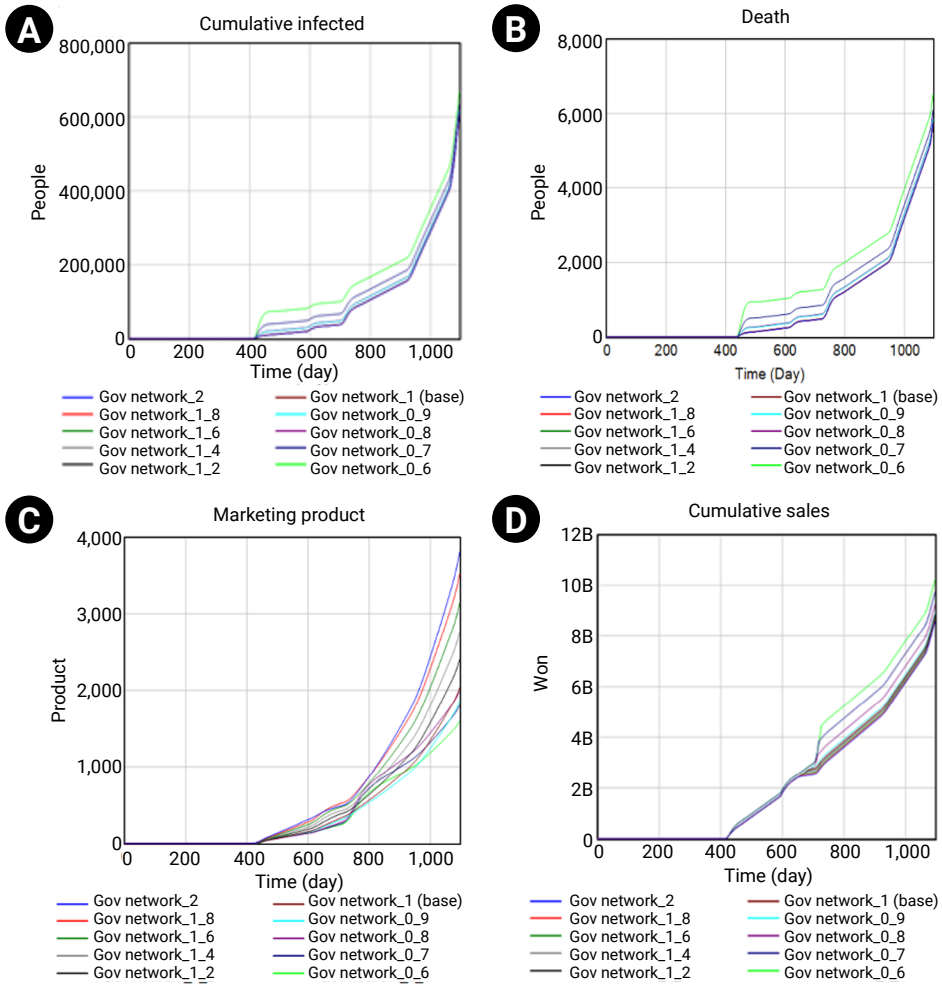



**Figure 6.** Impacts of the network. (A) Number of infected people. (B) Number of deceased people. (C) Number of marketing products. (D) Cumulative sales.

and comply with stringent regulatory standards [65–67]. The results demonstrate that higher levels of R&D investment are associated with faster market entry of IVD during a pandemic, thereby reducing overall public health damage (Scenario 1).

Policies designed to stimulate the market, such as increased government investment and strengthened network collaboration, were shown to be highly effective in achieving their intended objectives [68,69]. Among various forms of networking, collaboration between governments and IVD manufacturers is particularly critical in responding to infectious diseases, as large-scale outbreak responses are inherently government-led. As demonstrated in the results (Scenario 2), transparent government sharing of pathogen genetic information and policy direction enabled IVD manufacturers to rapidly develop diagnostics, which played a crucial role in limiting the spread of infection [27,28].

Taken together, these findings confirm that both tangible support, such as financial investment, and intangible support, such as network formation, play essential roles in securing critical IVD capacity during the early stages of an infectious disease crisis.

Once prototype products are prepared for market entry through sustained investment and collaboration, regulatory policies become necessary to enable rapid deployment. The model demonstrates that accelerating diagnostic availability by easing regulatory hurdles and shortening approval timelines is a powerful mechanism for reducing infections and deaths (Scenario 3). Procedural and regulatory innovations, particularly the EUA framework, similarly played a crucial role in the drug discovery field by substantially shortening approval timelines and enabling the rapid deployment of COVID-19 vaccines [31,70]. These findings suggest that strategically relaxing regulatory requirements to expand testing capacity is a key component of an effective pandemic response.


https://doi.org/10.24171/j.phrp.2025.0313

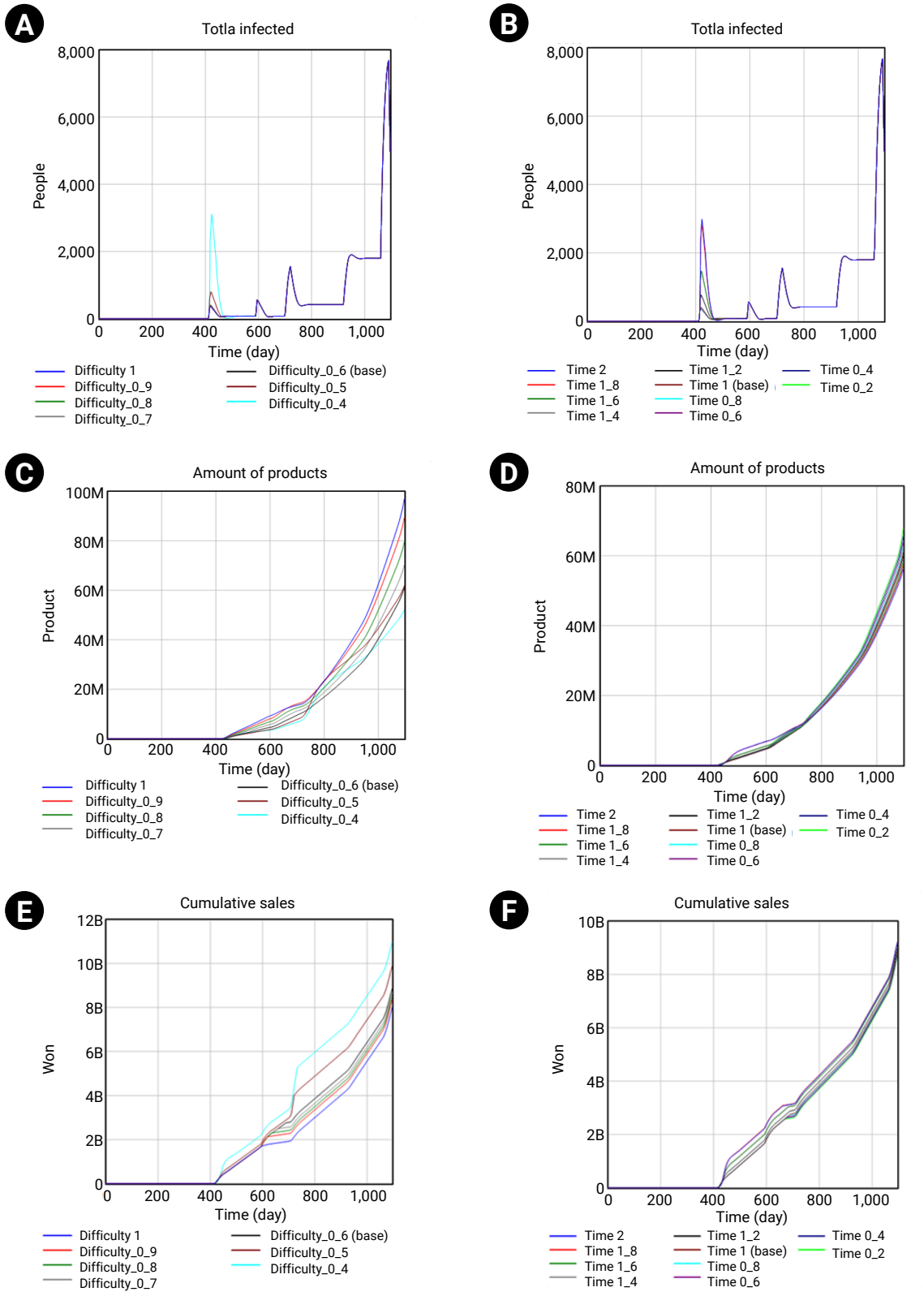



**Figure 7.** Impact of regulation on the number of daily infected individuals by regulatory difficulty (A) and approval time (B), the number of approved products by regulatory difficulty (C) and approval time (D), and cumulative sales by regulatory difficulty (E) and approval time (F).

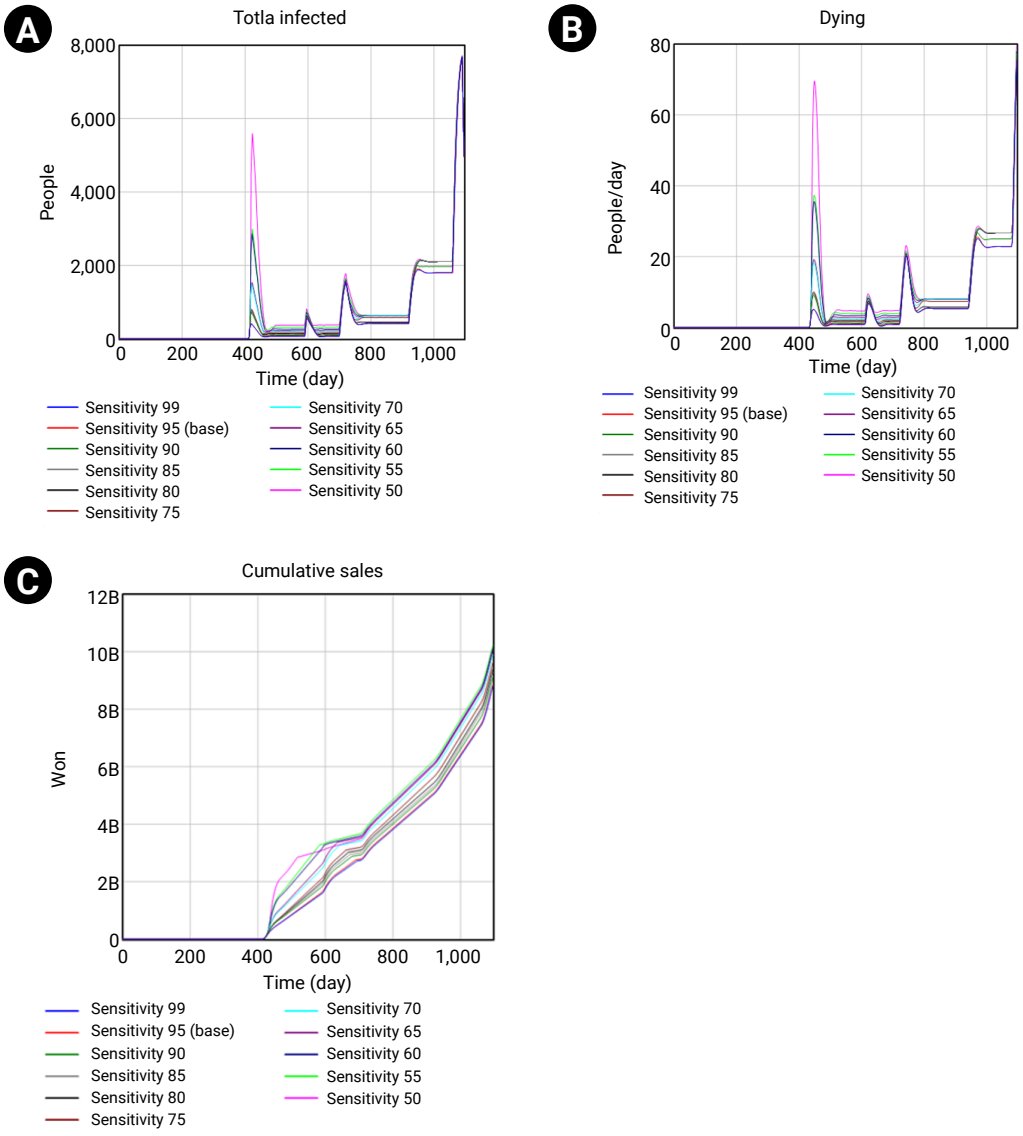



**Figure 8.** Impact of performance of the *in vitro* diagnostics. (A) Number of daily infected people. (B) Number of daily deceased people. (C) Cumulative sales.

However, this emphasis on speed introduces a significant risk. The simulation results indicate that infectious disease outcomes worsen when IVD quality is compromised (Scenario 4). False negative results, which are frequently associated with low test sensitivity, pose challenges at both policy and individual levels. At the policy level, false negatives can lead to missed opportunities for isolation and contact tracing, resulting in ineffective control strategies based on inaccurate epidemiological data [71–73]. At the individual level, false negatives may create a false sense of security that increases transmission risk. Conversely, false positives can result in unnecessary quarantines and personal restrictions [74].

This situation highlights a central dilemma faced by policymakers during infectious disease crises. On one hand, there is strong pressure to maximize regulatory speed in order to ensure widespread access to diagnostic testing. On the other hand, rapid approval processes increase the likelihood that low-performance tests may enter the market, potentially undermining public health outcomes. The core policy challenge therefore lies in managing the trade-off between regulatory speed and product quality. Addressing this challenge requires adaptive regulatory frameworks that can expedite diagnostic review processes while maintaining safeguards to prevent the approval of unreliable products.

Once an adequate supply of high-performance IVD has been secured, ensuring sufficient testing volume becomes


https://doi.org/10.24171/j.phrp.2025.0313

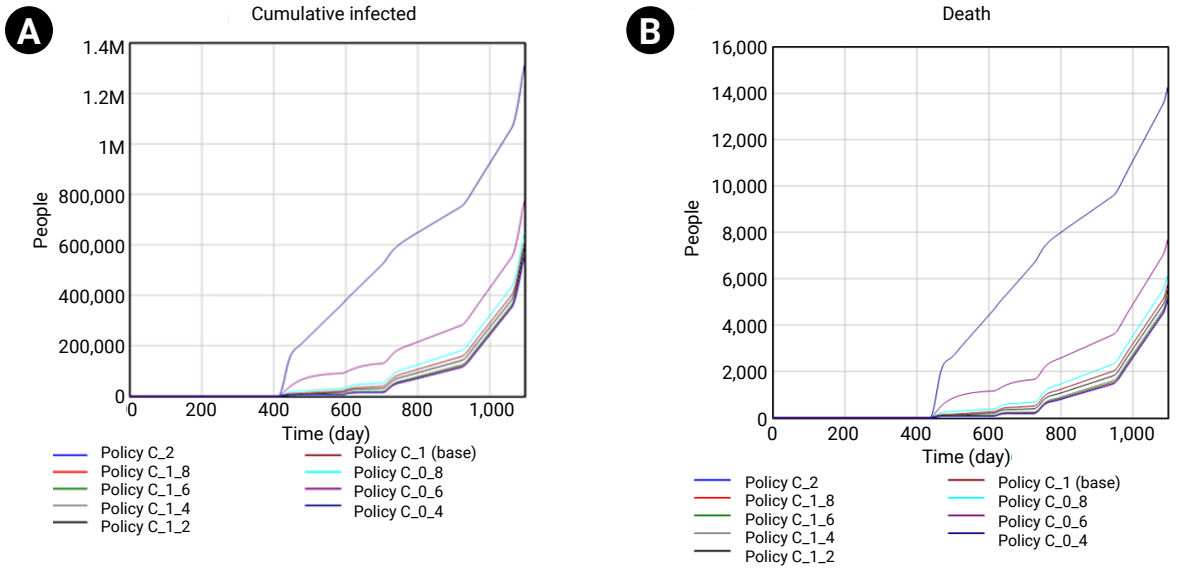



**Figure 9.** Impact of testing policy. (A) Number of infected people. (B) Number of deceased people.

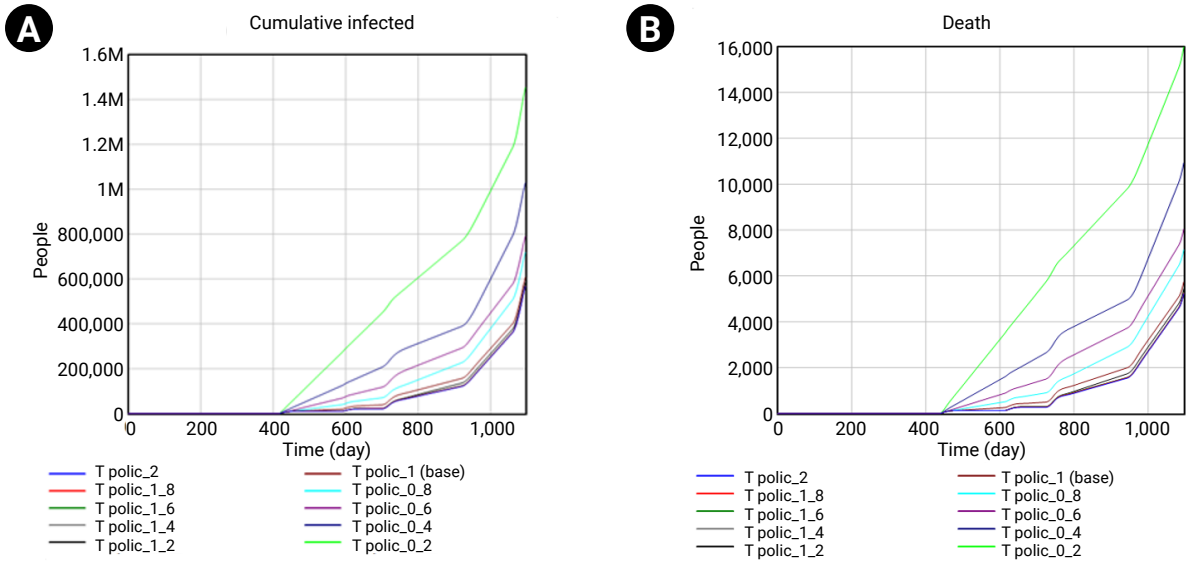



**Figure 10.** Impact of social distancing. (A) Number of infected people. (B) Number of deceased people.

critical. Consistent with previous studies [15,23,29], the simulation results confirm that proactive diagnostic testing plays a central role in reducing infection transmission (Scenario 5). Diagnostic testing forms the foundation of preventive measures, including epidemiological investigation, isolation, and treatment, which explains why governments implemented large-scale testing strategies during the COVID-19 pandemic [71,75,76].

As demonstrated in numerous studies, contact reduction measures such as social distancing and lockdowns effectively limit the spread of infectious diseases, with higher-intensity interventions yielding greater effects [72,77,78]. Consistent with this evidence, the present study found that increases in the intensity of contact reduction policies were associated with greater reductions in infections and deaths (Scenario 6).

In summary, contact reduction measures, including social distancing and isolation, are effective tools for breaking transmission chains when they are informed by accurate diagnostic testing data.

As demonstrated across the study scenarios, policy measures such as increased investment, network enhancement, and regulatory relaxation were associated with reductions in

**Table 1.** Summary of results

| No. | Scenario key factor | Results |
|---|---|---|
| 1 | R&D investment | Greater R&D investment leads to<br>• more rapid market entry for IVD<br>• a decrease in overall industry revenue. |
| 2 | Public-private collaboration | Enhanced government-industry collaboration leads to<br>• fewer infections and deaths,<br>• faster market entry for IVD,<br>• decreased firm revenue. |
| 3 | Regulatory policy | Increased regulatory difficulty and extended approval times for IVD are associated with<br>• a higher number of infections,<br>• a reduced number of new IVDs entering the market,<br>• an increase in firm revenue. |
| 4 | Sensitivity for diagnostic tests | Higher IVD sensitivity leads to<br>• a reduction in infections and deaths<br>• a decrease in firm revenue. |
| 5 | Testing intensity | More aggressive diagnostic testing policies are associated with<br>• a lower number of infections and deaths. |
| 6 | Contact reduction policy | More stringent social distancing policies result in<br>• a reduction in both infections and deaths. |

R&D, research and development; IVD, *in vitro* diagnostics.

expected revenue for the IVD industry (Scenarios 1–4). This outcome arises from 2 primary factors: intensified price competition resulting from increased product entry and a decline in patient numbers due to effective infection control. Reduced profitability driven by heightened competition is a well-documented phenomenon across industries. This pattern is particularly pronounced in the IVD sector, which, while structurally similar to the drug discovery industry, is characterized by lower technological entry barriers and faster development cycles, yet faces intense post-launch competition [79]. Importantly, this reduction in expected revenue is relative and may be progressively offset by broader market expansion driven by sustained public health investment, a pattern consistent with established theories of industrial development and innovation diffusion [80,81].

## Conclusion

In this study, the effectiveness of government epidemic control policies and the corresponding response of the IVD industry were examined using an SD model. The model provides a robust analytical framework for forecasting the impacts of different policy levers and for assessing how a pandemic influences the complex system of industrial innovation. By simulating multiple scenarios grounded in the Republic of Korea's COVID-19 experience, this research offers strategic insights that can inform responses to future public health challenges.

### Theoretical Implications

As defined by Schumpeter, innovation may be radical, emerging as a response to new environments, or incremental, driven by factors such as sustained R&D investment [32]. Historically, the infectious disease IVD industry has faced weaker market incentives for innovation than structurally similar sectors such as drug discovery, in part because treatment decisions can often be made based on symptoms without laboratory confirmation [8,19]. However, a pandemic creates an urgent and large-scale need that stimulates what has been described as "crisis-driven innovation" [20].

Drawing on existing literature and expert interviews, this study identifies 4 key factors driving innovation in the IVD industry: policy, investment, demand, and networks. The primary theoretical contribution of this study is the explicit modeling of the IVD value chain to demonstrate how these 4 factors are interconnected and mutually reinforcing. The model illustrates how these elements interact to accelerate the development and deployment of new diagnostics, influence disease control outcomes, and subsequently shape the next cycle of product development.

### Policy Implications

As demonstrated in this study, IVD serve as a critical tool for governments during infectious disease outbreaks. Because IVD can be developed relatively rapidly, they function as an essential bridging intervention to mitigate an epidemic while longer-term solutions, such as vaccines and therapeutics, are still under development. Policy efforts to



https://doi.org/10.24171/j.phrp.2025.0313

accelerate the adoption of IVD can be categorized according to the innovation factors proposed in this study: investment, networks, regulation, and the infrastructure required to meet demand. The policy implications associated with each of these factors are discussed below.

First, policy support and investment should be sustained during non-crisis periods. Just as continuous military investment is essential for national defense, sustained investment in diagnostic preparedness is fundamental to health security. The IVD industry's ability to rapidly develop diagnostics for a novel infectious disease depends on maintaining sufficient R&D capacity prior to a crisis. Accordingly, policy should be designed to preserve crisis-driven innovative momentum not only during emergencies but also in the intervals between them. To ensure preparedness for future public health emergencies, policymakers should establish mechanisms that promote long-term stability and growth, including strategic government stockpiling contracts, R&D tax incentives, and sustained public–private partnerships.

A continuously maintained public–private network that facilitates rapid and transparent information sharing, including regulatory guidance and epidemic control strategies, during non-crisis periods can substantially accelerate the development of next-generation diagnostic solutions [20,82,83]. Such investments ensure that when a pandemic emerges, the diagnostic industry can scale up immediately rather than initiating development from the outset.

From the perspective of individual manufacturers, maintaining sustained investment in IVD development is critical for both financial performance and long-term viability. Because the timing and scale of infectious disease outbreaks are inherently unpredictable, manufacturers face considerable challenges in consistently investing in R&D for infectious disease diagnostics [8]. Nevertheless, firms must prepare for technology development, regulatory approval processes, the rapid expansion of production capacity to meet sudden demand surges, supply-chain adjustments, funding acquisition strategies, and market positioning decisions [25]. Entering new markets during the early stages of an outbreak allows firms to capture early market dominance; therefore, continued investment despite uncertainty remains strategically important [84,85]. Moreover, manufacturers must closely monitor outbreak severity, government responses, and international developments to anticipate demand and to develop prudent investment strategies for securing raw materials and short-term labor in preparation for abrupt market fluctuations.

Second, quality must accompany quantity. As demonstrated in this study, rapidly securing IVD to enable aggressive diagnostic testing during the early stages of a pandemic is essential for effective epidemic control. In this context, the use of EUA, which reduced approval barriers to facilitate swift diagnostic deployment, contributed positively to containment efforts. However, the findings also indicate that low-sensitivity tests can generate inaccurate results that undermine containment strategies and ultimately exacerbate disease transmission.

In particular, lateral flow immunoassays, which were widely deployed during the COVID-19 response, contributed substantially to epidemic control by providing rapid, low-cost, point-of-care results without requiring complex equipment [86]. Nevertheless, these assays have a critical limitation in that their diagnostic performance is substantially inferior to that of PCR-based tests [87]. Consequently, as recommended by the World Health Organization and supported by prior studies [11], governments must carefully evaluate epidemiological data at each stage of a pandemic to balance testing throughput, speed, and accuracy in accordance with the characteristics of the diagnostic tools being implemented.

One practical approach to lowering entry barriers for the rapid introduction of IVD while simultaneously maintaining high performance is to closely monitor pathogenic changes and analyze them in conjunction with the performance of IVD already on the market. A clear distinction exists between analytical performance, which is evaluated in controlled laboratory environments, and clinical performance, which is assessed in real-world clinical settings and is influenced by multiple contextual factors [74].

Because pathogens, particularly viruses, continuously undergo mutation, alterations in genetic sequences and antigenic structures may occur, potentially reducing the performance of existing diagnostic reagents [88]. Accordingly, it is necessary to establish a robust post-market surveillance system through measures such as information-sharing platforms, including Global Initiative on Sharing All Influenza Data, which was actively utilized during the COVID-19 pandemic [82], as well as systematic data collection based on public–private collaboration.

Furthermore, the nature of a crisis renders traditional innovation pathways infeasible, shifting priorities toward the rapid deployment of existing technologies [89]. This observation suggests that pre-crisis efforts to establish tiered or expedited regulatory review pathways, linked to transparent and predefined performance benchmarks, represent a practical and scalable response strategy for future pandemics.

Third, comprehensive public health infrastructure, including large-scale diagnostic testing, epidemiological investigation, quarantine, and treatment, must be strengthened. During the COVID-19 pandemic, laboratories in the majority of countries

were unable to conduct required testing in a timely manner because of shortages in critical resources such as diagnostic reagents and trained personnel [14]. Large-scale containment policies implemented in response to pandemics also generate substantial socioeconomic costs due to reductions in social and economic activity [2,3,5]. By proactively establishing robust diagnostic testing infrastructure, policymakers can design response strategies that mitigate such socioeconomic harm during future crises [90]. Clinical laboratories should therefore no longer be viewed merely as ancillary support units but rather as frontline components of the public health system. This represents a critical domain that must be reinforced in preparation for future pandemics. Furthermore, diagnostic testing constitutes only 1 component of a broader response system. While diagnostic tests provide essential data to guide interventions, complementary measures, including effective contact tracing systems, supported isolation, and accessible treatment, must also be in place and adequately resourced.

Lastly, efforts aimed at cost reduction can ultimately result in greater overall expenditure. Although establishing the tangible and intangible infrastructure discussed above requires substantial upfront investment, countries that invested more heavily in their health sectors prior to the pandemic experienced significantly lower COVID-19 mortality rates. Specifically, a 1% increase in per capita health expenditure was associated with a 0.74% reduction in COVID-19 mortality [91]. Suppressing infection incidence is inherently more cost-effective than managing cases on a per-test basis [92]. Consequently, by maintaining higher levels of investment in the diagnostics sector during non-crisis periods, governments can respond to emerging health crises in a more cost-effective and resilient manner.

### Ideas for Future Research

This study has several limitations. First, modeling-based studies inherently reflect conditions at specific points in time and may not fully capture dynamic real-world changes, including viral mutations, evolving government policies, and shifts in population behavior [93]. To address this challenge, this study employs an SD model to examine the relationship between pandemic progression and industrial innovation in the IVD sector. This methodology is well-suited to analyzing complex systems characterized by feedback loops, time delays, and non-linear interactions, and it has been widely applied in studies of pandemic responses [94–97] and industrial innovation systems [98–102]. Despite these strengths, the present model necessarily simplifies certain complex processes; for example, it abstracts regulatory pathways and streamlines innovation trajectories, thereby omitting detailed approval sequences and specific market mechanisms.

Second, the model is grounded in the specific context of the Republic of Korea's COVID-19 response. As a result, the findings may not be directly generalizable to countries with differing healthcare systems, regulatory environments, and industrial structures.

Lastly, the scope of this study focuses primarily on immediate crisis response and does not explicitly account for operational constraints within public health infrastructure or the longer-term phases of preparedness and recovery [93].

Future research should build upon these limitations. Comparative analyses could assess the applicability of the model across diverse national contexts. In addition, insights derived from the present simulation should be complemented by quantitative studies using large-scale empirical datasets to further validate the findings. Finally, extending the model to incorporate more granular representations of regulatory processes, innovation systems, and public health infrastructure capacity would enable a more comprehensive understanding to inform global health policy.

## Supplementary Material

**Table S1.** Equations for the model of the IVD development process; **Table S2**. Equations for the model of the IVD approval process; **Table S3.** Equations for the model of the IVD marketing process; **Figure S1.** Comparison between empirical data and modeling data.Supplementary data are available at https://doi.org/10.24171/j.phrp.2025.0313.

## Notes

**Ethics Approval**
Not applicable.

**Conflicts of Interest**
The authors have no conflicts of interest to declare.

**Funding**
None.

**Availability of Data**
The datasets are not publicly available but are available from the corresponding author upon reasonable request.

**Authors' Contributions**

Conceptualization: MK, KS; Data curation: MK, KS; Formal analysis: MK; Investigation: MK; Methodology: MK, KS; Project administration: KS; Resources: MK, KS; Software: MK; Supervision: KS; Validation: all authors; Visualization: MK, HJ; Writing–original draft: all authors; Writing–review & editing: all authors. All authors read and approved the final manuscript.

## References

1. Costa D, Rohleder S, Bozorgmehr K. Impact of non-pharmaceutical interventions on COVID-19 incidence and deaths: cross-national natural experiment in 32 European countries. BMC Public Health 2024;24:2341.
2. Deb P, Furceri D, Ostry JD, et al. The economic effects of COVID-19 containment measures. Open Econ Rev 2022;33:1–32.
3. Demirguc-Kunt A, Lokshin M, Torre I. The sooner, the better: the early economic impact of non-pharmaceutical interventions during the COVID-19 pandemic. Policy Research Working Paper; No. 9257. World Bank Group; 2020.
4. Leduc S, Liu Z. The uncertainty channel of the coronavirus. Federal Reserve Bank of San Francisco; 2020.
5. Gupta H, Chaudhary R, Gupta S. COVID-19 impact on major stock markets. FIIb Bus Rev 2022;11:336–46.
6. Gamil Y, Alhagar A. The impact of pandemic crisis on the survival of construction industry: a case of COVID-19. Mediterr J Soc Sci 2020; 11:122–8.
7. Perwej A. The impact of pandemic COVID-19 on the Indian Banking System. Int J Recent Sci Res 2020;11:39873–83.
8. Kelly-Cirino CD, Nkengasong J, Kettler H, et al. Importance of diagnostics in epidemic and pandemic preparedness. BMJ Glob Health 2019;4:e001179.
9. Vandenberg O, Martiny D, Rochas O, et al. Considerations for diagnostic COVID-19 tests. Nat Rev Microbiol 2021;19:171–83.
10. Ciotti M, Nicolai E, Pieri M. Development and optimization of diagnostic assays for infectious diseases. Labmed Discov 2024;1: 100032.
11. Lu X, Du J, You M, et al. From crisis to innovation in point-of-care testing: lessons from the COVID-19 pandemic and future directions. Trends Analyt Chem 2025;184:118131.
12. Romantowski J, Gawinowska M, Trzonkowski P, et al. Can labs help with vaccination?: in vitro tests in diagnosis of allergy to COVID-19 vaccines: a systematic review. Immun Inflamm Dis 2025;13:e70206.
13. Gairolla J, Gupta P, Gupta P, et al. Techno-innovations and molecular methods for diagnosis of COVID-19: updates from India. J Mar Med Soc 2021;23:16–23.
14. Lippi G, Henry BM, Mattiuzzi C. The crucial role of laboratory medicine in addressing future public health infectious threats: insights gained from the COVID-19 pandemic. Diagnostics 2025;15:323.
15. Saez M, Tobias A, Varga D, et al. Effectiveness of the measures to flatten the epidemic curve of COVID-19. The case of Spain. Sci Total Environ 2020;727:138761.
16. Busk PK, Kristiansen TB, Engsig-Karup A. Assessment of the national test strategy on the development of the COVID-19 pandemic in Denmark. Epidemiologia (Basel) 2021;2:540–52.
17. Holt E. COVID-19 testing in Slovakia. Lancet Infect Dis 2021;21:32.
18. Herzlinger RE. Why innovation in health care is so hard. Harv Bus Rev 2006;84:58-66, 156.
19. Maresova P, Klimova B, Honegr J, et al. Medical device development process, and associated risks and legislative aspects: systematic review. Front Public Health 2020;8:308.
20. Coccia M. Problem-driven innovations in drug discovery: co-evolution of the patterns of radical innovation with the evolution of problems. Health Policy Technol 2016;5:143–55.
21. Coccia M. Sources of technological innovation: radical and incremental innovation problem-driven to support competitive advantage of firms. Technol Anal Strateg Manag 2017;29:1048–61.
22. Vashist SK. In vitro diagnostic assays for COVID-19: recent advances and emerging trends. Diagnostics 2020;10:202.
23. Santos S, Humbard M, Lambrou AS, et al. The SARS-CoV-2 test scale-up in the USA: an analysis of the number of tests produced and used over time and their modelled impact on the COVID-19 pandemic. Lancet Public Health 2025;10:e47–57.
24. Lu L, Peng J, Wu J, et al. Perceived impact of the COVID-19 crisis on SMEs in different industry sectors: evidence from Sichuan, China. Int J Disaster Risk Reduct 2021;55:102085.
25. Das S, Dunbar S. The COVID-19 pandemic: a diagnostic industry perspective. Front Cell Infect Microbiol 2022;12:862440.
26. Ogarte N, Rodelas R, Ong H, et al. Impact of COVID-19 pandemic to the profitability of Villarica Pawnshop Labo Branch, Philippines. J Manag Stud Dev 2023;2:1–12.
27. Sung H, Roh KH, Hong KH, et al. COVID-19 molecular testing in Korea: practical essentials and answers from experts based on experiences of emergency use authorization assays. Ann Lab Med 2020;40:439–47.
28. Kim W, Jung TY, Roth S, et al. Management of the COVID-19 pandemic in the Republic of Korea from the perspective of governance and public-private partnership. Yonsei Med J 2021;62:777–91.
29. Arora AS, Rajput H, Changotra R. Current perspective of COVID-19 spread across South Korea: exploratory data analysis and containment of the pandemic. Environ Dev Sustain 2021;23:6553–63.
30. Tromberg BJ, Schwetz TA, Perez-Stable EJ, et al. Rapid scaling up of COVID-19 diagnostic testing in the United States: the NIH RADx initiative. N Engl J Med 2020;383:1071–7.
31. Fialho BC, Gauss L, Soares PF, et al. Vaccine innovation meta-model for pandemic contexts. J Pharm Innov 2023;18:1145–93.
32. Malerba F. Innovation and the dynamics and evolution of industries: progress and challenges. Int J Ind Organ 2007;25:675–99.
33. Shefer D, Frenkel A. R&D, firm size and innovation: an empirical analysis. Technovation 2005;25:25–32.
34. Kleer R. Government R&D subsidies as a signal for private investors. Res Policy 2010;39:1361–74.
35. Metcalfe TA. Development of novel IVD assays: a manufacturer's perspective. Scand J Clin Lab Invest Suppl 2010;242:23–6.
36. Kogut B. The network as knowledge: generative rules and the emergence of structure. Strateg Manag J 2000;21:405–25.

37. Coccia M. Technological paradigms and trajectories as determinants of the R&D corporate change in drug discovery industry. Int J Knowl Learn 2015;10:29–43.
38. Hu W, Du J, Zhang W. Corporate social responsibility information disclosure and innovation sustainability: evidence from China. Sustainability 2020;12:409.
39. Institute of Medicine (US) Roundtable on Research and Development of Drugs, Biologics, and Medical Devices (US). Innovation and invention in medical devices: workshop summary. Hanna KE, Manning FJ, Bouxsein P, et al., editors. National Academies Press (US); 2001.
40. Pietzsch JB, Paté-Cornell ME. Early technology assessment of new medical devices. Int J Technol Assess Health Care 2008;24:36–44.
41. Engberg R, Altmann P. Regulation and technology innovation: a comparison of stated and formal regulatory barriers throughout the technology innovation process. J Technol Manag Innov 2015;10:85–91.
42. Peeling RW. Bridging diagnostics research, development and commercialization. In: Bawa R, Audette GF, Reese BE, editors. Handbook of clinical nanomedicine: law, business, regulation, safety, and risk. Pan Stanford Publishing; 2016. p. 85–98.
43. Ogrodnik PJ. Medical device design: innovation from concept to market. 2nd ed. Elsevier Science & Technology; 2019.
44. Tomaskova H, Maresova P, Penhaker M, et al. The business process model and notation of open innovation: the process of developing medical instrument. J Open Innov Technol Mark Complex 2019;5:101.
45. Shin KY, Lee SW, Kim SW. Policy Implication and improvement of the accuracy for R&D expenditure measurement [Internet]. STEPI Insight; 2023 [cited 2026 Jan 9]. Available from: https://www.stepi.re.kr/site/stepiko/report/View.do?reIdx=318&cateCont=A0501. Korean.
46. Shin Y, Choi K, Kim S. 2020 Medical device industry analysis report [Internet]. Korea Health Industry Development Institute; 2021 [cited 2026 Jan 9]. Available from: https://www.khidi.or.kr/board/view?linkId=48862773&menuId=MENU00085. Korean.
47. Holmdahl I, Buckee C. Wrong but useful: what COVID-19 epidemiologic models can and cannot tell us. N Engl J Med 2020;383:303–5.
48. Kang CR, Lee JY, Park Y, et al. Coronavirus disease exposure and spread from nightclubs, South Korea. Emerg Infect Dis 2020;26:2499–501.
49. Kim HJ, Hwang HS, Choi YH, et al. The delay in confirming COVID-19 cases linked to a religious group in Korea. J Prev Med Public Health 2020;53:164–7.
50. Carabelli AM, Peacock TP, Thorne LG, et al. SARS-CoV-2 variant biology: immune escape, transmission and fitness. Nat Rev Microbiol 2023;21:162–77.
51. Beeler JF. Chapter 24: Development and commercialization of in vitro diagnostics: applications for companion diagnostics. In: Shimasaki C, editor. Biotechnology entrepreneurship. Academic Press; 2014. p. 331–40.
52. Dobbs ME. Guidelines for applying Porter's five forces framework: a set of industry analysis templates. Compet Rev 2014;24:32–45.
53. Prasad V. Competition and innovation: evidence from third-party reprocessing in the medical device industry. Department of Economics, Duke University; 2020.
54. Lipsitch M, Dean NE. Understanding COVID-19 vaccine efficacy. Science 2020;370:763–5.
55. Andrews N, Stowe J, Kirsebom F, et al. COVID-19 vaccine effectiveness against the Omicron (B.1.1.529) variant. N Engl J Med 2022;386:1532–46.
56. Kirsebom FC, Andrews N, Stowe J, et al. COVID-19 vaccine effectiveness against the Omicron (BA.2) variant in England. Lancet Infect Dis 2022;22:931–3.
57. Rosenberg ES, Dorabawila V, Easton D, et al. COVID-19 vaccine effectiveness in New York State. N Engl J Med 2022;386:116–27.
58. Vasireddy D, Vanaparthy R, Mohan G, et al. Review of COVID-19 variants and COVID-19 vaccine efficacy: what the clinician should know? J Clin Med Res 2021;13:317–25.
59. Song SH, Song JH, Yun YM, et al. A study on the re-evaluation mechanism in the field of in vitro diagnosis. Health Insurance Review & Assessment Service; 2018. Korean.
60. Statistics Korea (KR). Population as of households and housing units [Internet]. Statistics Korea; 2019 [cited 2025 Apr 9]. Available from: https://kosis.kr/statHtml/statHtml.do?orgId=101&tblId=DT_1IN1502&conn_path=I2&language=en.
61. Statistics Korea (KR). Vital statistics (number) by month for provinces [Internet]. Statistics Korea; 2021 [cited 2025 Apr 9]. Available from: https://kosis.kr/statHtml/statHtml.do?orgId=101&tblId=DT_1B8000G&conn_path=I2&language=en.
62. Statistics Korea (KR). Vital statistics (Number) by month for provinces [Internet]. Statistics Korea; 2019 [cited 2025 Apr 9]. Available from: https://kosis.kr/statHtml/statHtml.do?orgId=101&tblId=DT_1B8000G&conn_path=I2&language=en.
63. Jung SM, Akhmetzhanov AR, Hayashi K, et al. Real-time estimation of the risk of death from novel coronavirus (COVID-19) infection: inference using exported cases. J Clin Med 2020;9:523.
64. Magazzini L, Pammolli F, Riccaboni M, et al. Patent disclosure and R&D competition in pharmaceuticals. Econ Innov New Technol 2009;18:467–86.
65. Provines CD. Overcoming organizational barriers to implementing value-based pricing in the medical devices & diagnostics industry. J Med Mark 2010;10:37–44.
66. Zuckerman DM, Brown P, Nissen SE. Medical device recalls and the FDA approval process. Arch Intern Med 2011;171:1006–11.
67. De Maria C, Di Pietro L, Lantada AD, et al. Safe innovation: on medical device legislation in Europe and Africa. Health Policy Technol 2018;7:156–65.
68. Nerkar A, Paruchuri S. Evolution of R&D capabilities: the role of knowledge networks within a firm. Manage Sci 2005;51:771–85.
69. Malerba F, McKelvey M. Knowledge-intensive innovative entrepreneurship integrating Schumpeter, evolutionary economics,



https://doi.org/10.24171/j.phrp.2025.0313

and innovation systems. Small Bus Econ (Dordr) 2020;54:503–22.
70. Medeiros MZ, Soares PF, Fialho BC, et al. Vaccine innovation model: a technology transfer perspective in pandemic contexts. Vaccine 2022;40:4748–63.
71. Peak CM, Kahn R, Grad YH, et al. Individual quarantine versus active monitoring of contacts for the mitigation of COVID-19: a modelling study. Lancet Infect Dis 2020;20:1025–33.
72. Hellewell J, Abbott S, Gimma A, et al. Feasibility of controlling COVID-19 outbreaks by isolation of cases and contacts. Lancet Glob Health 2020;8:e488–96.
73. Kretzschmar ME, Rozhnova G, Bootsma MC, et al. Impact of delays on effectiveness of contact tracing strategies for COVID-19: a modelling study. Lancet Public Health 2020;5:e452–9.
74. Deeks JJ, Ashby D, Takwoingi Y, et al. Lessons to be learned from test evaluations during the COVID-19 pandemic: RSS Working Group's Report on Diagnostic Tests. J R Stat Soc Ser A Stat Soc 2024;187:659–709.
75. Studdert DM, Hall MA. Disease control, civil liberties, and mass testing: calibrating restrictions during the COVID-19 pandemic. N Engl J Med 2020;383:102–4.
76. Rong XM, Yang L, Chu HD, et al. Effect of delay in diagnosis on transmission of COVID-19. Math Biosci Eng 2020;17:2725–40.
77. Murphy C, Lim WW, Mills C, et al. Effectiveness of social distancing measures and lockdowns for reducing transmission of COVID-19 in non-healthcare, community-based settings. Philos Trans A Math Phys Eng Sci 2023;381:20230132.
78. Faherty LJ, Nascimento de Lima P, Lim JZ, et al. Effects of non-pharmaceutical interventions on COVID-19 transmission: rapid review of evidence from Italy, the United States, the United Kingdom, and China. Front Public Health 2024;12:1426992.
79. Morel CM, McClure L, Edwards S, et al. Ensuring innovation in diagnostics for bacterial infection: implications for policy. European Observatory on Health Systems and Policies/WHO Regional Office for Europe; 2016.
80. Hammerschlag Z, Bick G, Luiz JM. The internationalization of African fintech firms: marketing strategies for successful intra-Africa expansion. Int Mark Rev 2020;37:299–317.
81. Niu B, Dong J, Dai Z, et al. Market expansion vs. intensified competition: overseas supplier's adoption of blockchain in a cross-border agricultural supply chain. Electron Commer Res Appl 2022;51:101113.
82. Khare S, Gurry C, Freitas L, et al. GISAID's role in pandemic response. China CDC Wkly 2021;3:1049–51.
83. Elbe S. Bioinformational diplomacy: global health emergencies, data sharing and sequential life. Eur J Int Relat 2021;27:657–81.
84. Arora A, Belenzon S, Dionisi B. First-mover advantage and the private value of public science. Res Policy 2023;52:104867.
85. Orellana A. First mover advantages in innovation waves. SSRN 2024 Dec 9 [Epub]. https://doi.org/10.2139/ssrn.5094199.
86. Bernuz M, Porras JC, Egri N, et al. Rapid diagnostic test for assessment of cellular immune response in a viral infection as a model. Sens Actuators B Chem 2024;417:136185.
87. Li C, Wu Y, Wang Y, et al. Recent advances in the detection of various biomarkers by lateral flow immunoassay: from hazardous substances to in vitro diagnosis. Coord Chem Rev 2025;545:217037.
88. Walker DM, Smith WA, Gale L, et al. CoMIT: a bioinformatic pipeline for risk-based prediction of COVID-19 test inclusivity. BMC Bioinformatics 2025;26:51.
89. Ardito L, Coccia M, Messeni Petruzzelli A. Technological exaptation and crisis management: evidence from COVID-19 outbreaks. Rd Manag 2021;51:381–92.
90. Coccia M. Pandemic prevention: lessons from COVID-19. Encyclopedia 2021;1:433–44.
91. Coccia M, Igor B. Effective health systems facing pandemic crisis: lessons from COVID-19 in Europe for next emergencies. Int J Health Gov 2024;29:89–111.
92. Plebani M, Cadamuro J, Vermeersch P, et al. A vision to the future: value-based laboratory medicine. Clin Chem Lab Med 2024;62:2373–87.
93. Coccia M. Sources, diffusion and prediction in COVID-19 pandemic: lessons learned to face next health emergency. AIMS Public Health 2023;10:145–68.
94. Chen J, Chou SY, Yu TH, et al. System dynamics analysis on the effectiveness of vaccination and social mobilization policies for COVID-19 in the United States. PLoS One 2022;17:e0268443.
95. Ershadi MM, Rise ZR. Uncertain SEIAR system dynamics modeling for improved community health management of respiratory virus diseases: a COVID-19 case study. Heliyon 2024;10:e24711.
96. Shin N, Kwag T, Park S, et al. Effects of operational decisions on the diffusion of epidemic disease: a system dynamics modeling of the MERS-CoV outbreak in South Korea. J Theor Biol 2017;421:39–50.
97. Vardavas R, de Lima PN, Baker L, et al. Modeling the disruptive Impact of the COVID-19 pandemic on nurses' supply and wages. Rand; 2024.
98. Hsieh Y, Chou Y. Modeling the impact of service innovation for small and medium enterprises: a system dynamics approach. Simul Model Pract Theory 2018;82:84–102.
99. Uriona M, Grobbelaar SS. Innovation system policy analysis through system dynamics modelling: a systematic review. Sci Polic 2019;46:28–44.
100. Maresova P. Impact of regulatory changes on innovations in the medical device industry comment on "Clinical decision support and new regulatory frameworks for medical devices: are we ready for it?: a viewpoint paper". Int J Health Policy Manag 2023;12:7262.
101. Samara E, Kilintzis P, Katsoras E, et al. A system dynamics approach for the development of a Regional Innovation System. J Innov Entrep 2024;13:26.
102. Nguyen LKN, McCabe H, Howick S, et al. Exploring the drivers of unsustainable pressures in health and social care: a qualitative system dynamics approach. Soc Sci Med 2025;371:117913.

phrp
OSONG PUBLIC HEALTH AND RESEARCH PERSPECTIVES

pISSN 2210-9099 eISSN 2233-6052
https://doi.org/10.24171/j.phrp.2025.0397
Osong Public Health Res Perspect 2026;17(1):50-60

Original Article

# Time-series decomposition and modeling of dengue cases in Malaysia, 2022–2024: a nationwide observational study

**Mohamad Afiq Amsyar Hamedin**[1], **Kamarul Imran Musa**[1], **Mohd Rahim Sulong**[2]

[1]Department of Community Medicine, School of Medical Science, Universiti Sains Malaysia, Kubang Kerian, Malaysia
[2]Disease Control Division, Ministry of Health Malaysia, Putrajaya, Malaysia

## ABSTRACT

**Objectives:** This study aimed to examine the temporal dynamics of dengue cases in Malaysia from 2022 to 2024 using seasonal-trend decomposition and time-series modeling.
**Methods:** Weekly dengue case counts from the national registry were analyzed across all states using seasonal-trend decomposition using LOESS (STL) to separate trend, seasonal, and irregular components. Autoregressive integrated moving average (ARIMA) and seasonal ARIMA (SARIMA) models were fitted to validate temporal structures, with model selection based on the Akaike information criterion (AIC), corrected AIC, and Bayesian information criterion. Diagnostic checks, including residual analysis and Ljung-Box testing, were performed to ensure model adequacy.
**Results:** Dengue incidence showed marked heterogeneity across states. STL decomposition indicated that long-term trends contributed more strongly to case dynamics than seasonality in most states, although seasonal influences were significant in the states of Kedah and Kelantan. Seasonal peak timing varied between states, highlighting differences in epidemic cycles. ARIMA and SARIMA modeling confirmed that no single temporal structure could adequately represent all states; while some series were well fitted by simple ARIMA models, others required seasonal adjustments. Residual diagnostics demonstrated that the selected models were statistically adequate.
**Conclusion:** Dengue dynamics in Malaysia are shaped by both trend and seasonal components, with considerable variation across states. Combining STL decomposition with ARIMA/SARIMA modeling strengthens the evidence base for state-specific forecasting and proactive vector control. Tailoring surveillance systems and interventions to local temporal patterns may improve early warning capacity and optimize resource allocation for dengue prevention.

**Keywords:** Dengue; Disease surveillance; Epidemiology; Malaysia; Time series analysis

**Received:** September 22, 2025
**Revised:** December 15, 2025
**Accepted:** December 18, 2025

Corresponding author:
Kamarul Imran Musa
Department of Community Medicine, School of Medical Science, Health Campus Universiti Sains Malaysia, 16150, Kubang Kerian, Kelantan, Malaysia
E-mail: drkamarul@usm.my

The opinions expressed by authors contributing to this journal do not necessarily reflect the opinions of the Korea Disease Control and Prevention Agency and Korea National Institute of Health.

© 2026 Korea Disease Control and Prevention Agency.
This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

## Introduction

Dengue fever is one of the most significant mosquito-borne viral infections worldwide, with an estimated 390 million infections occurring annually, of which nearly 96 million manifest clinically [1]. Over the past 2 decades, the global incidence of dengue has increased markedly, driven by rapid urbanization, globalization, climate variability, and the expanding geographic range of *Aedes aegypti* and *Aedes albopictus* mosquitoes [2,3]. The World Health Organization now regards dengue as one of the fastest-spreading arboviral diseases, with more than 100 countries reporting endemic transmission [4].

In Malaysia, dengue continues to pose a substantial public health burden, with recurrent epidemics occurring despite longstanding control efforts. Between 2015 and 2023, the country recorded hundreds of thousands of cases annually, and dengue remains a leading cause of morbidity and hospitalization, particularly in highly urbanized states such as Selangor, Johor, and the federal territories [5]. Multiple factors contribute to sustained dengue transmission, including unplanned urban growth, human mobility, rainfall-driven vector proliferation, and cyclical variations in population immunity [6,7]. The pronounced spatial and temporal heterogeneity of dengue across Malaysia underscores the importance of surveillance systems capable of capturing state-level dynamics, rather than relying solely on national aggregates.

Time-series methods have been widely applied in dengue research to characterize epidemic cycles, quantify seasonality, and forecast future outbreaks. Traditional approaches, including autoregressive integrated moving average (ARIMA) and seasonal ARIMA (SARIMA) models, remain among the most commonly used due to their interpretability and robustness for short-term forecasting [8]. For example, ARIMA/SARIMA models have been successfully applied in endemic settings such as Singapore, Thailand, and Brazil to predict dengue incidence with reasonable accuracy [9,10]. In recent years, hybrid approaches and machine learning models have increasingly been explored to enhance predictive performance [11,12]. However, despite their promise, many such studies focus on national-level summaries or single high-burden districts. This emphasis on aggregated data risks obscuring important state-level differences, where local climatic conditions, demographic structures, and vector ecology may shape dengue transmission in distinct ways [13].

To better understand these localized variations, decomposition approaches provide a valuable complement to classical time-series models. Seasonal-trend decomposition using LOESS (STL) is particularly useful because it separates observed data into trend, seasonal, and irregular components, thereby clarifying the relative contributions of long-term changes and recurrent cycles [14]. When combined with ARIMA/SARIMA modeling, STL enables a more comprehensive assessment of dengue dynamics by supporting both descriptive interpretation of temporal structure and predictive modeling of case counts.

This study therefore applied STL decomposition alongside ARIMA and SARIMA models to weekly dengue case data from Malaysia spanning 2022 to 2024. By examining both national- and state-level time series, the analysis seeks to capture heterogeneity in temporal patterns and to provide evidence supporting localized forecasting and vector control strategies. Such insights are essential for strengthening early warning systems and optimizing resource allocation in Malaysia's ongoing efforts to combat dengue.

### HIGHLIGHTS

- The study identified substantial heterogeneity in dengue dynamics across Malaysian states from 2022 to 2024.
- Long-term trends dominated overall patterns, while seasonal influences remained significant in certain states. The findings also revealed differing seasonal peak timings across states, indicating localized epidemic cycles.
- Autoregressive integrated moving average (ARIMA) and seasonal ARIMA models vary in suitability, with no single structure fitting all states.
- This research highlights the importance of state-specific forecasting and tailored vector control strategies for effective dengue prevention.

## Materials and Methods

### Study Design and Data Sources

This cross-sectional study utilized weekly dengue case counts for each state in Malaysia from January 1, 2022 to December 31, 2024, obtained from the Dengue Case Registry maintained by the Ministry of Health Malaysia. This registry systematically compiles all laboratory- and clinically confirmed dengue cases, providing a reliable data source for monitoring disease burden at the state level. Prior to analysis, the data were cleaned to remove duplicate records, correct inconsistencies, and assess the presence of missing values. Weekly case counts were then aggregated

to generate a continuous time series for each state.

## Study Area

This study was conducted in Malaysia, a country located in Southeast Asia with an approximate land area of 329,847 km². Malaysia comprises 13 states and 3 federal territories, which are further subdivided into a total of 160 administrative districts. Geographically, the nation is divided into Peninsular Malaysia, which borders Thailand, and East Malaysia, located on the island of Borneo. The country typically experiences a tropical rainforest climate, with environmental conditions influenced by 2 seasonal monsoons [15].

## Data Analysis

The temporal structure of dengue cases was first examined using STL, which decomposes a time series into 3 additive components:

$$Y_t = T_t + S_t + R_t,$$

where $Y_t$ represents the observed number of dengue cases at week t, $T_t$ reflects long-term changes, $S_t$ denotes the seasonal component representing recurrent cycles in transmission (e.g., monsoon-driven peaks), and $R_t$ is the irregular component capturing short-term fluctuations not explained by trend or seasonality [14]. STL decomposition was performed using the STL() function from the *feasts* package in R software [16]. The seasonal component was extracted using a periodic seasonal window (season (window="periodic")), which enforces stable annual seasonality across the series. All other STL parameters followed the default *feasts* implementation, including automatic LOESS span selection for trend extraction, standard low-pass filtering of the seasonal component, and iterative robustness updates to reduce the influence of outliers [14,17]. This approach ensured reproducibility and consistency across all state-level analyses.

ARIMA and SARIMA models were applied as linear Gaussian time-series approximations to weekly dengue case counts, an approach commonly used in epidemiological surveillance analyses when counts are sufficiently large to justify approximate normality assumptions [18]. Model identification followed a systematic diagnostic process. Prior to model estimation, stationarity and linearity properties of each time series were evaluated using the augmented Dickey-Fuller (ADF), Phillips-Perron (PP), and Kwiatkowski-Phillips-Schmidt-Shin (KPSS) tests for mean stationarity; Goldfeld-Quandt and Breusch-Pagan tests for variance stationarity; and Ramsey Regression Equation Specification Error Test (RESET), Terasvirta, and McLeod-Li tests to assess linearity and Autoregressive Conditional Heteroscedasticity (ARCH) effects [14]. Based on these diagnostics, appropriate differencing orders (d and D) or variance-stabilizing transformations were applied as needed. Parameter exploration was conducted using the auto.arima() algorithm from the *fable* package, which performs stepwise model selection across the ARIMA/SARIMA parameter space and evaluates competing models using the Akaike information criterion (AIC), AIC with finite-sample correction (AICc), and Bayesian information criterion (BIC). This procedure ensured a systematic and reproducible model search while maintaining transparency in the identification process [14]. The best-fitting model for each state was selected based on the lowest information criterion values. Given that the study period from 2022 to 2024 yielded a moderate number of weekly observations per state, the AICc was prioritized as the primary determinant of the optimal model. AICc adjusts for finite sample sizes and reduces the risk of overfitting associated with conventional AIC. BIC was used as a secondary reference to ensure that model parsimony was not compromised, as BIC applies a stronger penalty for model complexity. Final model selection therefore balanced goodness-of-fit, sample-size adjustment, and simplicity, with AICc serving as the principal selection metric [14].

To assess the adequacy of the fitted ARIMA/SARIMA models, post-estimation residual diagnostics were performed. Residual autocorrelation was evaluated using the Ljung-Box test, applied at 24 lags to capture short- and medium-term dependence in weekly data while avoiding the loss of statistical power associated with testing a full 52-week seasonal cycle. This choice aligns with methodological practice in weekly epidemiological time-series analyses, where approximately half-season windows provide a practical balance between sensitivity and parsimony. Residual autocorrelation was further examined through visual inspection of residual autocorrelation function (ACF) plots [14]. Homoscedasticity was assessed using the Breusch-Pagan test in conjunction with residual-versus-fitted value plots. Residual normality was evaluated using the Shapiro-Wilk test and supported by inspection of Q-Q plots to assess distributional shape. These diagnostic procedures were used as supplementary verification tools to determine whether key modeling assumptions were reasonably satisfied, rather than as formal proofs of model sufficiency [14].

All analyses were performed using R ver. 4.5.1 (R Foundation for Statistical Computing). Data wrangling and preprocessing were conducted using the *tidyverse* suite, and date handling


https://doi.org/10.24171/j.phrp.2025.0397

employed the *lubridate* package. STL decomposition was carried out using the *feasts* and *fabletools* packages, while ARIMA and SARIMA models were implemented using the *forecast* package. Visualization of decomposition results and model outputs was performed with *ggplot2* and arranged using *patchwork*.

### Ethics Statement

The research was conducted in accordance with the principles of the Declaration of Helsinki and received ethical clearance from the Human Research Ethics Committee of Universiti Sains Malaysia under approval code USM/JEPeM/KK/25010107. Additional approval was granted by the Malaysia Medical Research and Ethics Committee under the code NMRR ID-25-00144-OVW. This research was also supported by a Universiti Sains Malaysia Medical Research Grant 2025 (Project No: R501-LR-GPP001-0000002020-0000).

## Results

Figure 1 summarizes the monthly distribution of dengue cases in Malaysia from 2022 to 2024 and demonstrates clear temporal variability across states. Overall, most states exhibited distinct epidemic peaks in 2023, with the state of Selangor consistently recording the highest number of cases, surpassing 10,000 cases at its peak. Other states, including Johor, Sabah, and Terengganu, showed pronounced surges in mid-2023, whereas smaller states such as Perlis displayed lower case counts with less marked fluctuations. Seasonal recurrence of dengue cases was evident in nearly all states, with multiple peaks observed across the study period.

### STL Decomposition

The STL decomposition illustrated in Figure 2 quantified the relative contributions of trend and seasonality to dengue transmission dynamics for each state (Table 1). Seasonal strength values ranged from 0.27 in Sarawak, indicating weak seasonal influence, to 0.68 in Kelantan and Kedah, where seasonality played a more prominent role. In contrast, trend strength values were generally high across most states, exceeding 0.80 in Johor, Melaka, Selangor, and Perak, which suggests that long-term changes in transmission contributed more strongly to observed case counts than seasonal patterns. The timing of seasonal peaks and troughs varied between states, although many states exhibited recurrent peaks around mid-year. STL decomposition plots for all states are provided in Figure S1.

### ARIMA/SARIMA Models

Stationarity and linearity diagnostics were conducted prior to model estimation to verify that ARIMA and SARIMA assumptions were satisfied (Table S1). Mean stationarity

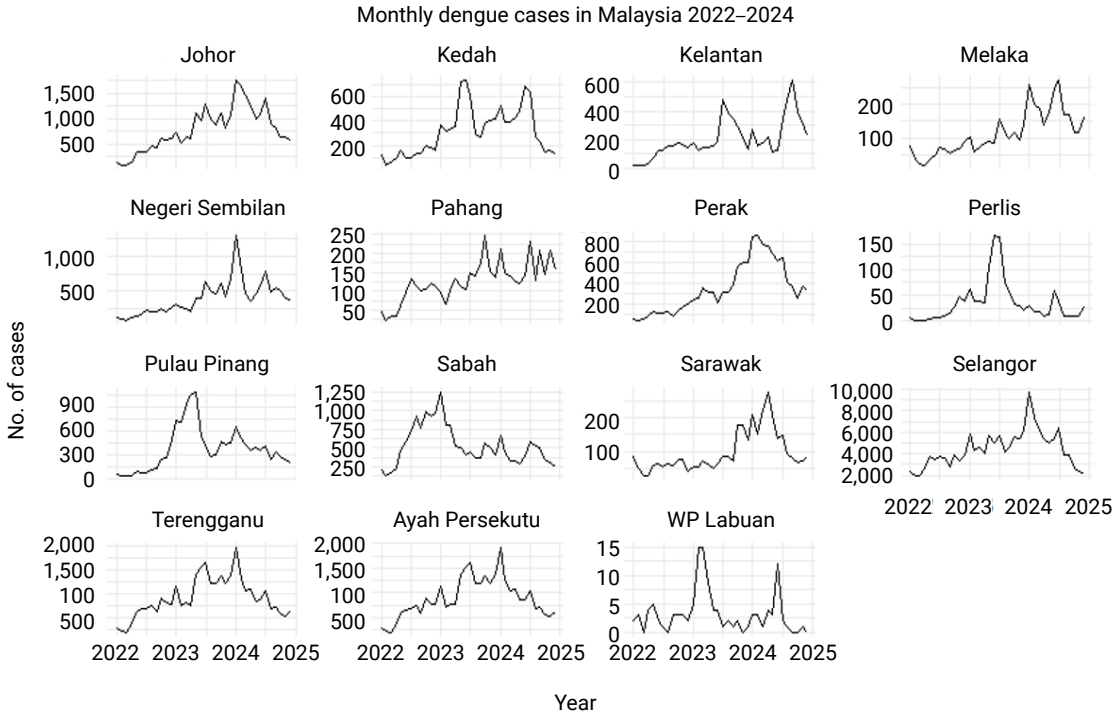



**Figure 1.** Monthly dengue cases for every state in Malaysia between 2022 and 2024.

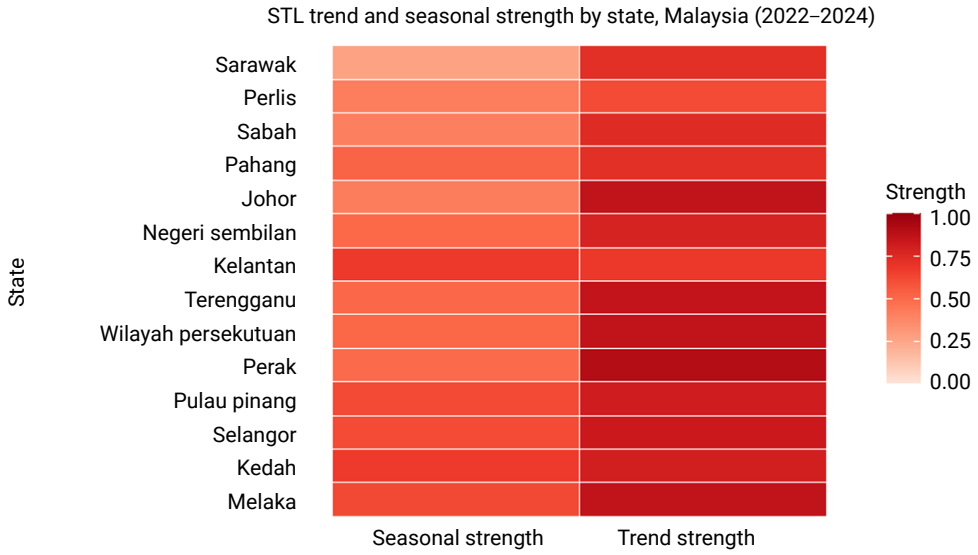



**Figure 2.** Heatmap of seasonal-trend decomposition using LOESS (STL) trend and seasonal strength values across Malaysian states (2022–2024). This figure displays the relative strength of the seasonal and trend components obtained from STL decomposition for each state. Darker shading represents higher component strength. The visualization highlights spatial heterogeneity in temporal drivers of dengue transmission across Malaysia.

**Table 1.** STL decomposition features of dengue cases by state in Malaysia

| State | Seasonal strength | Trend strength | Seasonal peak year | Seasonal trough year |
|---|---|---|---|---|
| Johor | 0.423 | 0.869 | 7 | 11 |
| Kedah | 0.672 | 0.805 | 6 | 9 |
| Kelantan | 0.679 | 0.684 | 9 | 5 |
| Melaka | 0.624 | 0.867 | 7 | 11 |
| Negeri Sembilan | 0.505 | 0.787 | 1 | 4 |
| Pahang | 0.523 | 0.725 | 7 | 2 |
| Perak | 0.497 | 0.908 | 1 | 9 |
| Perlis | 0.421 | 0.616 | 6 | 4 |
| Pulau Pinang | 0.619 | 0.813 | 1 | 8 |
| Sabah | 0.411 | 0.746 | 1 | 4 |
| Sarawak | 0.267 | 0.725 | 4 | 9 |
| Selangor | 0.618 | 0.835 | 1 | 11 |
| Terengganu | 0.507 | 0.862 | 1 | 3 |
| Wilayah Persekutuan | 0.509 | 0.866 | 1 | 3 |

STL, seasonal-trend decomposition using LOESS.

was assessed using the ADF, PP, and KPSS tests. The states of Johor, Melaka, Negeri Sembilan, Perak, Terengganu, and Wilayah Persekutuan demonstrated mean stationarity ($p < 0.05$ for ADF and PP tests and $p \geq 0.05$ for KPSS) and therefore did not require additional non-seasonal differencing ($d = 0$). Variance stationarity, evaluated using the Goldfeld-Quandt, Breusch-Pagan, Bartlett, and Levene tests, indicated heteroscedasticity in most states. Linearity diagnostics, including the Ramsey RESET, Terasvirta neural network, and McLeod-Li tests, detected significant nonlinearity or ARCH effects in the majority of states ($p < 0.05$), particularly those experiencing rapid epidemic fluctuations, such as Kelantan, Sabah, and Selangor. These findings supported the use of differencing and seasonal modeling to stabilize residual dynamics. Given the annual epidemiological cycle of dengue in Malaysia and the consistent seasonal components identified through STL decomposition, seasonal differencing ($D = 1$ with a 52-week seasonal period) was applied uniformly across all states. This adjustment is supported by strong STL seasonal strength values in several states, including Kelantan, Kedah, and Pulau Pinang, and ensures removal of yearly recurrence


https://doi.org/10.24171/j.phrp.2025.0397

in transmission patterns. Collectively, these diagnostic outcomes informed the differencing strategy, summarized as follows:

d=1 for 9 states with non-stationary mean
d=0 for the remaining 5 states, and
d=1 for all states due to consistent annual seasonal patterns identified in STL decomposition.

Post-differencing diagnostics demonstrated that ADF and PP tests were significant for all states ($p=0.01$), confirming mean stationarity after differencing (Table S2). KPSS tests were non-significant ($p=0.10$) across all states, further supporting stationarity. No ARCH effects were detected, indicating stable residual variance and no requirement for GARCH-type model extensions. Overall, these findings confirm that the selected differencing orders were appropriate and that all state-level series satisfied the assumptions required for SARIMA modeling. The non-seasonal differencing order (d), seasonal differencing order (D), and post-differencing stationarity diagnostics are summarized in Table 2.

Model selection using ARIMA and SARIMA approaches identified the most suitable specification for each state

**Table 2.** Differencing orders and stationarity diagnostic results for each Malaysian state

| State | d | D | ADF (*p*) | PP (*p*) | KPSS (*p*) |
|---|---|---|---|---|---|
| Johor | 0 | 1 | 0.01 | 0.01 | 0.1 |
| Kedah | 1 | 1 | 0.01 | 0.01 | 0.1 |
| Kelantan | 1 | 1 | 0.01 | 0.01 | 0.1 |
| Melaka | 0 | 1 | 0.01 | 0.01 | 0.1 |
| Negeri Sembilan | 1 | 1 | 0.01 | 0.01 | 0.1 |
| Pahang | 1 | 1 | 0.01 | 0.01 | 0.1 |
| Perak | 0 | 1 | 0.01 | 0.01 | 0.1 |
| Perlis | 1 | 1 | 0.01 | 0.01 | 0.1 |
| Pulau Pinang | 1 | 1 | 0.01 | 0.01 | 0.1 |
| Sabah | 1 | 1 | 0.01 | 0.01 | 0.1 |
| Sarawak | 1 | 1 | 0.01 | 0.01 | 0.1 |
| Selangor | 1 | 1 | 0.01 | 0.01 | 0.1 |
| Terengganu | 1 | 1 | 0.01 | 0.01 | 0.1 |
| Wilayah Persekutuan | 0 | 1 | 0.01 | 0.01 | 0.1 |

Values represent *p*-values for each test after differencing, confirming that the final transformed series meets SARIMA model assumptions.
ADF, augmented Dickey-Fuller; PP, Phillips-Perron; KPSS, Kwiatkowski-Phillips-Schmidt-Shin; ARIMA, autoregressive integrated moving average; SARIMA, seasonal ARIMA.

**Table 3.** SARIMA/ARIMA model Summary to represent temporality of dengue cases by state in Malaysia

| State | SARIMA/ARIMA order | AIC | AICc | BIC |
|---|---|---|---|---|
| Johor | ARIMA(0,0,1) | 497.18 | 497.7 | 502.92 |
| Kedah | ARIMA(0,1,1) | 382.01 | 382.27 | 385.79 |
| Kelantan | ARIMA(0,1,1)(0,0,1) (s=7) | 339.08 | 339.62 | 344.76 |
| Melaka | ARIMA(0,0,0) | 309.41 | 309.69 | 313.07 |
| Negeri Sembilan | ARIMA(0,0,0) | 441.3 | 441.56 | 445.09 |
| Pahang | ARIMA(0,0,0)(1,0,0) (s=7) | 356.54 | 357.07 | 362.28 |
| Perak | ARIMA(0,0,0) | 426.9 | 427.15 | 430.72 |
| Perlis | ARIMA(1,0,0) | 248.92 | 249.84 | 253.12 |
| Pulau Pinang | ARIMA(0,0,0) | 379.8 | 380.07 | 383.54 |
| Sabah | ARIMA(1,0,0) | 418.52 | 419.03 | 424.31 |
| Sarawak | ARIMA(0,1,0) | 281.65 | 282.98 | 291.31 |
| Selangor | ARIMA(0,1,1) | 625.29 | 625.54 | 629.11 |
| Terengganu | ARIMA(0,0,0) | 583.47 | 583.75 | 587.17 |
| Wilayah Persekutuan | ARIMA(0,1,1) | 443.46 | 443.73 | 447.2 |

ARIMA, autoregressive integrated moving average; SARIMA, seasonal ARIMA; AIC, Akaike information criterion; AICc, AIC with finite-sample correction; BIC, Bayesian information criterion.

based on AIC, AICc, and BIC values, as summarized in Table 3. Residual diagnostics revealed departures from ideal distributional assumptions in several states. Shapiro-Wilk tests indicated statistically significant deviations from residual normality, and Breusch-Pagan tests identified evidence of heteroscedasticity in some states (Table S3). Inspection of Q-Q plots Figure S2 demonstrated mild tail departures from normality. Importantly, residual independence was preserved across all fitted models. Ljung-Box tests at lag 24 showed no significant residual autocorrelation (Table 4), and residual ACF plots confirmed white-noise behavior across all states Figure S3, indicating that the ARIMA/SARIMA models adequately captured the temporal dependence structure of dengue incidence. Although residual non-normality and heteroscedasticity may affect the precision of prediction intervals, these features are commonly observed in infectious disease surveillance time series and do not invalidate model consistency or short-term forecasting performance. Accordingly, forecast uncertainty should be interpreted with appropriate caution in states exhibiting greater residual variability.

## Discussion

This study provides a state-level temporal analysis of dengue incidence in Malaysia from 2022 to 2024, revealing pronounced heterogeneity in transmission dynamics across states. Seasonal-Trend decomposition using STL demonstrated that both long-term trends and seasonal fluctuations contributed to observed dengue patterns, although the relative influence of these components varied substantially between states.

Most states exhibited high trend strength values (> 0.80), indicating that sustained structural determinants such as urbanization, demographic growth, and vector ecological adaptation exerted greater influence on dengue dynamics than short-term seasonal drivers. For example, Johor, Melaka, Perak, and Selangor all demonstrated strong trend dominance, consistent with prior studies showing that long-term environmental change and urban expansion increasingly shape dengue risk across Malaysia and Southeast Asia [13,15,19].

In contrast, states such as Kelantan displayed strong seasonal signatures, with seasonal strength values reaching 0.68. This state exhibited recurrent epidemic peaks during specific months, particularly around mid-year, consistent with rainfall-driven mosquito breeding cycles associated with the southwest monsoon [20–22]. In Kelantan, for instance, seasonal peaks were most prominent during the third quarter of each year, with troughs occurring earlier in the year. Such seasonal cycles echo findings from Thailand and Vietnam, where rainfall and temperature seasonality remain critical triggers for epidemic onset [23,24].

The weak seasonality observed in the Borneo region (Sabah and Sarawak) provides a contrasting pattern. In these states, dengue incidence was less tightly linked to seasonal climatic cycles and more influenced by gradual long-term increases. This pattern suggests that factors such as population mobility, land-use change, or sustained vector adaptation may play stronger roles than short-term rainfall variability. Studies from the Borneo region and eastern Indonesia have similarly documented weaker

**Table 4.** Model validity parameters using the Ljung-Box test

| State | SARIMA/ARIMA model | Ljung-Box statistic | Lower 95% CI | Upper 95% CI | *p* |
|---|---|---|---|---|---|
| Wilayah Persekutuan | ARIMA(0,1,1) | 38.45 | 12.40 | 39.36 | 0.051 |
| Terengganu | ARIMA(0,0,0) | 23.40 | 12.40 | 39.36 | 0.496 |
| Pulau Pinang | ARIMA(0,0,0) | 22.83 | 12.40 | 39.36 | 0.530 |
| Sabah | ARIMA(1,0,0) | 20.66 | 12.40 | 39.36 | 0.658 |
| Sarawak | ARIMA(0,1,0) | 17.28 | 12.40 | 39.36 | 0.836 |
| Kedah | ARIMA(0,1,1) | 19.53 | 12.40 | 39.36 | 0.723 |
| Melaka | ARIMA(0,0,0) | 17.34 | 12.40 | 39.36 | 0.834 |
| Negeri Sembilan | ARIMA(0,0,0) | 17.22 | 12.40 | 39.36 | 0.839 |
| Selangor | ARIMA(0,1,1) | 17.09 | 12.40 | 39.36 | 0.845 |
| Johor | ARIMA(0,0,1) | 15.58 | 12.40 | 39.36 | 0.903 |
| Pahang | ARIMA(0,0,0)(1,0,0) [7] | 14.89 | 12.40 | 39.36 | 0.924 |
| Perlis | ARIMA(1,0,0) | 13.00 | 12.40 | 39.36 | 0.966 |
| Kelantan | ARIMA(0,1,1)(0,0,1) [7] | 11.21 | 12.40 | 39.36 | 0.987 |
| Perak | ARIMA(0,0,0) | 1.96 | 12.40 | 39.36 | > 0.900 |

ARIMA, autoregressive integrated moving average; SARIMA, seasonal ARIMA; CI, confidence interval.
*p* > 0.05 suggests residual autocorrelation absents and no “white noise”.



https://doi.org/10.24171/j.phrp.2025.0397

seasonal dependence, reflecting ecological differences in forested and peri-urban environments [25–27]. Taken together, the STL results emphasize that while dengue dynamics in Malaysia are broadly trend-dominated, seasonal cycles continue to exert strong influence in a subset of states. This variability reinforces the need for locally tailored early warning systems that integrate both long-term and seasonal signals.

ARIMA and SARIMA modeling provided further insight into the temporal complexity of dengue transmission across Malaysian states. Model selection indicated that no single model structure was adequate for all states, confirming that dengue dynamics in Malaysia cannot be represented within a single temporal framework. The observed variation in optimal model structures likely reflects underlying environmental, demographic, and epidemiological heterogeneity across regions. States such as Kelantan (seasonal strength = 0.679) and Pahang (0.523) demonstrated strong recurring annual cycles, with dengue case peaks typically occurring between June and September. These peak periods coincide with Malaysia's inter-monsoon transition, which is characterized by intermittent rainfall, reduced water flushing, and warmer temperatures that collectively enhance Aedes breeding productivity [28]. In contrast to heavy rainfall during major monsoon seasons, which can wash away larvae and disrupt breeding habitats, inter-monsoon conditions promote the persistence of clean, stagnant water environments that favor *A. aegypti* proliferation and viral transmission [19,21,22]. This ecological mechanism supports the seasonal dependence detected in these states and justifies the inclusion of SARIMA terms in the optimal models—Kelantan: ARIMA(0,1,1)(0,0,1)(s = 7) and Pahang: ARIMA(0,0,0)(1,0,0) (s = 7) These findings align with previous studies in Malaysia demonstrating dengue amplification during inter-monsoon periods, reflecting predictable rainfall–breeding dynamics that sustain annual dengue resurgence [21,28].

Conversely, highly urbanized states such as Johor, Penang, and Selangor, despite recording high dengue case burdens, demonstrated weaker seasonal structuring. Continuous human mobility, extensive built environments, and relatively stable microclimatic conditions in dense urban settings reduce the dependence of Aedes proliferation on seasonal rainfall cycles, thereby attenuating predictable intra-annual fluctuations [28,29]. Consequently, dengue transmission in these states may be sustained year-round through persistent artificial breeding sites, including water storage containers, construction areas, and drainage systems, as well as uninterrupted mosquito–human contact [2,9]. This epidemiological profile supports the selection of non-SARIMA models for these settings.

Several states were best represented by highly parsimonious non-seasonal models, including ARIMA(0,0,0) for Melaka, Perak, Penang, and Terengganu. These simple model structures suggest that short-term dengue variability in these states is dominated by irregular fluctuations rather than persistent autocorrelation or strong seasonal cycles. Importantly, such models do not imply an absence of epidemiological drivers but instead reflect relatively weak temporal structure in the weekly surveillance data after differencing. In contrast, states with stronger seasonal or autocorrelated dynamics required more complex ARIMA or SARIMA specifications, underscoring heterogeneity in temporal dependence across Malaysia. While parsimony yielded the lowest information criterion values in the present analysis, future research incorporating cross-validation or out-of-sample predictive assessments would be valuable for evaluating the robustness and forecasting stability of these simpler models.

These findings mirror evidence from other Asian settings in which substantial subnational variability limits the applicability of a single forecasting framework and underscores the need for localized modeling approaches [30,31]. Although ARIMA and SARIMA models provide robust representations of historical temporal patterns and perform well for short-term forecasting, their reliance on past observations constrains predictive performance under conditions of abrupt structural change, such as climate anomalies or major public health interventions. In addition, prediction intervals derived from ARIMA/SARIMA models should be interpreted as approximate, particularly in states exhibiting greater residual variance, as uncertainty may not be fully captured by univariate specifications. Although extensive diagnostic procedures were conducted, these checks are intended to support model adequacy rather than to establish sufficiency, and the findings should therefore be interpreted in light of the known limitations of linear time-series models applied to surveillance data. Consequently, while these models remain valuable tools for near-term surveillance and planning, they should be complemented by integrated modeling approaches that incorporate climatic, entomological, and mobility-related covariates to improve outbreak prediction and uncertainty characterization [32].

This study advances dengue surveillance research in Malaysia by combining STL decomposition with ARIMA/SARIMA modeling to jointly characterize long-term trends and seasonal cycles, and by analyzing all 14 states individually to capture granular heterogeneity that is often obscured in national-level analyses. These state-specific insights can inform more targeted intervention strategies.

For example, states with pronounced seasonal peaks, such as Kelantan and Pahang, may benefit from strengthened vector control measures implemented ahead of predictable surges, whereas states characterized by year-round transmission may require sustained, structurally oriented vector management and urban sanitation efforts.

Nevertheless, several limitations should be acknowledged. Dengue case notifications may be affected by underreporting and diagnostic misclassification [33]. In addition, the models applied were univariate and did not incorporate climatic, entomological, or sociodemographic covariates known to influence dengue transmission. Previous studies have demonstrated that rainfall, temperature, humidity, vector indices, and population dynamics strongly shape dengue patterns in Malaysia and across the region [2,6]. The ARIMA/SARIMA framework adopted in this study assumes linearity and approximately Gaussian errors and therefore represents a statistical approximation when applied to count-based dengue surveillance data. While this approach is widely used to model temporal dependence and support short-term forecasting in settings with moderate to high case counts, it may not fully capture the mean–variance relationships intrinsic to count processes [34]. Future research should therefore explore variance-adaptive and count-based modeling approaches, including Poisson or negative binomial time-series models, generalized linear autoregressive models, or Bayesian state-space frameworks, which may better accommodate overdispersion and nonlinearity in dengue transmission dynamics.

Despite these limitations, the findings have important practical implications for dengue surveillance and control. STL-derived seasonal signatures and ARIMA/SARIMA-based forecasts can be integrated into operational decision-support systems and automated early warning dashboards to trigger alerts when observed or projected case counts exceed expected thresholds. Such systems could facilitate the timely mobilization of vector control resources, hospital preparedness, and targeted community engagement ahead of anticipated transmission peaks. Embedding these analytical tools within district- and state-level surveillance infrastructure would further support more proactive, data-driven dengue control strategies across Malaysia.

## Conclusion

This study highlights substantial heterogeneity in dengue dynamics across Malaysian states between 2022 and 2024. STL decomposition revealed that while long-term trends dominated overall patterns, seasonal influences remained significant in certain states, underscoring the value of localized temporal analyses. ARIMA and SARIMA modeling further confirmed that no single temporal structure adequately represents dengue dynamics across all states. Together, these complementary approaches strengthen the evidence base for state-specific forecasting systems and proactive vector control strategies in Malaysia. Importantly, tailoring surveillance and intervention efforts to local temporal dynamics has the potential to enhance early warning capacity, optimize resource allocation, and improve dengue prevention outcomes nationwide.

## Supplementary Material

**Figure S1.** Seasonal-trend decomposition using LOESS (STL) decomposition plot for every state; **Figure S2.** Q-Q plots of ARIMA/SARIMA residuals by state; **Figure S3.** Residual diagnostic for SARIMA/ARIMA models for every state (ACF and histogram); **Table S1.** Stationarity and linearity diagnostics for weekly dengue case series by state, Malaysia (2022–2024); **Table S2.** Post-differencing diagnostic test results for weekly dengue case series by state, Malaysia (2022–2024); **Table S3.** Residual diagnostic tests for ARIMA/SARIMA models by state. Supplementary data are available at https://doi.org/10.24171/j.phrp.2025.0397.

## Notes

### Ethics Approval

The research was conducted in accordance with the Declaration of Helsinki guidelines and received ethical clearance from the Human Research Ethics Committee of Universiti Sains Malaysia, under the approval code USM/JEPeM/KK/25010107. Additionally, the Malaysia Medical Research and Ethics Committee granted approval under the code NMRR ID-25-00144-OVW. Due to the retrospective nature of the study, the requirement for informed consent was waived.

### Conflicts of Interest

The authors have no conflicts of interest to declare.

### Funding

The research was conducted in accordance with the Declaration of Helsinki guidelines and received ethical clearance from the Human Research Ethics Committee of Universiti Sains Malaysia, under the approval code USM/JEPeM/KK/25010107. Additionally, the Malaysia Medical Research and Ethics Committee granted approval under the code NMRR ID-25-00144-OVW. This research also was supported by a Universiti Sains Malaysia, Medical Research Grant 2025 with Project No: R501-LR-GPP001-0000002020-0000.

### Availability of Data

The datasets are not publicly available but can be obtained from the corresponding author upon reasonable request.

### Authors' Contributions

Conceptualization: all authors; Data curation: all authors; Formal

analysis: MAAH, KIM Methodology: all authors; Project administration: MAAH, KIM; Resources: all authors; Visualization: all authors; Writing–original draft: MAAH; Writing–review & editing: all authors. All authors read and approved the final manuscript.

## References

1. Bhatt S, Gething PW, Brady OJ, et al. The global distribution and burden of dengue. Nature 2013;496:504–7.
2. Kraemer MU, Reiner RC, Brady OJ, et al. Past and future spread of the arbovirus vectors Aedes aegypti and Aedes albopictus. Nat Microbiol 2019;4:854–63.
3. Messina JP, Brady OJ, Golding N, et al. The current and future global distribution and population at risk of dengue. Nat Microbiol 2019; 4:1508–15.
4. World Health Organization (WHO) (CH). Dengue and severe dengue [Internet]. WHO; 2022 [cited 2025 Sep 21]. Available from: https://www.who.int/news-room/fact-sheets/detail/dengue-and-severe-dengue.
5. Li Z, Gurgel H, Dessay N, et al. Semi-supervised text classification framework: an overview of dengue landscape factors and satellite Earth observation. Int J Environ Res Public Health 2020;17:4509.
6. Cheong YL, Leitao PJ, Lakes T. Assessment of land use factors associated with dengue cases in Malaysia using boosted regression trees. Spat Spatiotemporal Epidemiol 2014;10:75–84.
7. Hii YL, Zhu H, Ng N, et al. Forecast of dengue incidence using temperature and rainfall. PLoS Negl Trop Dis 2012;6:e1908.
8. Hasan P, Khan TD, Alam I, et al. Dengue in tomorrow: predictive insights from ARIMA and SARIMA models in Bangladesh: a time series analysis. Health Sci Rep 2024;7:e70276.
9. Racloz V, Ramsey R, Tong S, et al. Surveillance of dengue fever virus: a review of epidemiological models and early warning systems. PLoS Negl Trop Dis 2012;6:e1648.
10. Ezanno P, Andraud M, Beaunee G, et al. How mechanistic modelling supports decision making for the control of enzootic infectious diseases. Epidemics 2020;32:100398.
11. Ho TS, Weng TC, Wang JD, et al. Comparing machine learning with case-control models to identify confirmed dengue cases. PLoS Negl Trop Dis 2020;14:e0008843.
12. Adde A, Roucou P, Mangeas M, et al. Predicting dengue fever outbreaks in French Guiana using climate indicators. PLoS Negl Trop Dis 2016;10:e0004681.
13. Zhu S, Niu L, Aamir M, et al. Spatial and seasonal variations in air-soil exchange, enantiomeric signatures and associated health risks of hexachlorocyclohexanes (HCHs) in a megacity Hangzhou in the Yangtze River Delta region, China. Sci Total Environ 2017;599-600:264–72.
14. Hyndman RJ, Athanasopoulos G. Forecasting: principles and practice. 3rd ed. OTexts; 2021.
15. Tang KH. Climate change in Malaysia: trends, contributors, impacts, mitigation and adaptations. Sci Total Environ 2019;650:1858–71.
16. Bandara K, Hyndman RJ, Bergmeir C. MSTL: A seasonal-trend decomposition algorithm for time series with multiple seasonal patterns. Int J Oper Res 2025;52:79–98.
17. Cleveland RB, Cleveland WS, McRae JE, et al. STL: a seasonal-trend decomposition. J Off Stat 1990;6:3–73.
18. Chen X, Moraga P. Assessing dengue forecasting methods: a comparative study of statistical models and machine learning techniques in Rio de Janeiro, Brazil. Trop Med Health 2025;53:52.
19. Abdul Hadi Z, Che Dom N, Ishak AR, et al. Geospatial dynamics of dengue fever density in Kuantan, Malaysia: GIS-based approach. Geogr Environ Sustain 2025;18:54–64.
20. Masrani AS, Nik Husain NR, Musa KI, et al. Prediction of dengue incidence in the Northeast Malaysia based on weather data using the generalized additive model. Biomed Res Int 2021;2021:3540964.
21. Singh S, Herng LC, Sulaiman LH, et al. The effects of meteorological factors on dengue cases in Malaysia. Int J Environ Res Public Health 2022;19:6449.
22. Masrani AS, Nik Husain NR, Musa KI, et al. Trends and spatial pattern analysis of dengue cases in Northeast Malaysia. J Prev Med Public Health 2022;55:80–7.
23. Louis VR, Phalkey R, Horstick O, et al. Modeling tools for dengue risk mapping: a systematic review. Int J Health Geogr 2014;13:50.
24. Suphanchaimat R, Thammavijaya P, Taweewigyakarn P, et al. Systemic investigation of dengue incidence and control measures in Surin, Thailand, 2018. Outbreak Surveill Investig Response OSIR J 2019;12:15–23.
25. Kunasagran PD, Rahim A, Syed SS, et al. Spatio-temporal analysis of dengue cases in Sabah. Malays J Med Heal Sci 2023;19:88–94.
26. Murphy A, Rajahram GS, Jilip J, et al. Incidence and epidemiological features of dengue in Sabah, Malaysia. PLoS Negl Trop Dis 2020;14: e0007504.
27. Sasmono RT, Santoso MS, Pamai YW, et al. Distinct dengue disease epidemiology, clinical, and diagnosis features in Western, Central, and Eastern regions of Indonesia, 2017-2019. Front Med (Lausanne) 2020;7:582235.
28. Cheong YL, Burkart K, Leitao PJ, et al. Assessing weather effects on dengue disease in Malaysia. Int J Environ Res Public Health 2013;10:6319–34.
29. Abdullah NAMH, Dom NC, Salleh SA, et al. Dengue's climate conundrum: how vegetation and temperature shape mosquito populations and disease outbreaks. BMC Public Health 2025;25:4.
30. Alam KE, Ahmed MJ, Chalise R, et al. Time series analysis of dengue incidence and its association with meteorological risk factors in Bangladesh. PLoS One 2025;20:e0323238.
31. Zhao X, Li K, Ang CK, et al. A deep learning based hybrid architecture for weekly dengue incidences forecasting. Chaos Solitons 2023;168: 113170.
32. Lowe R, Gasparrini A, Van Meerbeeck CJ, et al. Nonlinear and delayed impacts of climate on dengue risk in Barbados: a modelling study. PLoS Med 2018;15:e1002613.

33. Shepard DS, Undurraga EA, Halasa YA, et al. The global economic burden of dengue: a systematic analysis. Lancet Infect Dis 2016; 16:935–41.
34. Mills C, Falconi-Agapito F, Carrera JP, et al. Multi-model approach to understand and predict past and future dengue epidemic dynamics. R Soc Open Sci 2025;12:241870.


https://doi.org/10.24171/j.phrp.2025.0397

phrp
OSONG PUBLIC HEALTH AND RESEARCH PERSPECTIVES

pISSN 2210-9099 eISSN 2233-6052
https://doi.org/10.24171/j.phrp.2025.0467
Osong Public Health Res Perspect 2026;17(1):61-71

**Original Article**

# A multi-city outbreak of *Salmonella* Enteritidis infections linked to bakery products, Republic of Korea

**Da Seul Kim[1], Soon-Young Seo[1], Dong Hwi Kim[1], Yeon Hee Woo[1], Deborah Lee[1], Se Jeong Yang[1], Junyoung Kim[2], Eunkyung Shin[2], Byungsun Jung[3], Eunmi Lee[3], Min Jung Lee[4], Young-Joon Park[5]**

[1]Division of Infectious Disease Control, Korea Disease Control and Prevention Agency, Cheongju, Republic of Korea
[2]Division of Bacterial Disease Control, Korea Disease Control and Prevention Agency, Cheongju, Republic of Korea
[3]Foodborne Disease Prevention and Surveillance Division, Ministry of Food and Drug Safety, Cheongju, Republic of Korea
[4]Food Microbiology Division, Ministry of Food and Drug Safety, Cheongju, Republic of Korea
[5]Division of Emergency Preparedness and Response, Korea Disease Control and Prevention Agency, Cheongju, Republic of Korea

## ABSTRACT

**Objectives:** In May 2025, clusters of salmonellosis were identified in 7 cities in the Republic of Korea, all associated with consumption of identical bakery products. This investigation aimed to characterize the outbreak, identify potential contributing factors, and inform strategies for preventing similar multi-facility foodborne outbreaks.

**Methods:** A case series study was conducted among individuals who consumed Manufacturer H's Product I and Product II on May 15–16, 2025 at 7 facilities ($n$=1,235). Clinical specimens from symptomatic individuals, retained food samples, and environmental samples were collected and tested. Food-exposure histories were assessed, and active case finding was implemented across all supplied facilities. Traceback investigations were conducted at the manufacturer, distributor, and egg farms. Human and food isolates underwent pulsed-field gel electrophoresis (PFGE) and whole-genome sequencing (WGS).

**Results:** A total of 323 cases met the outbreak case definition (attack rate, 26.2%), of which 48 were laboratory-confirmed. *Salmonella* Enteritidis was isolated from both clinical specimens and retained bakery products. PFGE patterns were indistinguishable between human and food isolates, and WGS demonstrated high genetic relatedness. These findings confirmed a common-source outbreak linked to the implicated bakery products.

**Conclusion:** This outbreak underscores the value of integrating epidemiological investigation, active case finding, and molecular typing to identify common food vehicles in outbreaks involving widely distributed manufactured foods. Coordinated collaboration between public health and food safety authorities is essential for the effective detection, response, and prevention of multi-facility foodborne outbreaks.

**Keywords:** Disease outbreaks; Epidemiology; *Salmonella* Enteritidis

**Received:** October 23, 2025
**Revised:** December 30, 2025
**Accepted:** January 4, 2026

Corresponding author:
Young-Joon Park
Division of Emergency Preparedness and Response, Korea Disease Control and Prevention Agency, 187 Osongsaengmyeong 2-ro, Osong-eup, Heungdeok-gu, Cheongju 28159, Republic of Korea
E-mail: pahmun@korea.kr

The opinions expressed by authors contributing to this journal do not necessarily reflect the opinions of the Korea Disease Control and Prevention Agency and Korea National Institute of Health.

© 2026 Korea Disease Control and Prevention Agency.
This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

## Introduction

Salmonellosis caused by non-typhoidal *Salmonella* (NTS) is an acute gastroenteritis of global public health concern. *Salmonella* is a Gram-negative, rod-shaped bacterium belonging to the Enterobacteriaceae family [1]. Based on O, H, and Vi antigens, *Salmonella* is classified into 6 subspecies and over 2,500 serotypes, approximately 10% of which are associated with human infection [1,2]. *Salmonella* spp. primarily reside in domestic and wild animals, including poultry, swine, and cattle. Most human infections are foodborne and originate from contaminated animal products; secondary transmission occurs through contaminated water, fresh produce, or direct contact. Typical symptoms of salmonellosis include watery diarrhea, abdominal pain, fever, headache, nausea, and vomiting. The incubation period is typically 6–72 hours but can occasionally extend up to 16 days [3–7].

Globally, NTS is a leading cause of diarrheal disease. The Centers for Disease Control and Prevention estimates that NTS causes approximately 1.35 million infections annually in the United States, most of which are attributable to foodborne transmission [4]. In the Republic of Korea, *Salmonella* is designated as a notifiable infectious disease and is monitored through a nationwide sentinel surveillance system managed by the Korea Disease Control and Prevention Agency (KDCA) [3]. *Salmonella* is among the most frequently reported bacterial agents of water- and foodborne outbreaks, with approximately 3,000 cases of salmonellosis reported annually [8,9]. Incidence generally increases during the hot, humid summer months [1,4], and common vehicles include mixed dishes (e.g., *gimbap*) and egg products [10]. When a cluster of salmonellosis is suspected, local governments initiate a comprehensive epidemiological investigation. This mandated process involves patient interviews, environmental assessments, and the collection of human, retained food, and environmental specimens for laboratory testing [3]. This framework enables a rapid public health response to prevent further disease spread.

Among *Salmonella* serotypes, *Salmonella* Enteritidis is the most frequently isolated serotype worldwide and in the Republic of Korea, largely due to its strong association with egg-laying poultry [11–13]. Although localized outbreaks linked to single food establishments are common, large-scale, multi-city outbreaks involving complex manufactured foods, such as bakery products, pose unique challenges for public health authorities [14–19]. In such outbreaks, prompt and accurate identification of the contaminated source, along with precise characterization of transmission pathways using integrated epidemiological and laboratory data, is essential for effective control and prevention [20].

### HIGHLIGHTS

- This study investigated a multi-city outbreak of *Salmonella* Enteritidis associated with commercially manufactured bakery products in the Republic of Korea.
- An integrated epidemiological investigation combined with active case finding and molecular typing was conducted to identify the common food vehicle and transmission pathway.
- Genomic analyses using pulsed-field gel electrophoresis and whole-genome sequencing provided strong evidence linking clinical cases to contaminated bakery products.
- The findings demonstrate the value of coordinated public health and food safety responses supported by laboratory-based surveillance in managing complex foodborne outbreaks.

On May 21, 2025, two initial clusters of diarrheal illness were identified at 2 facilities located in separate cities in Chungcheongbuk-do. In response, local governments, a regional office of the Ministry of Food and Drug Safety (MFDS), and the provincial office of education initiated an epidemiological investigation. On May 22, MFDS identified a shared exposure to bakery products from the same manufacturer and proactively requested a temporary suspension of distribution and sales to prevent further spread. On June 2, cultures of patient specimens and retained food samples from both initial facilities yielded *Salmonella* of the same serotype. The KDCA subsequently classified the events as a common-source outbreak and identified 2 additional facilities that had consumed the same products, bringing the total to 4. Active case finding across all recipient facilities later identified 3 additional symptomatic clusters, resulting in a total of 7 affected facilities. This event represents a significant multi-city foodborne outbreak linked to a complex manufactured food item in the Republic of Korea.

Therefore, the KDCA conducted an extensive epidemiological investigation and laboratory analysis. The objective of this study was to characterize the multi-city outbreak of *S.* Enteritidis infections linked to bakery products, identify the specific food source and transmission route through the integration of epidemiological and laboratory findings, and provide critical insights for the prevention and control



https://doi.org/10.24171/j.phrp.2025.0467

of future complex foodborne outbreaks in the Republic of Korea.

## Materials and Methods

### Study Population

The study population comprised symptomatic individuals who developed illness after consuming the suspected bakery products, namely Product I (use-by October 12, 2025) and II (use-by September 21, 2025), produced by Manufacturer H. Among 250 facilities supplied with these bakery items, 7 facilities reported symptomatic individuals ($n$=1,811) who experienced symptoms such as diarrhea, vomiting, or abdominal pain, or who received a clinical diagnosis of *Salmonella* infection. Public health center staff in the 7 affected cities conducted food-consumption (exposure) surveys. Among 1,596 respondents, duplicate responses, individuals who were absent on the serving date or did not consume the bakery items, and individuals whose symptom onset preceded product consumption were excluded. The final analytic cohort comprised 1,235 persons.

To identify additional clusters, the presence of symptomatic persons in the remaining 246 facilities was verified, excluding the 4 Facilities (A–D) already reported in the KDCA outbreak reporting system. In parallel, among 282 waterborne and foodborne outbreak reports submitted between January and May 2025, eight events with pulsed-field gel electrophoresis (PFGE) patterns matching those of the present outbreak were reviewed to assess whether the implicated bakery items had been consumed.

To evaluate potential contamination points along the production–distribution chain, inspections were conducted at 2 manufacturing sites, including the bakery and the liquid egg–processing facility, as well as at the distributor and supplying egg farms (Figure 1).

### Case Definition

A case was defined as an individual from a facility that served either of the 2 bakery products on May 15–16, 2025, who developed illness within the maximum incubation period for *Salmonella* infection after consumption and met one or more of the following criteria: (1) ≥3 episodes of diarrhea within 24 hours; (2) ≥2 episodes of diarrhea within 24 hours accompanied by fever or abdominal pain; (3) ≥1 episode of vomiting.

In addition, any individual in whom *Salmonella* was detected by rectal swab or stool culture was included as a case regardless of symptoms.

### Data Collection

Local public health centers administered questionnaires adapted from national guidelines. For each facility, food histories were obtained for the 3-day period preceding the first symptomatic case or the documented serving date of the implicated products. The scope of data collection varied by facility: in Facilities E–G, questionnaires focused specifically on the implicated bakery items, whereas in Facilities D and G, surveys were limited to symptomatic persons only.

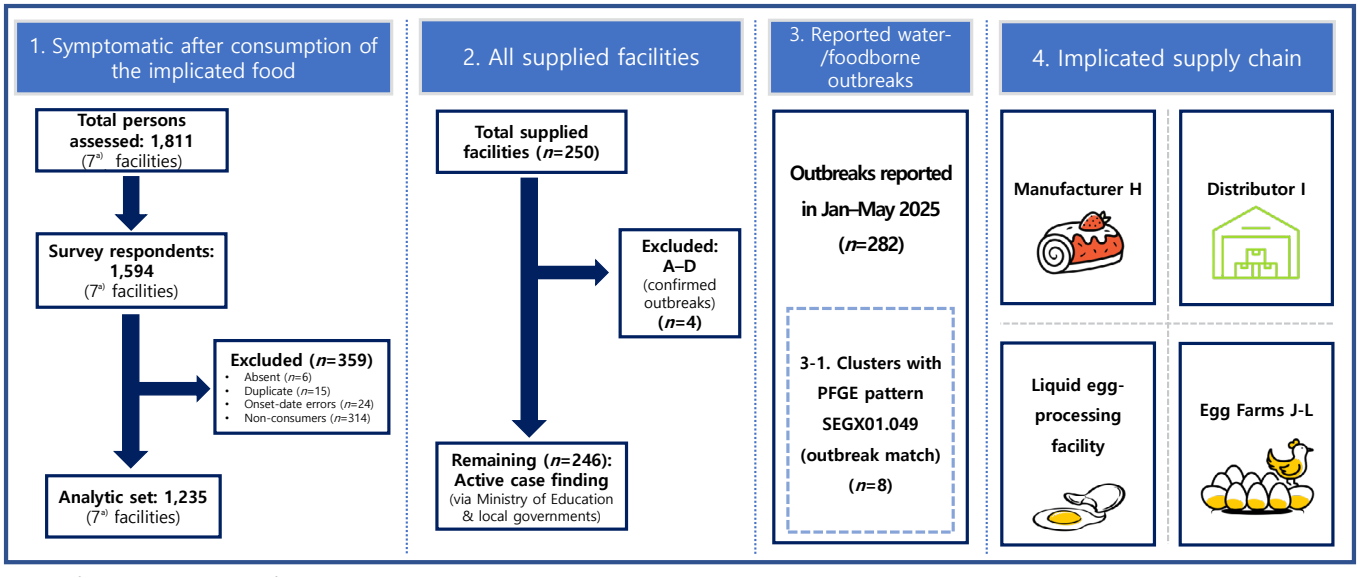



**Figure 1.** Subjects of multi-city outbreak of *Salmonella* Enteritidis. [a]Seven facilities including three identified through active surveillance.

## Study Design

Multiple lines of evidence supported the identification of a common-source outbreak, including shared consumption of identical bakery products among affected individuals, appropriate temporality between product consumption and illness onset, and laboratory confirmation of an identical *Salmonella* serotype in both patient specimens and retained food samples. Based on these converging findings, a descriptive case series was conducted to summarize clinical features, incubation periods, and epidemic curves among reported cases.

## Active Case Finding

A line list of 250 recipient facilities supplied by Distributor I with the implicated bakery products was obtained. Excluding the 4 Facilities (A–D) already reported to the KDCA outbreak reporting system, active case finding was conducted in the remaining 246 facilities to identify additional outbreaks. Case-finding activities were coordinated through the Ministry of Education and local governments.

In parallel, 282 waterborne and foodborne outbreak reports submitted to the KDCA outbreak reporting system between January 1 and May 31, 2025, were reviewed, and the PulseNet Korea database was queried. Eight outbreaks with PFGE patterns indistinguishable from those of the initial 4 clusters were identified, and consumption of the implicated bakery products at those facilities was assessed.

## Laboratory Testing

Testing of *Salmonella*-positive stool specimens, including rectal swabs, retained food samples, and environmental specimens (e.g., food-preparation utensils), was conducted by the Research Institutes of Public Health and Environment. For specimens tested at healthcare facilities, polymerase chain reaction was used to identify organisms at the *Salmonella* genus level (i.e., *Salmonella* spp.).

For Facilities E, F, and G, which were identified through active case finding, the maximum incubation period had elapsed by the time of investigation, and no actively symptomatic cases remained. Therefore, additional clinical specimens could not be collected from affected individuals. However, stool specimens were collected from food-handling staff at Facility E for testing.

PFGE and whole-genome sequencing (WGS) analyses of human and retained food specimens that tested positive for *Salmonella* were performed by the Division of Bacterial Diseases at the KDCA.

## Traceback Investigation

To elucidate potential contamination routes, on-site field investigations were conducted across the full production–distribution continuum, including the bakery manufacturer (Manufacturer H), the primary distributor (Distributor I), the liquid egg–processing facility, and the source egg farms. The investigation was guided by 3 predefined hypotheses addressing distinct stages of exposure risk: contamination introduced via raw materials, workforce-associated transmission during handling, and cross-contamination occurring within the production process.

### Manufacturer H

At Manufacturer H, hygiene practices and production protocols were evaluated in a systematic and structured manner. Raw material safety was assessed through a comprehensive review of ingredient lists, along with microbiological testing of available ingredient lots and process water. Workforce hygiene was evaluated by examining employee health records, gastrointestinal symptom logs, mandatory hygiene training documentation, and food-handler certification status. To assess the production environment, the facility layout was mapped in detail to verify segregation between hygiene zones, and 11 environmental swabs were collected from food-contact surfaces, production equipment, and packaging areas. In addition, microbiological testing was performed on 4 finished bakery products produced at the manufacturer. Both environmental and finished-product samples obtained from Manufacturer H were tested for *Salmonella*.

### Downstream and upstream facilities

The investigation extended downstream to Distributor I to evaluate cold-chain management and recall implementation. Upstream investigations were carried out by the MFDS at the liquid egg–processing facility and its supplying farms. Microbiological tracing was conducted by collecting 3 liquid egg samples from the processor and 84 raw egg samples from the source farms to identify the origin of the implicated pathogen.

## Statistical Analysis

Local public health center staff administered surveys and compiled responses using a standardized Microsoft Excel data-entry template to ensure consistency across facilities. The assembled dataset was analyzed using Excel ver. 2021 (Microsoft) and RStudio ver. 4.5.1 (Posit, PBC) to generate descriptive statistics, summarize outbreak characteristics, and calculate incubation periods.

## Ethical Considerations

This study was approved by the Institutional Review Board (IRB) of the KDCA (IRB No. KDCA-2025-10-08-PE-01). Because



https://doi.org/10.24171/j.phrp.2025.0467

the research utilized secondary data collected by local governments as part of routine public health response activities, informed consent from individual participants was not required.

## Results

### Epidemiologic Investigation

Between May 15 and May 30, 2025, cases were identified in 7 facilities located in 7 cities across 6 provinces. This represented 2.8% (7/250) of all facilities that received bakery products from the same manufacturer on May 15–16, 2025. Product I was served at all 7 facilities on May 15–16, whereas Product II was served only at Facility B on May 15. Accordingly, Facility B was the only facility at which both products were consumed.

#### Attack rate and demographic and clinical characteristics

A total of 323 individuals with gastrointestinal illness who met the outbreak case definition were identified. Among respondents who submitted stool specimens, 48 tested positive for *Salmonella* spp., yielding a confirmed-case attack rate (AR) of 3.9% (48/1,235) (Table 1). When 4 additional *Salmonella*-positive individuals identified among nonrespondents were included, the total number of positive individuals increased to 52.

Age-specific ARs varied across age groups: 25.5% (97/380) among children aged <10 years, 30.6% (225/736) among adolescents aged 10–19 years, and 3.1% (1/32) among adults in their 40s, while no cases occurred in other age groups.

Among the 323 cases, 69.7% were aged 10–19 years, and 50.8% were male. Nearly all affected individuals (99.7%) were students. Illness onset began on May 15, 2025, at Facility E and on May 16, 2025, at the remaining facilities. Diarrhea was the most frequently reported symptom (96.9%), followed by abdominal pain and fever. The incubation period ranged from 6.0 to 347.6 hours, with a mean of 94.3 hours, a median of 77.8 hours, and an interquartile range of 78.5 hours (Table 2).

#### Epidemic curve

Products I and II were served on May 15–16, 2025, across the seven facilities. Excluding 2 individuals with unknown symptom-onset times, facility-specific epidemic curves were constructed using data from 321 cases. The first symptomatic case occurred at facility E on May 15, 2025; in the remaining

**Table 2.** Demographic and clinical characteristics of cases in the outbreak of *Salmonella* Enteritidis

| Characteristic | Case |
|---|---|
| Sex | |
| Male | 164 (50.8) |
| Female | 159 (49.2) |
| Age (y) | |
| ≤9 | 97 (30.0) |
| 10–19 | 225 (69.7) |
| ≥20 | 1 (0.3) |
| Position | |
| Students | 322 (99.7) |
| School staff | 0 (0) |
| Food handler | 1 (0.3) |
| Symptoms[a] | |
| Diarrhea | 313 (96.9) |
| Vomiting | 65 (20.1) |
| Fever | 178 (55.1) |
| Abdominal pain | 258 (79.9) |
| Chills | 137 (42.4) |
| Nausea | 145 (44.9) |
| Headache | 120 (37.2) |
| Others[b] | 2 (0.6) |
| Incubation period | 94.3 (6–347.6) |

Data are presented as *n* (%) or mean (minimum–maximum).
[a]Data include multiple responses per respondent. [b]Myalgia and body ache.

**Table 1.** Attack rate of cases and confirmed cases by facilities

| Facility | No. of exposed | Case | AR of cases (%) | Confirmed case[a] | AR of confirmed cases (%) |
|---|---|---|---|---|---|
| Total | 1,235 | 323 | 26.2 | 48 | 3.9 |
| A | 502 | 173 | 34.5 | 18 | 3.6 |
| B | 178 | 32 | 18.0 | 7 | 3.9 |
| C | 52 | 18 | 34.6 | 4 | 7.7 |
| D | 77[b] | 31 | 40.3 | 13 | 16.9 |
| E | 208 | 45 | 21.6 | 3 | 1.4 |
| F | 216 | 22 | 10.2 | 2 | 0.9 |
| G | 2[b] | 2 | 100.0 | 1 | 50.0 |

AR, attack rate.
[a]Confirmed case defined as polymerase chain reaction or culture-confirmed *Salmonella* from a rectal swab or stool; 4 positives among nonrespondents were excluded. [b]At Facilities D and G, the exposure denominators reflect data collected from groups with symptomatic cases only.

six facilities, symptom onset first occurred on May 16, 2025. Additional cases were reported from May 17 onward, with the final case occurring at Facility E on May 30, 2025 (Figure 2).

### Common exposure assessment

All 7 facilities received Product I, which was produced on the same day by Manufacturer H and distributed through Distributor I. No other common exposures were identified. Facility B also received Product II, which was produced by the same manufacturer (Table 3).

## Active Case Finding

From January to May 2025, 282 reported outbreaks of waterborne and foodborne diseases were reviewed by local public health centers; none involved exposure to the 2 implicated bakery products. Among 246 additional facilities supplied with these products, 3 facilities (E, F, and G) reported gastrointestinal illness following consumption of products with the same use-by dates as those in the initial clusters. In addition, analysis of the PulseNet Korea database identified 8 other clusters sharing the same *Salmonella* genotype as those in Facilities A–D; exposure assessments in these clusters found no evidence of consumption of the implicated bakery products.

## Laboratory Testing

Across the 7 facilities, 151 individuals were tested, of whom 52 (34.4%) were positive for *Salmonella* spp., including 41 cases of *S*. Enteritidis. Additionally, 2 individuals tested positive for *Staphylococcus aureus* (Table 4). Of the 52 *Salmonella*-positive individuals, 48 were classified as cases (including 1 food handler); detections identified at healthcare facilities are included.

Among the 7 facilities, retained bakery product samples

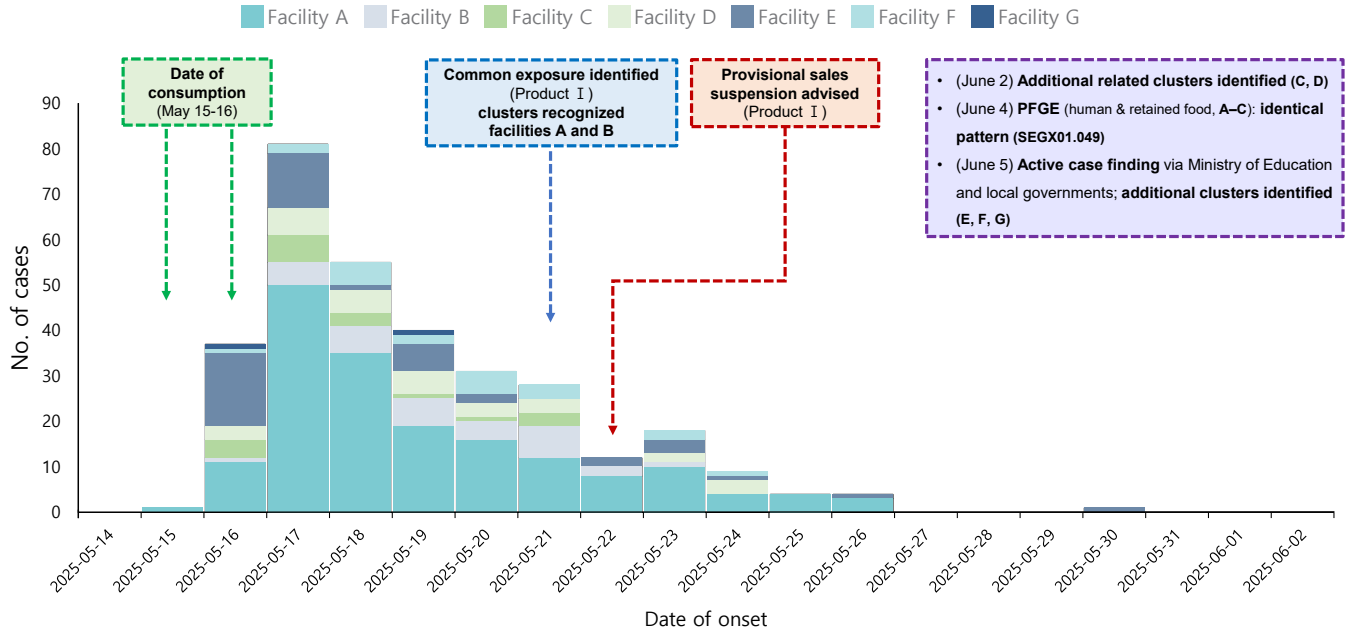



**Figure 2.** Epidemic curve of the multi-city outbreak of *Salmonella* Enteritidis

**Table 3.** Types of bakery products and consumption date by facilities

| Facility | Types of bakery products consumed | Manufacturer | Date of consumption |
|---|---|---|---|
| A | Product I | Manufacturer H | 2025-05-15 |
| B | Product I, II | Manufacturer H | 2025-05-15 |
| C | Product I | Manufacturer H | 2025-05-16 |
| D | Product I | Manufacturer H | 2025-05-15 |
| E | Product I | Manufacturer H | 2025-05-15 |
| F | Product I | Manufacturer H | 2025-05-15 |
| G | Product I | Manufacturer H | 2025-05-15 |

All items in Product I and Product II were from the same lot number, respectively.



https://doi.org/10.24171/j.phrp.2025.0467

from Facilities A and B tested positive for *S*. Enteritidis. Testing at the remaining facilities was not possible because the retention period had elapsed. All 214 environmental samples collected from Facilities A–E tested negative for *Salmonella* spp. (Table 5).

The KDCA and the MFDS conducted PFGE and WGS analyses on *S*. Enteritidis isolates from human specimens (39 isolates across Facilities A–D) and retained food samples (3 isolates from Facilities A and B). PFGE patterns were identical across all isolates (SEGX01.049-A26.016). Core-genome multilocus sequence typing (cgMLST) placed all isolates within the same cluster (HC5-2301; Global IIa clade) (Figure 3). Whole-genome single-nucleotide polymorphism (wgSNP) analysis showed ≤7 SNP differences between clinical isolates ($n$=4) and retained food isolates ($n$=1), indicating very high genetic relatedness. All isolates also shared the same RE_2010 phage type, providing additional confirmation of the outbreak's clonal origin.

## Traceback Investigation

### Manufacturer H

Manufacturer H was a large-scale bakery company producing 88 items for corporate clients. Although the manufacturer maintained Hazard Analysis and Critical Control Points certification, last renewed in February 2025, a targeted audit conducted shortly after the outbreak identified specific nonconformities in process control and environmental maintenance.

*Raw materials*

Both implicated products contained unpasteurized liquid eggs (whole egg in Product I and egg white in Product II) supplied by the same processor. Although lot-specific raw materials from the implicated production date were unavailable for testing, except for salt, storage conditions were compliant with regulatory standards. Routine potable-water testing conducted from January to May 2025 confirmed the absence of bacteriological contamination.

*Workforce*

No symptomatic illness or recent sick leave was reported among the 107 staff members. All production personnel held valid health certificates, and routine hygiene compliance audits showed no significant violations on the implicated production dates.

*Process-associated and environmental factors*

While finished bakery products from other dates and environmental swabs were negative for *Salmonella* spp., the investigation identified a critical cross-contamination risk. Production areas were segregated by product type and internally organized into general, semi-clean, and clean zones with restricted inter-zone movement. In the semi-clean zone, dough shaping and oven baking were conducted in proximity, and shared transport racks were used across different hygiene zones. This layout suggested a plausible pathway for cross-contamination between raw egg–handling areas and heat-treated finished products.

**Table 4.** Laboratory results from human specimens

| Pathogen | No. of positive results | Remarks |
|---|---|---|
| *Salmonella*-positive | 52 | 48 Were classified as cases; positives identified at healthcare facilities are included |
| *Salmonella* Enteritidis | 41 | |
| *Salmonella* spp. | 11 | |
| *Staphylococcus aureus* | 2 | Types B and C |

**Table 5.** Environmental sampling results by facilities

| Category | Facility | Specimen type | *n* | Result |
|---|---|---|---|---|
| Bakery-retained products | A | Product I | 1 | *Salmonella* Enteritidis |
| | B | Product I | 1 | *S*. Enteritidis |
| | | Product II | 1 | *S*. Enteritidis |
| Environmental sampling | A, B, C, D, E[a)] | Others: retained food, cooking utensils, cooking water, drinking water | 214 | ND |

ND, not detected.

[a)]Environmental sampling was not performed at Facilities F and G because the field investigation occurred long after outbreak recognition.

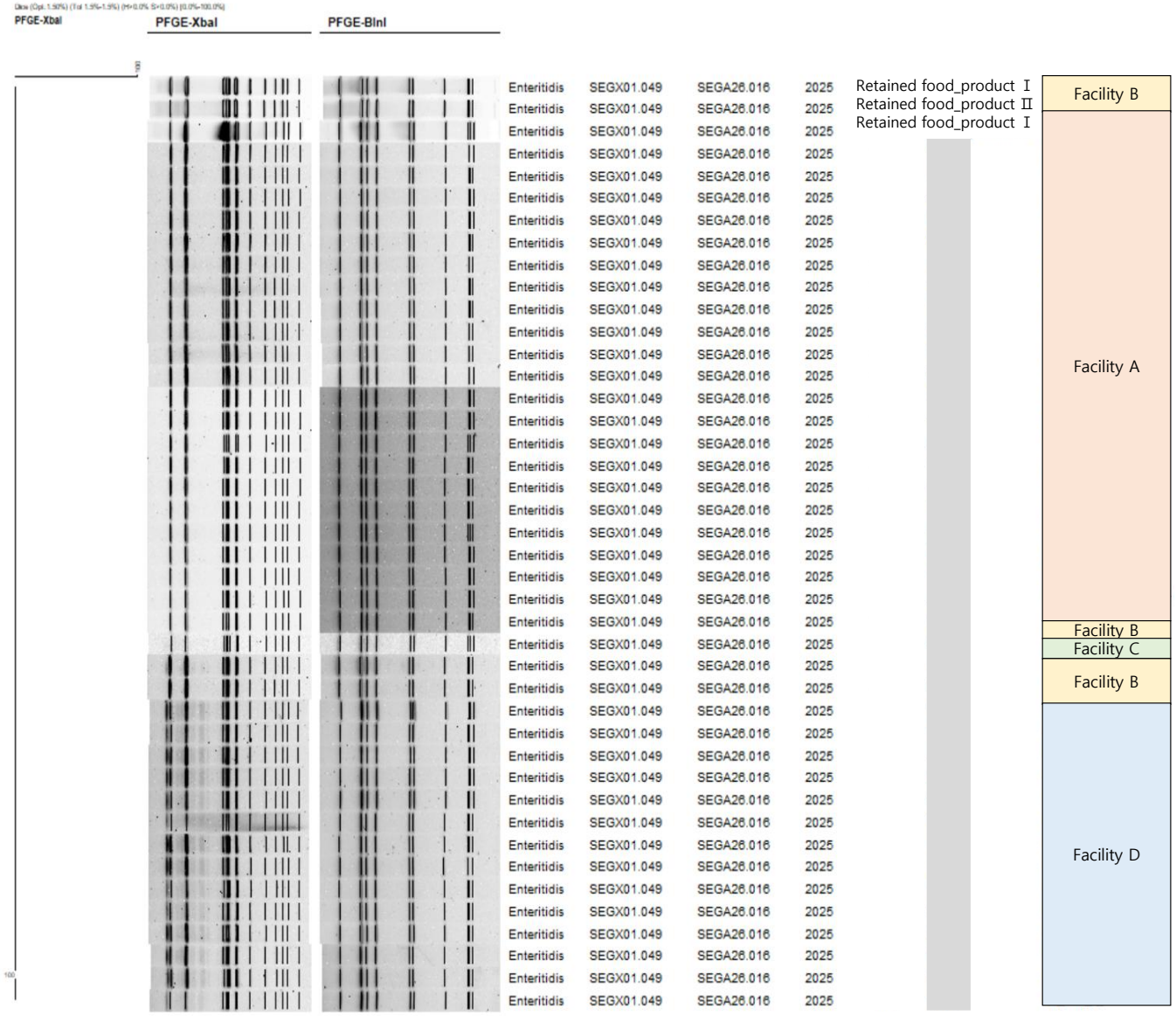



**Figure 3.** Pulsed-field gel electrophoresis (PFGE) profiles of outbreak-related *Salmonella* Enteritidis isolates associated with bakery product consumption

**Distributor I**

On-site inspections of Distributor I conducted in June 2025 confirmed that cold-chain integrity was maintained during storage and transport. Transaction logs showed no irregularities, and the recall of Products I and II was successfully verified.

**Liquid egg processor and source farms**

Microbiological analysis of products from the liquid egg–processing facility met all regulatory standards. Among the 3 source farms (Farm J, K and L), *Salmonella* Thompson was isolated exclusively from eggshell surfaces at Farm J. Samples from Farm I and J, as well as from the internal contents of eggs from Farm K and L, yielded negative results.

## Discussion

This outbreak resembled a previous nationwide salmonellosis outbreak in 2018 that was linked to chocolate cake. In that earlier event, investigations were conducted in 60 schools across 12 provinces, assessing 33,918 individuals; of these, 2,975 (8.8%) were classified as cases and 749 (2.2%) were laboratory confirmed [12]. In the present investigation, among the 1,235 exposed individuals, 323 (26.2%) met the case definition and



https://doi.org/10.24171/j.phrp.2025.0467

52 (4.2%) had laboratory-confirmed *Salmonella* infection. Accordingly, although fewer individuals were affected overall, the AR was approximately 2-to 3-fold higher.

The identification of this outbreak as a common-source event was fundamentally supported by laboratory-based genotyping. PFGE demonstrated indistinguishable patterns between clinical and retained food isolates, while WGS further placed all isolates within the same cluster. This laboratory evidence provided strong epidemiological support implicating the commonly consumed food item and facilitated the early identification of 3 additional epidemiologically linked clusters. Querying the PulseNet Korea database identified other *Salmonella* outbreaks with matching genotypes; however, the absence of epidemiological linkage to the present event allowed delimitation of the spatial and temporal scope of this outbreak. These findings reaffirm that genotyping is central to source attribution, assessment of geographic spread, supply-chain traceback, production stoppage, and product recalls. Internationally, PFGE and WGS, deployed through the PulseNet network, are established tools used at the national level to rapidly identify etiologic agents of foodborne outbreaks and to trigger early control measures, including interruption of distribution and initiation of recalls [14,15,21–24]. In the Republic of Korea, the application of PFGE and WGS is recommended as early as possible during investigations of waterborne and foodborne outbreaks, together with strengthened capacity for rapid analysis, interpretation, and interagency data sharing.

With the common source confirmed, we evaluated 3 hypotheses regarding the specific contamination route. For raw materials, only lots produced on different dates were available, and all tested negative. Detection of *S*. Thompson on eggshells from one supplier farm suggested possible upstream egg contamination; however, the serotype mismatch with the outbreak isolates (*S*. Enteritidis) limited causal inference. Personnel records identified no gastrointestinal illness or hygiene breaches on the production day. Regarding the production process, negative results from other products and environmental samples argued against persistent contamination. However, dough shaping involving unpasteurized liquid egg and oven baking occurred within the same semi-clean zone. In addition, shared transport racks and dual handling by some workers were consistent with transient cross-contamination. In summary, while a definitive route could not be determined due to discarded specimens, transient cross-contamination during production remained the most plausible explanation.

The difficulty in pinpointing the contamination source was likely linked to the unusually long incubation period observed in this outbreak. Although *Salmonella* infection generally manifests within 6 to 72 hours [1,3], substantially longer incubation periods have been documented in low-dose exposures [5,6,25,26]. In this outbreak, although the bacterial load could not be quantified, the observation that cases were identified in only 7 of 250 recipient facilities suggests that contamination was not uniform and likely occurred at low concentrations. This interpretation is consistent with previous outbreak investigations in which lightly contaminated food vehicles were associated with prolonged incubation periods [6,19,20,25], supporting the inference that low-dose exposure contributed to the extended incubation observed here.

These biological characteristics, namely low-dose contamination and extended incubation, pose significant challenges for early outbreak recognition. Compared with the 2018 chocolate-cake outbreak, which enabled early recognition due to its immediate reporting [11], the present outbreak experienced delays in the implementation of control measures because of limited early case identification. Similar patterns have been reported internationally. Outbreaks in Japan, Singapore, and the United States have highlighted how cross-contamination and complex supply chains can obscure early detection [8,15,18]. Multi-country outbreaks in Europe further indicate that fragmented surveillance systems can delay the identification of a common exposure [27–29].

To overcome these inherent challenges, strengthening coordinated and proactive collaboration between public health and food safety authorities is essential for improving responses to future multi-institutional foodborne outbreaks [8,14,15,18,27–29]. In this outbreak, rapid interagency communication was facilitated through structured information sharing between the KDCA and the MFDS. Specifically, the list of recipient facilities provided by the MFDS enabled the KDCA to expand active case finding across multiple jurisdictions in a timely manner. Upon notification, the MFDS promptly conducted an on-site sanitary inspection and recommended a voluntary temporary suspension of sales. As the potential for nationwide spread emerged, investigative leadership was escalated to the national level, enabling a coordinated response involving local governments and the Ministry of Education.

Building on this experience, future response measures should include strengthened real-time, preemptive sharing of outbreak signals and systematic integration of clinical and food genomic data. Such coordinated sharing would provide essential foundational data for rapid source attribution and enhance preparedness for complex, multi-

facility foodborne outbreaks [8,14,15,18,27–29].

Finally, several limitations of this investigation must be acknowledged. First, the staggered recognition of clusters resulted in some cases resolving before clinical specimens could be collected, and some facilities were unable to secure retained food samples. Second, the retention period for food samples had elapsed, and lot-matched raw materials were no longer available, limiting environmental and ingredient sampling and constraining definitive elucidation of the contamination route. Third, recall bias may have affected reports of food exposure, particularly among young children, for whom histories relied on proxy reports from caregivers.

## Conclusion

This multi-city outbreak, linked to the consumption of bakery products across multiple facilities nationwide, highlights the necessity of coordinated, multi-agency responses in managing large-scale foodborne outbreaks. Collaborative efforts among relevant government agencies enabled timely detection of the outbreak and prevention of further spread. Moreover, the application of molecular analyses, including PFGE and WGS, facilitated rapid source identification and detection of additional cases. Collectively, these findings underscore the pivotal role of both interagency collaboration and laboratory-based evidence in strengthening foodborne outbreak investigations and response systems.

## Notes

### Ethics Approval

This study was approved by the Institutional Review Board of KDCA (No: KDCA-2025-10-08-PE-01). The informed consent was waived because of the retrospective nature of this study.

### Conflicts of Interest

The authors have no conflicts of interest to declare.

### Funding

None.

### Availability of Data

The datasets are not publicly available but are available from the corresponding author upon reasonable request.

### Authors' Contributions

Conceptualization: YJP; Data curation: DSK, SJY; Formal analysis: DSK; Investigation: DSK, SS, DHK, YHW, JK, ES, BJ, EL, MJL; Methodology: DSK, SS, YJP; Project administration: DSK, SS, YHW, DL, YJP; Supervision: SS, YJP; Visualization: DSK, JK, ES; Writing–original draft: DSK, JK, ES; Writing–review & editing: all authors. All authors read and approved the final manuscript.

### Acknowledgements

The authors express their gratitude to the participating local public health centers, 17 metropolitan cities and provinces, Ministry of Education, and each Regional Center for Disease Control and Prevention.

## References

1. World Health Organization (WHO) (CH). Salmonella (non-typhoidal) [Internet]. WHO; 2018 [cited 2025 Jul 30]. Available from: https://www.who.int/news-room/fact-sheets/detail/salmonella-(non-typhoidal).
2. Food and Agriculture Organization of the United Nations; World Health Organization (WHO) (CH). Measures for the control of non-typhoidal Salmonella spp. in poultry meat: meeting report. Microbiological Risk Assessment Series No. 45 [Internet]. WHO; 2023 [cited 2025 Jul 30]. Available from: https://www.who.int/publications/i/item/9789240078826.
3. Korea Disease Control and Prevention Agency (KDCA) (KR). Guidelines for the control of waterborne and foodborne infectious diseases, 2025. KDCA; 2025. Korean.
4. Centers for Disease Control and Prevention (CDC) (US). Salmonella infection (Salmonellosis) [Internet]. CDC; 2024 [cited 2025 Jul 17]. Available from: https://www.cdc.gov/salmonella/about/index.html.
5. Eikmeier D, Medus C, Smith K. Incubation period for outbreak-associated, non-typhoidal salmonellosis cases, Minnesota, 2000-2015. Epidemiol Infect 2018;146:423–9.
6. Mintz ED, Cartter ML, Hadler JL, et al. Dose-response effects in an outbreak of Salmonella Enteritidis. Epidemiol Infect 1994;112:13–23.
7. Glynn JR, Palmer SR. Incubation period, severity of disease, and infecting dose: evidence from a Salmonella outbreak. Am J Epidemiol 1992;136:1369–77.
8. Korea Disease Control and Prevention Agency (KDCA) (KR). Infectious disease statistics portal [Internet]. KDCA; 2025 [cited 2025 Jul 1]. Available from: https://dportal.kdca.go.kr/. Korean.
9. Korea Disease Control and Prevention Agency (KDCA) (KR). Annual report on infectious disease surveillance [Internet]. KDCA; 2025 [cited 2025 Jul 1]. Available from: https://kdca.go.kr/kdca/2861/subview.do?enc = Zm5jdDF8QEB8JTJGYmJzJTJGa2RjYSUyRjU1JTJGMjI4MzA3JTJGYXJ0Y2xWaWV3LmRvJTNGcGFzc3dvcmQlM0QlMjZyZ3NCZ25kZVN0ciUzRCUyNmZpbmRPcG53cmQlM0QlMjZmaW5kV29yZCUzRCVFQyU5NyVCMCVFQiVCMyVCNCUyNnJnc0VuZGRlU3RyJTNEJTI2ZmluZFR5cGUlM0RzaiUyNmZpbmRDbFNlcSUzRCUyNnBhZ2UlM0QxJTI2. Korean.
10. Hwang MJ, Park SY, Kim H, et al. Waterborne and foodborne disease outbreaks in the Republic of Korea, 2023. Public Health Wkly Rep 2025;18:17–32. Korean.
11. Matsui T, Suzuki S, Takahashi H, et al. Salmonella Enteritidis outbreak associated with a school-lunch dessert: cross-contamination and a long incubation period, Japan, 2001. Epidemiol Infect 2004;132:873–9.
12. Shin E, La TM, Yoo J, et al. Emergence of distinct Salmonella enterica serovar Enteritidis lineage since 2020, South Korea. Emerg Infect Dis 2025;31:1386–93.



https://doi.org/10.24171/j.phrp.2025.0467

13. Centers for Disease Control and Prevention (US). Outbreaks of Salmonella serotype Enteritidis infection associated with eating shell eggs: United States, 1999-2001. MMWR Morb Mortal Wkly Rep 2003;51:1149–52.
14. Korea Disease Control and Prevention Agency (KDCA) (KR). Annual report on epidemiological investigations of infectious diseases, 2018. KDCA; 2018. p. 107–23. Korean.
15. Ladd-Wilson SG, Morey K, Koske SE, et al. Notes from the field: multistate outbreak of Salmonella Agbeni associated with consumption of raw cake mix: five states, 2018. MMWR Morb Mortal Wkly Rep 2019;68:751–2.
16. Madad A, Vasser M, Viazis S, et al. An international outbreak investigation of Salmonella Enteritidis infections in the United States and Canada linked to peaches - 2020. J Food Prot 2025;88:100519.
17. Sobel J, Griffin PM, Slutsker L, et al. Investigation of multistate foodborne disease outbreaks. Public Health Rep 2002;117:8–19.
18. Solhan S, Chan PP, Kurupatham L, et al. An outbreak of gastroenteritis caused by Salmonella enterica serotype Enteritidis traced to cream cakes. Western Pac Surveill Response J 2011;2:23–30.
19. Centers for Disease Control and Prevention (CDC) (US). Summary of possible multistate enteric disease outbreaks, 2017-2020 [Internet]. CDC; 2024 [cited 2025 Jul 30]. Available from: https://www.cdc.gov/foodborne-outbreaks/php/data-research/summary-2017-2020.html.
20. Dong K, Song D, Li S, et al. Significance of whole-genome sequencing for the traceability of foodborne pathogens: during the processing of meat and dairy products. Foods 2025;14:1410.
21. World Health Organization (WHO) (CH). Whole genome sequencing for foodborne disease surveillance: landscape paper [Internet]. WHO; 2018 [cited 2025 Aug 19]. Available from: https://iris.who.int/handle/10665/272430.
22. Lewis K, Vasser M, Garman K, et al. Notes from the field: multistate, multiserotype outbreak of Salmonella infections linked to cashew brie: United States, 2021. MMWR Morb Mortal Wkly Rep 2023;72:589–90.
23. Federman SS, Jenkins E, Wilson C, et al. An investigation of an outbreak of Salmonella Typhimurium infections linked to cantaloupe: United States, 2022. Food Control 2024;166:110733.
24. Jenkins E, Cripe J, Whitney BM, et al. An outbreak investigation of Salmonella Weltevreden illnesses in the United States linked to frozen precooked shrimp imported from India-2021. J Food Prot 2024;87:100360.
25. Rejnmark L, Stoustrup O, Christensen I, et al. Impact of infecting dose on severity of disease in an outbreak of food-borne Salmonella Enteritidis. Scand J Infect Dis 1997;29:37–40.
26. Abe K, Saito N, Kasuga F, et al. Prolonged incubation period of salmonellosis associated with low bacterial doses. J Food Prot 2004;67:2735–40.
27. European Food Safety Authority; European Centre for Disease Prevention and Control (IT). Multi-country outbreak of Salmonella Enteritidis infections linked to Polish eggs. EFSA J 2017;14:1353E.
28. European Food Safety Authority; European Centre for Disease Prevention and Control (ECDC) (IT). Multi-country outbreak of Salmonella Enteritidis sequence type (ST)11 infections linked to poultry products in the EU/EEA and the United Kingdom [Internet]. ECDC; 2021 [cited 2025 Dec 15]. Available from: https://www.ecdc.europa.eu/en/publications-data/salmonella-enteritidis-multi-country-poultry-joint-outbreak-risk-assessment.
29. European Food Safety Authority; European Centre for Disease Prevention and Control (IT). Multi-country outbreak of Salmonella Enteritidis sequence type (ST)11 infections linked to eggs and egg products-8 February 2022. EFSA J 2022;19:7180E.

phrp
OSONG PUBLIC HEALTH AND RESEARCH PERSPECTIVES

pISSN 2210-9099 eISSN 2233-6052
https://doi.org/10.24171/j.phrp.2025.0510
Osong Public Health Res Perspect 2026;17(1):72-82

**Original Article**

# Reciprocal associations between smartphone overdependence and anxiety in adolescents: evidence from a nationally representative survey in the Republic of Korea

**Eunok Park**

College of Nursing and Health and Nursing Research Instutute, Jeju National University, Jeju, Republic of Korea

## ABSTRACT

**Objectives:** Smartphone overdependence (SOD) and anxiety are major concerns in adolescent mental health; however, few studies have examined their bidirectional relationship. This study aimed to examine reciprocal associations between SOD and anxiety among adolescents.

**Methods:** A secondary analysis was conducted with data from 50,975 adolescents in the 19th Korea Youth Risk Behavior Survey. SOD was measured using the SOD scale, and anxiety was assessed using the generalized anxiety disorder 7-item scale. Multivariable logistic regression analyses were conducted to examine reciprocal associations, adjusting for sociodemographic factors, perceived stress, loneliness, and depressive symptoms.

**Results:** Moderate to severe anxiety was found in 12.6% of participants, and 3.3% were classified as being at high risk for SOD. In adjusted models, the model with anxiety as the outcome demonstrated higher predictive performance (concordance rate, 86.5%) than the model with SOD as the outcome (77.3%). Adolescents at high risk for SOD had higher odds of reporting anxiety, and those with severe anxiety had higher odds of being classified as at high risk for SOD. Stress, loneliness, and smartphone use time were also identified as significant predictors.

**Conclusion:** SOD and anxiety were strongly associated with each other among adolescents. Integrated approaches addressing both digital behavior and mental health may help inform strategies to reduce psychological distress. Public health strategies may benefit from considering both aspects when screening for problematic smartphone use and anxiety.

**Keywords:** Addictive behavior; Adolescent; Anxiety; Korea Youth Risk Behavior Survey; Smartphone

**Received:** November 19, 2025
**Revised:** December 25, 2025
**Accepted:** January 9, 2026

Corresponding author:
Eunok Park
College of Nursing and Health and Nursing Research Instutute, Jeju National University, 102 Jejudaehak-ro, Jeju 63243, Republic of Korea
E-mail: eopark@jejunu.ac.kr

## Introduction

With the rapid advancement of technology, the use of computers, smartphones, and other electronic devices has increased dramatically. While this surge in technology has brought

The opinions expressed by authors contributing to this journal do not necessarily reflect the opinions of the Korea Disease Control and Prevention Agency and Korea National Institute of Health.

© 2026 Korea Disease Control and Prevention Agency.
This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

numerous benefits, it has also resulted in negative health consequences associated with excessive use [1,2]. The problematic use of smartphones and the internet has given rise to smartphone dependence, which is characterized by excessive reliance on digital devices. This dependence has led to several unintended consequences, including smartphone addiction, impaired social interactions, reduced productivity, and mental health concerns such as anxiety and depression [3,4]. Research continues to accumulate, demonstrating a strong association between problematic smartphone use (PSU) and mental health conditions, including depression and anxiety [5–9].

The World Health Organization has officially recognized technology addiction as a global issue, noting that excessive internet use can impair an individual's ability to manage time, energy, and focus [1,2,10]. The pervasive integration of smartphones into daily life has made it increasingly difficult for adolescents to regulate their use, often resulting in overdependence or addiction. Globally, the median prevalence of PSU among children and young people has been reported as 23.3% (range, 14.0%–31.2%) [11]. In the Republic of Korea, the prevalence of smartphone overdependence (SOD) among adolescents reached 40.1% in 2023, nearly double the prevalence observed in adults (22.7%) [3]. The risk of SOD has increased sharply, rising from 29.3% in 2018 to 40.1% in 2023, including 5.2% in the high-risk group and 34.9% in the potential risk group [3,12]. Anxiety is also increasingly prevalent among adolescents. Keyes and Platt [13] reported a significant rise in adolescent anxiety and identified digital technology, including smartphone use, as a novel risk factor contributing to these trends.

Numerous studies have explored the association between SOD and anxiety [4,6,7,9,14–17]. Some studies have examined anxiety as a psychological correlate of SOD, while others have focused on anxiety as a mental health outcome associated with excessive smartphone use [6–9,16–18]. Examining reciprocal associations between SOD and anxiety is essential for understanding how these conditions may interact within adolescent populations. Such evidence may inform screening approaches for identifying at-risk groups and guide the development of future public health strategies. Considering smartphone dependence and anxiety as interconnected conditions may also contribute to improved therapeutic outcomes and enhanced mental well-being. The purpose of this study was to investigate the relationship between SOD and anxiety among adolescents. Specifically, this study examined the association between SOD and anxiety from a reciprocal perspective.

By examining these associations, this study sought to contribute empirical evidence that may support future research and intervention planning focused on adolescent mental health and digital behaviors. Given the cross-sectional design, this study emphasized identifying reciprocal associations rather than inferring causal relationships. Ultimately, this study aimed to contribute to improving mental health outcomes and promoting healthier digital habits among adolescents.

***HIGHLIGHTS***

- This study examined reciprocal associations between smartphone overdependence and anxiety among adolescents using a nationally representative dataset.
- The model with anxiety as the outcome showed higher predictive performance than the model with smartphone overdependence as the outcome in multivariable analyses.
- Higher levels of smartphone use, stress, loneliness, and depressive symptoms were significantly associated with both anxiety and smartphone overdependence, underscoring the importance of integrated mental health and digital-behavior approaches in school settings.

## Materials and Methods

### Design

We conducted a secondary analysis using a nationally representative cross-sectional dataset derived from the 19th Korea Youth Risk Behavior Survey (KYRBS). The data were collected via a web-based survey administered between August and November 2023, and the dataset was downloaded from the Korea Disease Control and Prevention Agency (KDCA)'s KYRBS website [19].

### Participants

The survey targeted Korean middle and high school students aged 12 to 18 years. Using stratified random sampling, 400 middle schools and 400 high schools were selected nationwide. Within each selected school, 1 classroom per grade was randomly chosen, and all students in those classrooms were invited to participate in the survey. To ensure voluntary participation and anonymity, standardized procedures were implemented. School teachers trained by the KDCA explained the study purpose and participation process. Students then anonymously completed a web-based, self-administered questionnaire in their school

computer laboratories during class time. Of the initial sample of 56,935 students across 800 schools, 52,880 students from 799 schools participated, yielding a response rate of 92.9% [20]. After excluding participants with missing data on key variables, including smartphone usage time, SOD, and generalized anxiety disorder (GAD), a total of 50,975 adolescents were included in the final analysis. This exclusion process ensured that the analytic dataset permitted a more accurate and reliable assessment of the relationship between smartphone use and anxiety.

## Measurements

### Generalized anxiety disorder

GAD was assessed using the GAD 7-item scale (GAD-7), a widely validated instrument developed by Spitzer et al. [21]. The GAD-7 evaluates symptoms such as nervousness, anxiety, excessive worry, and irritability through 7 items assessing the frequency of these symptoms over the preceding 2 weeks. Participants responded to each item using a 4-point Likert scale ranging from 0 (not at all) to 3 (nearly every day), yielding a total score ranging from 0 to 21. Scores were categorized as follows: 0–4 (minimal), 5–9 (mild anxiety), 10–14 (moderate anxiety), and 15–21 (severe anxiety). In the present study, the GAD-7 demonstrated high internal consistency, with a Cronbach's α of 0.91, indicating excellent reliability.

### Smartphone overdependence

SOD, as defined by the Ministry of Science, ICT and Future Planning and the Korea Information Society Development Institute (2016), refers to excessive reliance on smartphones that interferes with daily functioning. The SOD scale (SOS) was used to assess this construct and consists of 10 items across 3 subscales: salience (prioritizing smartphone use over other activities), loss of control (difficulty regulating smartphone use), and problematic outcomes (physical discomfort, social conflicts, and impairments in family, school, or work settings). Each item is scored on a 4-point Likert scale, producing total scores ranging from 10 to 40. Based on SOS scores, SOD was classified into 3 categories: normal risk (10–23), potential risk (24–30), and high risk (31–40), with higher scores indicating greater levels of smartphone reliance. In this study, the SOS demonstrated strong internal consistency, with a Cronbach's α of 0.91. The psychometric properties of the SOS have been recently revalidated among Korean adolescents, confirming its 3-factor structure and robust internal consistency [22]. Although the validated version proposed a 9-item structure, the present study employed the original 10-item version to ensure comparability with the national monitoring system and to allow classification into the 3 official SOD risk categories.

### Covariates

Covariates included demographic and psychosocial factors: sex (male or female), school level (middle school or high school), living area (urban or rural), academic performance (categorized as high, intermediate, or low), and socioeconomic status (upper, moderate, or lower). Smartphone usage time was assessed by asking participants to report their average daily smartphone use on weekdays and weekends, including hours and minutes. These values were converted into minutes and used to calculate a weighted average daily smartphone usage, accounting for 5 weekdays and 2 weekend days. The resulting daily average was categorized into 5 groups: less than 2 hours per day, 2–5 hours per day, 5–10 hours per day, 10–15 hours per day, and more than 15 hours per day. This approach enabled a more accurate estimation of habitual smartphone use by accounting for differences between weekday and weekend patterns. Additional covariates included perceived stress (classified as "a little" or "a lot"), depressive feelings (yes or no), and loneliness (yes or no).

## Statistical Analysis

All analyses were conducted using SAS ver. 9.4 (SAS Institute Inc.), with sampling weights applied to account for the complex survey design and to ensure national representativeness. Descriptive statistics were used to summarize participants' general characteristics, and Chi-square tests were performed to compare the prevalence of anxiety and SOD across participant characteristics. To examine associations between SOD and anxiety, 2 multivariable logistic regression models were specified: one with anxiety as the dependent variable and the other with SOD as the dependent variable. Covariates were selected a priori based on prior literature and theoretical relevance and included sex, school level, living area, socioeconomic status, academic performance, perceived stress, depressive symptoms, and loneliness. Before model estimation, multicollinearity among independent variables was assessed using variance inflation factors (VIFs) and collinearity diagnostics derived from ordinary least squares regression. All VIF values were close to 1 (range, 1.01–1.56), and intercept-adjusted condition indices were well below commonly accepted thresholds, indicating no evidence of problematic multicollinearity. Odds ratios (ORs) and 95% confidence intervals (CIs) were estimated to quantify associations. Model performance was evaluated using percent concordance, and Somers' D statistics were examined to assess model discrimination.


https://doi.org/10.24171/j.phrp.2025.0510

### IRB Approval

This study utilized publicly available data from the 19th KYRBS, conducted by the KDCA in collaboration with the Ministry of Education. Informed consent was obtained from all participants by the KDCA prior to data collection. Ethical approval for this secondary analysis was exempted by the Institutional Review Board of Jeju National University (approval number: JJNU-IRB-2024-086), as the study involved analysis of anonymized national survey data.

## Results

### General Characteristics of the Participants

The general characteristics of the participants in the study are summarized in Table 1. Among the 50,975 participants, 50.9% were male and 49.1% were female. Participants were relatively evenly distributed by school level, with 51.4% attending middle school and 48.6% attending high school. Most participants resided in urban areas (94.2%), whereas 5.8% lived in rural areas. Regarding socioeconomic status, 43.2% of participants were classified as upper class, 45.2% as middle class, and 11.6% as lower class. In terms of academic performance, 37.8% were categorized in the upper test score group, 29.4% in the middle group, and 32.7% in the lower group. Smartphone use varied across participants: 6.9% reported using smartphones for less than 2 hours per day, 49.8% for 2 to 5 hours per day, 37.2% for 5 to 10 hours per day, 4.8% for 10 to 15 hours per day, and 1.3% for more than 15 hours per day.

For perceived stress, 74.2% of participants reported experiencing "a little" stress, whereas 25.8% reported experiencing "a lot" of stress. With respect to depressive symptoms, 74.2% reported no depression, while 25.8% reported experiencing depression. Similarly, 81.8% of participants reported not experiencing loneliness, whereas 18.2% reported experiencing loneliness. Regarding GAD, 63.8% of participants were classified as having minimal anxiety, 23.6% as mild anxiety, 8.2% as moderate anxiety, and 4.4% as severe anxiety. For SOD, 71.6% of participants were classified as normal, 25.0% as being at potential risk, and 3.3% as being at high risk.

**Table 1.** Comparison of the participants' general characteristics ($n$ = 50,975)

| Characteristic | Category | Total $n$ (weighted %) |
|---|---|---|
| Sex | Male | 25,484 (50.9) |
| | Female | 25,491 (49.1) |
| School | Middle school | 27,642 (51.4) |
| | High school | 23,333 (48.6) |
| Residential area | Urban | 46,943 (94.2) |
| | Rural | 4,032 (5.8) |
| Socioeconomic status | Upper | 21,466 (43.2) |
| | Moderate | 23,312 (45.2) |
| | Lower | 6,197 (11.6) |
| Academic performance | High | 19,200 (37.8) |
| | Intermediate | 15,003 (29.4) |
| | Low | 16,772 (32.7) |
| Smartphone use (h/d) | <2 | 3,482 (6.9) |
| | ≥2 and ≤5 | 24,979 (49.8) |
| | >5 and ≤10 | 19,322 (37.2) |
| | >10 and ≤15 | 2,489 (4.8) |
| | >1 | 703 (1.3) |
| Perceived stress | A little | 31,994 (74.2) |
| | A lot | 18,981 (25.8) |
| Depression | No | 37,719 (74.2) |
| | Yes | 13,256 (25.8) |
| Loneliness | No | 41,772 (81.8) |
| | Yes | 9,203 (18.2) |
| Generalized anxiety disorder | Minimal | 32,597 (63.8) |
| | Mild | 11,997 (23.6) |
| | Moderate | 4,168 (8.2) |
| | Severe | 2,213 (4.4) |
| Smartphone overdependence | Normal | 36,671 (71.6) |
| | Potential risk | 12,669 (25.0) |
| | High risk | 1,635 (3.3) |

### Prevalence Rates of Anxiety and SOD by General Characteristics

The prevalence of anxiety differed significantly according to participants' general characteristics (Table 2). Overall, female adolescents exhibited a substantially higher prevalence of anxiety (16.4%) compared with male adolescents (8.9%) ($p$ < 0.001). School level was not significantly associated with anxiety prevalence, with middle school students reporting a prevalence of 13.0% and high school students 12.2% ($p$ = 0.051). Similarly, living area was not associated with anxiety prevalence, with urban residents reporting a prevalence of 12.6% and rural residents 11.7% ($p$ = 0.283). Economic status showed a significant association with anxiety, as adolescents in the lower economic group exhibited the highest prevalence (20.9%), compared with those in the upper (11.2%) and middle (11.8%) economic groups ($p$ < 0.001). Academic performance was also associated with anxiety prevalence, with the lower performance group reporting a higher prevalence (15.3%) than the upper (11.7%) and middle (10.7%) performance groups ($p$ < 0.001).

Smartphone use was significantly associated with anxiety prevalence. The lowest prevalence of anxiety was observed among adolescents who used smartphones for less than 2 hours per day (9.4%), whereas the highest prevalence was observed among those who used smartphones for more

**Table 2.** The prevalence of anxiety and smartphone overdependence by general characteristics

| Variable | Anxiety | | | Smartphone overdependence | | |
|---|---|---|---|---|---|---|
| | Weighted % | Rao-Scott $\chi^2$ | *p* | Weighted % | Rao-Scott $\chi^2$ | *p* |
| Total | 12.6 | | | 3.3 | | |
| Sex | | | | | | |
| Male | 8.9 | 57.84 | <0.001 | 2.5 | 68.03 | <0.001 |
| Female | 16.4 | | | 4.1 | | |
| School | | | | | | |
| Middle school | 13.0 | 3.82 | 0.051 | 3.3 | 0.29 | 0.591 |
| High school | 12.2 | | | 3.4 | | |
| Residential area | | | | | | |
| Urban | 12.6 | 1.15 | 0.283 | 3.3 | 2.63 | 0.105 |
| Rural | 11.7 | | | 2.7 | | |
| Socioeconomic status | | | | | | |
| Upper | 11.2 | 360.22 | <0.001 | 3.0 | 90.83 | <0.001 |
| Moderate | 11.8 | | | 3.0 | | |
| Lower | 20.9 | | | 5.6 | | |
| Academic performance | | | | | | |
| High | 11.7 | 148.01 | <0.001 | 2.8 | 145.91 | <0.001 |
| Intermediate | 10.7 | | | 2.3 | | |
| Low | 15.3 | | | 4.8 | | |
| Smartphone use (h/d) | | | | | | |
| <2 | 9.4 | 314.75 | <0.001 | 0.4 | 610.53 | <0.001 |
| ≥2 and ≤5 | 10.6 | | | 1.7 | | |
| >5 and ≤10 | 14.6 | | | 4.7 | | |
| >10 and ≤15 | 20.1 | | | 9.0 | | |
| >15 | 22.8 | | | 15.2 | | |
| Perceived stress | | | | | | |
| A little | 3.5 | 8,896.64 | <0.001 | 2.0 | 411.12 | <0.001 |
| A lot | 27.95 | | | 5.6 | | |
| Depression | | | | | | |
| No | 6.05 | 6,818.15 | <0.001 | 2.3 | 388.23 | <0.001 |
| Yes | 31.5 | | | 6.1 | | |
| Loneliness | | | | | | |
| No | 6.3 | 9,421.14 | <0.001 | 2.3 | 538.32 | <0.001 |
| Yes | 41.0 | | | 7.7 | | |
| Generalized anxiety disorder | | | | | | |
| Minimal | | | | 1.5 | 1,617.74 | <0.001 |
| Mild | | | | 4.3 | | |
| Moderate | | | | 7.1 | | |
| Severe | | | | 17.0 | | |
| Smartphone overdependence | | | | | | |
| Normal | 9.1 | 1,753.24 | <0.001 | | | |
| Potential risk | 19.0 | | | | | |
| High risk | 40.2 | | | | | |

than 15 hours per day (22.8%) ($p<0.001$). Perceived stress showed a strong association with anxiety, with individuals reporting “a lot” of stress exhibiting an anxiety prevalence of 27.9%, compared with 3.5% among those reporting lower stress levels ($p<0.001$). In addition, adolescents reporting depression (31.5%) and loneliness (40.9%) demonstrated markedly higher anxiety prevalence compared with those without depression (6.0%) and loneliness (6.3%) ($p<0.001$). Anxiety prevalence also differed significantly across SOD categories. Adolescents in the high-risk SOD group exhibited an anxiety prevalence of 40.2%, compared with 19.0% in the potential risk group and 9.1% in the normal


https://doi.org/10.24171/j.phrp.2025.0510

group ($p < 0.001$).

SOD also differed significantly according to general characteristics (Table 2). Female adolescents exhibited a higher prevalence of SOD (4.1%) than male adolescents (2.5%) ($p < 0.001$). School level was not significantly associated with SOD prevalence, with rates of 3.3% among middle school students and 3.4% among high school students ($p = 0.591$). Economic status showed a significant association with SOD, with the lower economic group exhibiting a prevalence of 5.6%, compared with 3.0% in both the upper and middle economic groups ($p < 0.001$). Academic performance was also significantly associated with SOD prevalence, with adolescents in the lower performance group reporting a higher prevalence (4.8%) than those in the upper (2.8%) and middle (2.3%) performance groups ($p < 0.001$).

Regarding smartphone usage time, adolescents who used smartphones for more than 15 hours per day exhibited the highest prevalence of SOD (15.2%), whereas those who used smartphones for less than 2 hours per day exhibited the lowest prevalence (0.4%) ($p < 0.001$). Perceived stress was also significantly associated with SOD, with adolescents reporting higher stress levels showing a prevalence of 5.6%, compared with 2.0% among those reporting lower stress levels ($p < 0.001$). Depression and loneliness were similarly associated with SOD prevalence, with higher prevalence observed among adolescents experiencing depression (6.1%) and loneliness (7.7%), compared with those without depression (2.3%) and loneliness (2.3%) ($p < 0.001$). Notably, SOD prevalence increased progressively with greater anxiety severity. Adolescents with minimal anxiety exhibited a low prevalence of SOD (1.5%), whereas those with severe anxiety exhibited a substantially higher prevalence (17.0%) ($p < 0.001$), indicating a clear graded association between anxiety severity and SOD.

### The Multivariable Logistic Model of Anxiety and SOD

The multivariable logistic regression analysis included multiple independent variables to assess their associations with anxiety and SOD. The variables examined were sex, school level, living area, socioeconomic status, student test scores, smartphone usage, perceived stress, depression, loneliness, and GAD. These factors were analyzed simultaneously to evaluate their relationships with both anxiety and SOD, thereby allowing for a comprehensive assessment of the interrelationships among these variables.

In the analysis of anxiety, several variables emerged as significant predictors. Female adolescents had 1.28 times higher odds of experiencing anxiety compared with male adolescents (OR, 1.28; $p < 0.001$). High school students exhibited a slightly lower likelihood of anxiety than middle school students (OR, 0.93; $p = 0.041$). Adolescents from lower economic backgrounds had 27% higher odds of anxiety compared with those from upper economic backgrounds (OR, 1.27; $p < 0.001$). Perceived stress, depression, and loneliness were the strongest predictors of anxiety. Adolescents reporting high levels of stress had nearly fivefold higher odds of anxiety (OR, 4.90; $p < 0.001$), while those reporting depression had almost threefold higher odds (OR, 2.86; $p < 0.001$), and those reporting loneliness had nearly fourfold higher odds (OR, 3.88; $p < 0.001$). In addition, adolescents classified as being at potential risk for SOD had 1.76 times higher odds of anxiety (OR, 1.76; $p < 0.001$), whereas those classified as being at high risk for SOD had 3.51 times higher odds of anxiety (OR, 3.51; $p < 0.001$).

In the analysis of SOD, female adolescents were not significantly more likely to exhibit SOD compared with male adolescents ($p = 0.112$). Adolescents residing in rural areas had 27% lower odds of SOD compared with those residing in urban areas (OR, 0.73; $p = 0.021$). Economic status demonstrated a protective association, with adolescents from middle economic backgrounds being 16% less likely to exhibit SOD compared with those from upper economic backgrounds (OR, 0.84; $p = 0.004$). Smartphone usage time was the strongest predictor of SOD. Adolescents who used smartphones for more than 15 hours per day had 26.66 times higher odds of SOD compared with those who used smartphones for less than 2 hours per day (OR, 26.66; $p < 0.001$). Loneliness was also a significant predictor of SOD (OR, 1.25; $p = 0.004$). In addition, GAD was significantly associated with SOD, with adolescents experiencing severe anxiety showing 7.68 times higher odds of SOD (OR, 7.68; $p < 0.001$).

Regarding model performance, the anxiety model demonstrated a percent concordance of 86.5% and a Somers' D value of 0.737, indicating strong predictive ability. The Akaike information criterion (AIC) for the anxiety model was 1,883,104.2, suggesting good overall model fit. In comparison, the SOD model demonstrated a percent concordance of 77.3% and a Somers' D value of 0.566, reflecting weaker predictive performance relative to the anxiety model. The AIC for the SOD model was 722,196.71, indicating acceptable model fit but lower predictive capacity. Overall, both models were statistically significant; however, the model predicting anxiety demonstrated superior fit and discrimination compared with the model predicting SOD (Table 3).

## Discussion

This study found that anxiety was significantly associated with SOD. These findings are consistent with previous

**Table 3.** Factors influencing anxiety and smartphone overdependence: multivariable logistic regression

| Dependent<br>Independent (ref.) | Category | OR (95% CI) | *p* | Percent concordance (%) | Somers' D | F | *p* |
|---|---|---|---|---|---|---|---|
| Anxiety | | | <0.001 | 86.5 | 0.737 | 708.28 | |
| Sex (male) | Female | 1.28 (1.19–1.37) | <0.001 | | | | <0.001 |
| School (middle school) | High school | 0.93 (0.86–1.00) | 0.041 | | | | 0.041 |
| Residential area (urban) | Rural | 0.92 (0.80–1.05) | 0.200 | | | | 0.200 |
| Economic status (upper) | Middle | 0.99 (0.92–1.07) | 0.872 | | | | 0.872 |
| | Lower | 1.27 (1.15–1.40) | <0.001 | | | | <0.001 |
| Students' test scores (upper) | Middle | 0.93 (0.85–1.02) | 0.109 | | | | 0.109 |
| | Lower | 1.00 (0.92–1.08) | 0.974 | | | | 0.974 |
| Smartphone use (<2 h/d) | ≥2 and ≤5 | 0.96 (0.82–1.12) | 0.568 | | | | 0.568 |
| | >5 and ≤10 | 0.95 (0.81–1.11) | 0.510 | | | | 0.510 |
| | >10 and ≤15 | 1.01 (0.83–1.23) | 0.938 | | | | 0.938 |
| | >15 | 1.00 (0.75–1.35) | 0.981 | | | | 0.981 |
| Perceived stress (less) | A lot | 4.90 (4.53–5.29) | <0.001 | | | | <0.001 |
| Depression (no) | Yes | 2.86 (2.66–3.07) | <0.001 | | | | <0.001 |
| Loneliness (no) | Yes | 3.88 (3.59–4.19) | <0.001 | | | | <0.001 |
| Smartphone overdependence (normal risk) | Potential risk | 1.76 (1.64–1.90) | <0.001 | | | | <0.001 |
| | High risk | 3.51 (3.04–4.06) | <0.001 | | | | <0.001 |
| Percent concordant = 86.5%; Somers' D = 0.737; F = 708.28; *p* < 0.001 | | | | | | | |
| Smartphone overdependence | | | <0.001 | 77.3 | 0.566 | 108.43 | |
| Sex (male) | Female | 1.11 (0.98–1.26) | 0.112 | | | | 0.112 |
| School (middle school) | High school | 0.98 (0.87–1.10) | 0.743 | | | | 0.743 |
| Residential area (urban) | Rural | 0.73 (0.56–0.95) | 0.021 | | | | 0.021 |
| Economic status (upper) | Middle | 0.84 (0.75–0.95) | 0.004 | | | | 0.004 |
| | Lower | 1.03 (0.87–1.22) | 0.737 | | | | 0.737 |
| Students' test scores (upper) | Middle | 0.76 (0.65–0.89) | 0.001 | | | | 0.001 |
| | Lower | 1.14 (0.99–1.30) | 0.071 | | | | 0.071 |
| Smartphone use (<2 h/d) | ≥2 and ≤5 | 4.10 (1.97–8.52) | 0.000 | | | | 0.000 |
| | >5 and ≤10 | 9.74 (4.68–20.29) | <0.001 | | | | <0.001 |
| | >10 and ≤15 | 16.60 (7.87–35.03) | <0.001 | | | | <0.001 |
| | >15 | 26.66 (12.41–57.29) | <0.001 | | | | <0.001 |
| Perceived stress (less) | A lot | 1.16 (1.01–1.34) | 0.036 | | | | 0.036 |
| Depression (no) | Yes | 1.07 (0.93–1.23) | 0.317 | | | | 0.317 |
| Loneliness (no) | Yes | 1.25 (1.07–1.46) | 0.004 | | | | 0.004 |
| Generalized anxiety disorder (minimal) | Mild | 2.38 (2.05–2.77) | <0.001 | | | | <0.001 |
| | Moderate | 3.44 (2.81–4.20) | <0.001 | | | | <0.001 |
| | Severe | 7.68 (6.19–9.52) | <0.001 | | | | <0.001 |
| Percent concordant = 77.3%; Somers' D = 0.566; F = 108.43; *p* < 0.001 | | | | | | | |

Ref., reference; OR, odds ratio; CI, confidence interval.

studies reporting significant associations between anxiety and SOD [8,17,18]. In addition, higher levels of SOD were associated with increased odds of anxiety, aligning with prior studies that examined anxiety in relation to SOD [6,7,15,16,23]. Notably, recent longitudinal evidence further supports this association. A prospective cohort study among Chinese adolescents reported that new-onset or persistent smartphone dependence was associated with an increased subsequent risk of anxiety symptoms, whereas cessation of dependence was not associated with elevated risk, suggesting that sustained problematic use may precede later emotional difficulties [24]. In the multivariate logistic regression analyses, the magnitude of the associations between anxiety and SOD was attenuated compared with univariate models (Table S1). This finding is consistent with the results reported by Jo et al. [9], who observed a reduction in the effect size of GAD after adjusting for relevant covariates. This pattern suggests that the association between anxiety and SOD may be moderated by other psychosocial factors, such as stress, loneliness, and smartphone usage



https://doi.org/10.24171/j.phrp.2025.0510

time, reflecting a multifactorial and context-dependent interaction. After adjustment for key covariates, statistically significant associations between anxiety and SOD persisted, indicating robust reciprocal associations rather than causal effects. This interpretation is consistent with longitudinal findings suggesting reciprocal pathways between problematic mobile phone use and internalizing symptoms. For example, a longitudinal study among Korean adolescents demonstrated bidirectional associations between mobile phone addiction and depressive symptoms over time, indicating that psychological distress may both contribute to and result from problematic phone use [25]. Taken together, these findings underscore the importance of considering the broader psychosocial context in which these variables are associated, as focusing on a single factor may obscure the complexity of adolescent mental health.

Anxiety has been shown to be strongly associated with psychological factors such as stress, loneliness, and depression, as well as with SOD and sociodemographic characteristics including female sex and lower socioeconomic status. Our findings are consistent with those of Yang et al. [23], who reported significant associations between PSU and depression and anxiety in their systematic review. Similarly, Lee and Lee [7] reported significant associations among SOD, anxiety, and suicidal ideation across genders. Specifically, girls with PSU demonstrated substantially higher odds of anxiety compared with their non-PSU counterparts [7]. These findings further support the interpretation that SOD is closely associated with adverse mental health outcomes. This pattern is also consistent with prior research indicating that females tend to report higher levels of anxiety and depression [6,7]. Taken together, the consistency across studies highlights the close association between excessive smartphone use and adolescent mental health, suggesting that interventions addressing smartphone use may represent relevant components of broader mental health strategies for both genders. However, longitudinal evidence also suggests that these associations may not be uniform across subgroups. A recent longitudinal study from the Republic of Korea reported that increased smartphone use predicted poorer mental health outcomes particularly among female adolescents, highlighting potential heterogeneity by gender and contextual factors [26].

In contrast, SOD was most strongly associated with the amount of time spent using smartphones, with anxiety, loneliness, and stress also showing significant associations. In the present study, smartphone usage time demonstrated the strongest association with SOD. This finding is consistent with the results reported by Cha et al. [27], who observed that the prevalence of smartphone dependence was 17.9% among adolescents using smartphones for less than 4 hours per day and increased to 30.5% among those using smartphones for more than 4 hours per day, indicating that higher usage time is associated with a greater likelihood of smartphone dependence. Similarly, previous studies have reported significant associations between smartphone usage time and smartphone addiction among adolescents [28–30]. Prior studies have also reported female sex as being significantly associated with SOD [28,29], whereas sex was not significantly associated with SOD in the present study. Chu et al. [31] reported significant associations between depressive symptoms and smartphone dependency, and Lee [32] similarly reported associations between depressive symptoms, loneliness, and SOD regardless of sex. In contrast, depression was not significantly associated with SOD in this study. Elhai et al. [4] reported that, without adjusting for other relevant variables, depression was consistently associated with PSU with at least medium effect sizes. In the present study, however, depression did not emerge as a significant factor influencing SOD. Conversely, Oh and Heo [33] reported significant associations between SOD and depression. With respect to loneliness, this study identified a significant association between loneliness and SOD, whereas Lapierre et al. [30] reported contrasting findings, suggesting that smartphone addiction significantly influenced loneliness in a longitudinal context. Taken together, these findings suggest that the relationships among SOD, depression, and loneliness are complex and potentially reciprocal, warranting further investigation using longitudinal designs [30,33]. Furthermore, previous research has reported divergent findings regarding the association between anxiety and SOD. In the present study, anxiety was significantly associated with SOD, whereas Hussain et al. [34] reported no significant association between anxiety and PSU in analyses that included personality traits. These discrepancies may reflect differences in the covariates included and the conceptual frameworks applied across studies. The present study incorporated psychosocial variables such as stress, loneliness, anxiety, and smartphone usage time, whereas Chu et al. [31] emphasized factors including self-esteem, aggressiveness, affective parenting attitudes, peer attachment, and resilience, and Hussain et al. [34] focused primarily on personality traits.

The findings from this study, together with those of previous studies, suggest that the statistical significance of variables associated with SOD may vary depending on the set of factors included in the analysis. These findings indicate that the association between anxiety and SOD is more complex than a simple unidirectional pattern. Although anxiety was significantly associated with SOD,

an association in the opposite direction was also observed after accounting for other relevant factors. This highlights the need for future research to explore the diverse and interacting variables associated with SOD more thoroughly. By incorporating a broader range of psychological and interpersonal factors, future studies may provide a more nuanced understanding of how these variables collectively relate to smartphone dependency. From a practical perspective, these findings suggest that interventions addressing SOD may be relevant for adolescent mental health. While it remains important to manage anxiety directly, addressing smartphone use may represent a complementary consideration within broader mental health strategies. Accordingly, integrated approaches that combine psychological support with behavioral guidance on smartphone use warrant further evaluation in future interventional studies. These findings underscore the importance of considering a wider range of factors in both research and practice when examining the interconnected nature of technology use and mental health. Importantly, this study identified a significant disparity in anxiety prevalence by socioeconomic status. Adolescents from lower-income households exhibited higher levels of psychological distress, suggesting that future prevention efforts may benefit from prioritizing socioeconomically disadvantaged populations.

This study highlights the importance of addressing SOD and anxiety as interconnected issues in adolescent populations. The findings suggest that schools may consider comprehensive approaches that integrate emotional regulation support with guidance on healthy smartphone use. Given the observed reciprocal associations, focusing on a single dimension may be insufficient to fully address adolescent well-being. Multitiered systems of support, involving school nurses, counselors, and mental health professionals, may facilitate the identification of students at risk and the delivery of appropriate support. Anxiety has been shown to be significantly associated with suicidal ideation, suicide planning, and suicide attempts among adolescents [35]; therefore, addressing both anxiety and PSU may have implications that extend beyond emotional well-being.

This study contributes to a deeper understanding of the relationship between anxiety and SOD; however, several limitations should be acknowledged. First, the cross-sectional nature of the data limits the ability to infer causality between SOD and anxiety. Although bidirectional associations were observed, longitudinal designs are required to establish temporal precedence. Second, all variables, including smartphone usage, anxiety symptoms, and SOD levels, were assessed using self-reported questionnaires, which may be subject to recall bias or social desirability bias. Future studies would benefit from incorporating objective measures, such as digital usage tracking or clinician-administered anxiety assessments. In addition, several key psychosocial constructs, including stress, loneliness, and depressive symptoms, were measured using brief or dichotomized items, which may not fully capture their multidimensional nature. Furthermore, this study did not account for several well-established confounders, such as sleep duration and quality, physical activity, family environment, academic stress, and experiences including cyberbullying, all of which may influence both smartphone use and anxiety. Finally, although the sample is representative of Korean adolescents, cultural, educational, and technological differences may limit the generalizability of these findings to adolescents in other countries. Cross-national research is needed to determine whether similar patterns are observed across diverse sociocultural contexts.

## Conclusion

In conclusion, this study demonstrates a significant reciprocal association between anxiety and SOD among adolescents. Adolescents with higher levels of smartphone use exhibited greater odds of anxiety, while those with elevated anxiety levels showed higher odds of SOD. These findings suggest that integrated approaches addressing both mental health and digital behavior may be particularly relevant, especially for females and adolescents from lower socioeconomic backgrounds. As smartphone use continues to increase globally, public health and school-based initiatives may benefit from considering the psychological correlates of digital engagement. Addressing these interconnected factors may contribute to more effective strategies aimed at promoting adolescent mental health.

## Supplementary Material

**Table S1.** The reciprocal effects of anxiety and smartphone overdependence: univariate logistic regression. Supplementary data are available at at https://doi.org/10.24171/j.phrp.2025.0510.

## Notes

### Ethics Approval

This study was exempted by the Institutional Review Board of Jeju National University (approval number: JJNU-IRB-2024-086), and was performed in accordance with the principles of the Declaration of Helsinki. This study used publicly available data from the 19th KYRBS, conducted by the KDCA and the Ministry of Education. Informed


https://doi.org/10.24171/j.phrp.2025.0510

consent was obtained from all participants by the KDCA prior to data collection.

### Conflicts of Interest
The author has no conflicts of interest to declare.

### Funding
None.

### Availability of Data
The data supporting the findings of this study are openly available from the KYRBS, hosted by the KDCA (https://www.kdca.go.kr/yhs/). These data do not have a DOI and can be accessed by registering and logging into the system. The User Guide is also available on the same homepage.

### Acknowledgements
This study was based on data from the 19th Korea Youth Risk Behavior Survey (2023), conducted by the Ministry of Education, the Ministry of Health and Welfare, and the Korea Disease Control and Prevention Agency. The author gratefully acknowledges these organizations for providing access to the data. All analyses and interpretations presented in this article are solely the responsibility of the author and do not necessarily reflect the official views of the data-providing institution.

## References

1. Poznyak V. Public health implications of excessive use of the internet and other communication and gaming platforms [Internet]. World Health Organization; 2018 [cited 2025 May 27]. Available from: https://www.who.int/news/item/13-09-2018-public-health-implications-of-excessive-use-of-the-internet-and-other-communication-and-gaming-platforms.
2. World Health Organization (WHO) (CH). Public health implications of excessive use of the internet, computers, smartphones and similar electronic devices: meeting report; Main Meeting Hall, Foundation for Promotion of Cancer Research, National Cancer Research Centre, Tokyo, Japan; 27-29 August 2014. WHO; 2015.
3. Ministry of Science and ICT; National Information Society Agency (KR). The survey on smartphone overdependence, 2023. Ministry of Science and ICT, National Information Society Agency; 2024. Korean.
4. Elhai JD, Dvorak RD, Levine JC, et al. Problematic smartphone use: a conceptual overview and systematic review of relations with anxiety and depression psychopathology. J Affect Disord 2017;207:251–9.
5. Stankovic M, Nesic M, Cicevic S, et al. Association of smartphone use with depression, anxiety, stress, sleep quality, and internet addiction. Empirical evidence from a smartphone application. Pers Individ Dif 2021;168:110342.
6. Noh D, Shim MS. Factors influencing smartphone overdependence among adolescents. Sci Rep 2024;14:7725.
7. Lee MS, Lee H. Problematic smartphone use and its relationship with anxiety and suicidal ideation among South Korean adolescents. Psychiatry Investig 2023;20:843–52.
8. Cao M, Yang H, Chen D. Relationship between anxiety and problematic smartphone use in first-year junior high school students: moderated mediation effects of physical activity and school adjustment. Behav Sci (Basel) 2023;13:901.
9. Jo S, Baek IC, Fava M, et al. Association of smartphone overuse with depression, anxiety, and other addictive behaviors: a nationwide community sample of Korean adults. Psychiatry Res 2021;304:114133.
10. Dresp-Langley B, Hutt A. Digital addiction and sleep. Int J Environ Res Public Health 2022;19:6910.
11. Sohn SY, Rees P, Wildridge B, et al. Prevalence of problematic smartphone usage and associated mental health outcomes amongst children and young people: a systematic review, meta-analysis and GRADE of the evidence. BMC Psychiatry 2019;19:356.
12. Ministry of Science and ICT; National Information Society Agency (KR). The survey on smartphone overdependence, 2020. Ministry of Science and ICT, National Information Society Agency; 2021. Korean.
13. Keyes KM, Platt JM. Annual research review: Sex, gender, and internalizing conditions among adolescents in the 21st century: trends, causes, consequences. J Child Psychol Psychiatry 2024;65:384–407.
14. Lee SR, Kim EY, Ha S, et al. Mediating effect of stress recognition on the effect of generalized anxiety disorder on smartphone dependence. J Clin Med 2023;12:7359.
15. Lee YS, Joo JH, Shin J, et al. Association between smartphone overdependence and generalized anxiety disorder among Korean adolescents. J Affect Disord 2023;321:108–13.
16. Ratan ZA, Parrish AM, Zaman SB, et al. Smartphone addiction and associated health outcomes in adult populations: a systematic review. Int J Environ Res Public Health 2021;18:12257.
17. Yun H, Choi EK. Association between smartphone overdependence and mental health in South Korean adolescents: a secondary data analysis. Child Health Nurs Res 2024;30:87–96.
18. Wang A, Wang Z, Zhu Y, et al. The prevalence and psychosocial factors of problematic smartphone use among Chinese college students: a three-wave longitudinal study. Front Psychol 2022;13:877277.
19. Ministry of Education Korea Disease Control and Prevention Agency (KR). The 19th Korea Youth Risk Behavior Survey statistics 2023. Korea Disease Control and Prevention Agency; 2024. Korean.
20. Ministry of Education; Korea Disease Control and Prevention Agency (KR). User's guidelines of the raw data from the Korea Youth Risk Behavior Survey (The 1st-19th). Korea Disease Control and Prevention Agency; 2024. Korean.
21. Spitzer RL, Kroenke K, Williams JB, et al. A brief measure for assessing generalized anxiety disorder: the GAD-7. Arch Intern Med 2006;166:1092–7.
22. Park E, Noh JW. Towards a valid and reliable smartphone overdependence scale: factor analysis, and measurement invariance testing. Psychiatry Res 2025;352:116663.
23. Yang J, Fu X, Liao X, et al. Association of problematic smartphone use with poor sleep quality, depression, and anxiety: a systematic review and meta-analysis. Psychiatry Res 2020;284:112686.
24. Li Y, Lin YF, Wu H, et al. Changes in smartphone dependence and depressive and anxiety symptoms among Chinese adolescents. BMC Med 2025;23:523.
25. Jun S. The reciprocal longitudinal relationships between mobile phone

addiction and depressive symptoms among Korean adolescents. Comput Human Behav 2016;58:179–86.
26. Rudolf R, Kim N. Smartphone use, gender, and adolescent mental health: longitudinal evidence from South Korea. SSM Popul Health 2024;28:101722.
27. Cha JH, Choi YJ, Ryu S, et al. Association between smartphone usage and health outcomes of adolescents: a propensity analysis using the Korea youth risk behavior survey. PLoS One 2023;18:e0294553.
28. Lee EJ, Kim YK, Lim S. Factors influencing smartphone addiction in adolescents. Child Health Nurs Res 2017;23:525–33. Korean.
29. Choi SW, Kim DJ, Choi JS, et al. Comparison of risk and protective factors associated with smartphone addiction and internet addiction. J Behav Addict 2015;4:308–14.
30. Lapierre MA, Zhao P, Custer BE. Short-term longitudinal relationships between smartphone use/dependency and psychological well-being among late adolescents. J Adolesc Health 2019;65:607–12.
31. Chu HS, Tak YR, Lee H. Exploring psychosocial factors that influence smartphone dependency among Korean adolescents. PLoS One 2020;15:e0232968.
32. Lee J. Effect of loneliness and depressive symptoms on smartphone overdependence among South Korean adolescents: a nationwide cross-sectional study. Korean J Health Promot 2022;22:1–9.
33. Oh WO, Heo YJ. Exploring the link between smartphone overdependence, depression, and suicidal behaviors through the mediating effect of lifestyle risk behaviors among South Korean adolescents: a cross-sectional study using national big data. J Pediatr Health Care 2024;38:298–309.
34. Hussain Z, Griffiths MD, Sheffield D. An investigation into problematic smartphone use: the role of narcissism, anxiety, and personality factors. J Behav Addict 2017;6:378–86.
35. Park E, Park S. Gender-specific predictors of suicidal ideation, planning, and attempts among adolescents. Curr Psychol 2025;44:15157–67.


https://doi.org/10.24171/j.phrp.2025.0510

phrp
OSONG PUBLIC HEALTH AND RESEARCH PERSPECTIVES

pISSN 2210-9099 eISSN 2233-6052
https://doi.org/10.24171/j.phrp.2025.0204
Osong Public Health Res Perspect 2026;17(1):83-93

**Original Article**

# Correlates and co-occurrence of risk factors for non-communicable diseases among adolescents in schools in Karnataka, India: a cross-sectional study

**Tejaswini Bangalore Darukaradhya[1], Krishnamurthy Jayanna[1,2], Shivaraj Nallur Somanna[3], Sony Sequeira[1], Shalini Chandrashekar Nooyi[3]**

[1]Division of Public Health, Faculty of Life and Allied Health Sciences, M.S. Ramaiah University of Applied Sciences, Bengaluru, India
[2]Center for Integrative Health and Wellbeing, Bengaluru, India
[3]Department of Community Medicine, Ramaiah Medical College, M.S. Ramaiah University of Applied Sciences, Bengaluru, India

## ABSTRACT

**Objectives:** Non-communicable disease (NCD) risk among adolescents represents a growing concern due to modifiable, lifestyle-related behavioral risk factors. Early identification and control of these factors are essential for prevention. This study assessed the correlates and co-occurrence of NCD-related lifestyle risk factors among school-going adolescents in Karnataka, India, aiming to inform intervention development.

**Methods:** Screening was conducted among 1,100 school adolescents aged 13–16 years from 8 randomly selected urban and rural schools in Karnataka. Data were collected using a validated self-administered questionnaire covering sociodemographic characteristics and social cognitive theory predictors of lifestyle practices. Descriptive statistics, chi-square tests, and logistic regression were employed.

**Results:** Of the 1,100 adolescents surveyed, 552 and 548 were from urban and rural areas, respectively. Both groups reported high rates of insufficient fruit and vegetable (FV) intake (96.7% and 67.7%, respectively), inadequate physical activity (96.7% and 68.6%), tobacco use (5.6% and 11.5%), and alcohol consumption (5.6% and 10.8%). On logistic regression, urban adolescents were significantly more likely than rural peers to exhibit multiple behavioral risk factors, with 19-fold higher odds of having ≥1 factor (adjusted odds ratio [AOR], 19.04; $p < 0.001$) and 4-fold higher odds of having ≥2 (AOR, 4.06; $p < 0.001$). Parental (particularly maternal) education was associated with NCD risk (AOR, 1.82; $p = 0.001$). Physical inactivity significantly co-occurred with low FV intake (71.7%) and junk food consumption (72.8%).

**Conclusion:** Unhealthy lifestyle behaviors among adolescents displayed significant co-occurrence, underscoring the critical need for comprehensive, theory-based school interventions to address multiple interconnected risk factors and mitigate the burden of NCDs.

**Keywords:** Adolescent; Health risk behaviors; Lifestyle; Noncommunicable diseases

**Received:** June 10, 2025
**Revised:** December 10, 2025
**Accepted:** January 11, 2026

Corresponding author:
Tejaswini Bangalore Darukaradhya
Division of Public Health, Department of Allied Health Sciences, Faculty of Life and Allied Health Sciences, M.S. Ramaiah University of Applied Sciences, Bengaluru, Karnataka 560054, India
E-mail: drtejaswini02@gmail.com

The opinions expressed by authors contributing to this journal do not necessarily reflect the opinions of the Korea Disease Control and Prevention Agency and Korea National Institute of Health.

© 2026 Korea Disease Control and Prevention Agency.
This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

## Introduction

Non-communicable diseases (NCDs) impose a growing public health burden, accounting for approximately 74% of deaths worldwide, with over 85% of premature NCD deaths occurring in low- and middle-income countries (LMICs) [1]. Major NCDs include cardiovascular diseases, chronic respiratory diseases, type 2 diabetes, and cancer. These conditions are primarily driven by behavioral risk factors that often emerge during childhood and adolescence and are shaped by social determinants such as socioeconomic status and education [2]. Behavioral risk factors, also known as modifiable lifestyle factors, include unhealthy diet, inadequate physical activity, tobacco use, and harmful alcohol consumption [1].

School-going adolescents are particularly susceptible to unhealthy lifestyles that may persist into adulthood and adversely affect health outcomes, increasing the risk of premature morbidity and mortality [3–5]. Adolescence is a critical developmental period characterized by rapid physical, psychological, and social transitions that can shape health behaviors and attitudes, making it an opportune window for preventive interventions and health promotion [3,5]. The approximately 1.2 billion adolescents (10–19 years old) worldwide—90% of whom live in LMICs—often face structural and contextual challenges that compound health risks [6]. In India, evidence indicates substantial variation in behavioral risk profiles across urban and rural settings and between private and public school adolescents, impacted by differences in access, exposure, and socioeconomic context [7–9].

Alongside behavioral risk factors, socialization, technology, and environmental influences can substantially affect adolescent decision-making, shaping health behaviors and well-being [10]. One Indian study reported that excessive social media use was associated with poor sleep, stress, and unhealthy lifestyle choices [11], while another study suggested that school climate may negatively influence adolescent health [12]. These factors can have lasting effects, highlighting the need for multifactorial interventions.

Schools represent a key setting for promoting healthy lifestyle behaviors among adolescents, providing a platform for comprehensive health education and interventions [13]. Implementing health-promoting initiatives within schools can enable outreach to large numbers of adolescents and support positive behavior change, ultimately reducing the burden of NCDs and promoting sustainable health outcomes [13].

Surveys in India and elsewhere have reported a high prevalence of risk behaviors and unhealthy lifestyles among adolescents, supporting the need for interventions within educational settings. A recent national cross-sectional survey among 15–17-year-olds reported 3.1% tobacco use, 25.2% inadequate physical activity, 6.2% overweight, and 1.8% obesity [13]. A survey in Tanzania similarly reported a high prevalence of combined risk factors (17.6% unhealthy diet and inadequate physical activity), emphasizing the importance of adopting a strategic, multifactorial approach rather than focusing on single risk factors [14].

A review published in India reported that young people (10–24 years old) are vulnerable to a range of intrinsic and extrinsic factors that affect health and safety. Nearly 10%–30% of adolescents experience behaviors and conditions that adversely affect health, warranting urgent attention from policymakers and public health professionals. If not addressed early, NCDs can impose a substantial burden on Indian society in terms of mortality, morbidity, disability, and socioeconomic losses [15]. The present study was conducted as part of a program to inform the development and implementation of interventions for adolescents in urban (Bengaluru) and rural (Chikkaballapura district) areas of South Karnataka. The specific objectives were to assess the correlates and co-occurrence of lifestyle risk factors among school-going adolescents in Karnataka that predispose them to NCDs.

### HIGHLIGHTS

- Adolescents in Karnataka, India, display a high prevalence of lifestyle-related risk factors for non-communicable diseases (NCDs). Urban adolescents have a significantly higher likelihood of multiple risk factors, highlighting geographic health disparities. The findings reinforce the need for comprehensive, theory-driven school-based interventions to promote sustainable health behaviors and reduce the long-term burden of NCDs.

## Materials and Methods

### Study Design

A cross-sectional design was adopted to investigate NCD-related lifestyle risk factors among school-going adolescents.



https://doi.org/10.24171/j.phrp.2025.0204

## Setting

The study was conducted in 2 districts of Karnataka, India: Bengaluru (urban) and Chikkaballapura (rural). Both public and private schools in urban and rural areas were selected to ensure diversity and contextual representation of the region's cultural and socioeconomic contexts.

## Participants

School-going adolescents aged 13–16 years were randomly selected using a multistage sampling strategy. First, Bengaluru and Chikkaballapura districts were chosen as field practice areas of a private institution (M.S. Ramaiah University of Applied Sciences) in Karnataka. Bengaluru, the urban state capital, has a diverse metropolitan population, whereas Chikkaballapura provides rural demographic representation. Second, within each district, 4 schools were randomly selected using probability proportional to enrollment size. Third, classes from grades 8 to 10 were included. Fourth, all eligible adolescents aged 13–16 years were invited to participate. Informed consent was obtained from both students and parents/guardians. A total of 1,100 adolescents participated in the study (a 100% response rate).

## Sample Size

The sample size was calculated based on Dorle et al. [16] using prevalence estimates for physical activity (68.9% with intervention vs. 35.1% without). Assuming 95% confidence, 90% power, a 10% risk difference, and 5% loss to follow-up, the required minimum sample size was 1,100 participants. Physical activity was selected for the sample size estimation as part of a broader intervention program because of its variability, statistical strength, and relevance to adolescent risk profiling.

## Variables

The outcome variables included unhealthy diet (low fruit and vegetable [FV] intake, junk food consumption, and sugar-sweetened beverage [SSB] consumption), physical inactivity, tobacco use, and alcohol consumption. Exposure variables included sociodemographic characteristics (gender, age, residence, parental education, and occupation) and environmental influences. All variables were dichotomized into favorable and unfavorable categories based on World Health Organization (WHO) standards or daily guidelines (Table 1).

## Data Collection and Measurements

Data were collected using a pre-validated, pilot-tested questionnaire developed through a 5-step approach. The tool covered sociodemographic characteristics, NCD knowledge, lifestyle behaviors (dietary habits, physical activity, tobacco use, and alcohol consumption), and environmental influences (peer pressure, media exposure, and cultural norms). Standardized items were incorporated from the Food Frequency Questionnaire [17], the Global School-based Student Health Survey [18], the Global Youth Tobacco Survey [19], the WHO STEPwise approach to NCD risk factor surveillance instrument [20], and prior research. Pilot testing among 180 adolescents informed refinements; the Cronbach α internal consistency coefficient was 0.85. Trained teachers administered the questionnaire in classrooms.

**Table 1.** Outcome variables and operational definitions

| Variable | Definition | Classification criteria |
|---|---|---|
| 1. Unhealthy diet (composite) | Includes 3 dietary components reflecting poor nutritional habits: FV consumption, junk food, and SSBs | See subcomponents below |
| FV consumption | Less than 5 servings per day (approximately 400 g); indicates inadequate dietary consumption | Never or less than once a day versus more than once a day |
| Junk/processed food consumption | Foods high in fat, salt, and sugar with low nutritive value | Daily or more than once a day versus less than once a day |
| SSB consumption | Consumption exceeding 50 g of free sugars per day | Daily or more than once a day versus less than once a day |
| 2. Physical inactivity | Insufficient bodily movement requiring energy expenditure (at least 60 min/d of moderate-to-vigorous physical activity in the past 7 days) | Never or insufficient versus daily or sufficient |
| 3. Tobacco use | Use of any smoked (cigarette, cigar, pipe) or smokeless (gutkha, zarda, paan masala, khaini) tobacco in the past 30 days | Yes versus no |
| 4. Alcohol consumption | Consumption of any form of alcohol in the past 30 days | Yes versus no |

FV, fruit and vegetable; SSB, sugar-sweetened beverage.

### Statistical Analysis

Descriptive statistics were used to summarize participant characteristics and the prevalence of lifestyle-related risk factors. Chi-square tests were used to assess associations between risk behaviors and sociodemographic variables. Univariate logistic regression was used to estimate crude odds ratios (ORs) and 95% confidence intervals (CIs); variables displaying significance at $p < 0.05$ were entered into multivariable models using backward stepwise elimination. Diagnostic checks (assumptions of a binary outcome and independence of observations, multicollinearity assessed using variance inflation factors, outliers assessed using the Cook distance, and model fit assessed using the Hosmer-Lemeshow test) were performed systematically and are reported in Supplementary Material 1. For the co-occurrence analysis, ≥2 behavioral risk factors were operationally defined as the presence of 2 or more unfavorable lifestyle behaviors (diet, physical inactivity, tobacco use, and alcohol consumption). Pairwise co-occurrence was assessed descriptively, and overall clustering was analyzed using logistic regression with a binary outcome (≥2 vs. <2 risk factors). All analyses were conducted using IBM SPSS ver. 20.0 (IBM Corp.), with $p$-values of less than 0.05 considered to indicate statistical significance.

### Ethical Consideration

This study was approved by the institutional ethics committee of Ramaiah Medical College prior to study initiation (Ref no: MSRMC/EC/AP-02/11-2022). Permission was obtained from the schools, and written informed consent from parents/guardians and assent from the adolescents were secured. The study was prospectively registered in the Clinical Trials Registry (CTRI) of India (registration number: CTRI/2023/01 /048977). Data were kept confidential and anonymized before analysis.

## Results

### Participant Characteristics

The study included 1,100 school-going adolescents aged 13–16 years (Table 2). Of these, 46.0% ($n = 506$) were ≤14 years old and 54.0% ($n = 594$) were >14 years old. The sample comprised 50.2% urban and 49.8% rural adolescents, with 54.6% girls and 45.4% boys. Overall, 63.2% of participants' fathers and 34.0% of mothers had primary- or secondary-level education. Regarding occupation, 54.5% of fathers were unskilled workers and 77.5% of mothers were homemakers. Clustering of lifestyle risk factors was common: 95% reported ≥1 risk factor, 86% reported ≥2, 70% had ≥3, 13% had ≥4, and 3% had 5 or 6. This pattern reflects the increasing burden of risk as the number of co-occurring factors rises.

**Table 2.** Sociodemographic characteristics of school-going adolescents ($n = 1,100$)

| Variable | Category | Frequency (%) |
|---|---|---|
| Age (y) | ≤14 | 506 (46.0) |
| | >14 | 594 (54.0) |
| School location | Urban area | 552 (50.2) |
| | Rural area | 548 (49.8) |
| Gender | Boys | 499 (45.4) |
| | Girls | 601 (54.6) |
| Father's education | Primary | 237 (21.5) |
| | Secondary | 695 (63.2) |
| | Diploma/degree | 45 (4.1) |
| | No formal education | 123 (11.2) |
| Mother's education | Primary | 240 (21.8) |
| | Secondary | 374 (34.0) |
| | Diploma/degree | 10 (0.9) |
| | No formal education | 476 (43.3) |
| Father's occupation[a)] | Skilled | 66 (6.0) |
| | Semiskilled | 428 (38.9) |
| | Unskilled | 600 (54.5) |
| | No employment | 6 (0.5) |
| Mother's occupation | Homemaker | 853 (77.5) |
| | Working | 247 (22.5) |
| Behavioral risk factors | One risk factor | 1,047 (95.2) |
| | Two risk factors | 943 (85.7) |
| | Three risk factors | 765 (69.5) |
| | Four risk factors | 143 (13.0) |
| | Five or 6 risk factors | 32 (2.9) |

Adolescents' characteristics across demographic factors are presented as numbers and percentages.
[a)]Classification is based on the Indian National Classification of Occupations.

### Associations between Sociodemographic Variables and Lifestyle Behaviors

Table 3 displays significant associations between sociodemographic variables and lifestyle practices among adolescents. Chi-square analysis indicated that school location (urban vs. rural) was significantly associated with FV intake ($\chi^2 = 159$, $p < 0.001$), junk food intake ($\chi^2 = 71.5$, $p < 0.001$), SSB intake ($\chi^2 = 44.07$, $p < 0.001$), physical activity ($\chi^2 = 152$, $p < 0.001$), tobacco use ($\chi^2 = 12.17$, $p < 0.001$), and alcohol consumption ($\chi^2 = 9.71$, $p < 0.001$). Additionally, age (≤14 years vs. >14 years) was associated with FV intake ($\chi^2 = 12.5$, $p = 0.001$) and alcohol consumption ($\chi^2 = 4.3$, $p < 0.001$). Parental education was significantly associated with FV intake (father's education: $\chi^2 = 10.7$, $p = 0.013$; mother's education: $\chi^2 = 37.1$, $p < 0.001$), physical activity (father's education: $\chi^2 = 10.1$, $p = 0.018$; mother's education: $\chi^2 = 17.9$, $p < 0.001$), and tobacco use (father's education: $\chi^2 = 15.9$, $p = 0.001$; mother's



https://doi.org/10.24171/j.phrp.2025.0204

https://doi.org/10.24171/j.phrp.2025.0204

**Table 3.** Associations between non-communicable disease risk factors and demographic variables among adolescents

| Variable | Proportion of adolescents with inadequate FV intake | | Proportion of adolescents with unhealthy diet (junk) | | Proportion of adolescents consuming SSBs | | Proportion of adolescents with physical inactivity | | Proportion of adolescents using tobacco | | Proportion of adolescents consuming alcohol | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Never or <once a day | $\chi^2/p$ | Daily >once a day | $\chi^2/p$ | Daily >once a day | $\chi^2/p$ | Never or insufficient PA | $\chi^2/p$ | Daily >once a day | $\chi^2/p$ | Daily >once a day | $\chi^2/p$ |
| Gender | | 0.5/0.479 | | 0.006/0.939 | | 0.136/0.712 | | 0.261/0.609 | | 0.529/0.467 | | 0.067/0.796 |
| Boy ($n$=499) | 415 (83.2) | | 416 (83.4) | | 326 (65.3) | | 416 (83.4) | | 46 (9.2) | | 42 (8.4) | |
| Girl ($n$=601) | 490 (81.5) | | 500 (83.2) | | 399 (66.4) | | 494 (82.2) | | 48 (8.0) | | 48 (8.0) | |
| School location | | 159/0.001 | | 71.5/0.001 | | 44.07/0.001 | | 152.24/0.001 | | 12.17/0.001 | | 9.71/0.002 |
| Urban area ($n$=552) | 534 (96.7) | | 512 (92.8) | | 416 (75.4) | | 534 (96.7) | | 31 (5.6) | | 31 (5.6) | |
| Rural area ($n$=548) | 371 (67.7) | | 404 (73.7) | | 309 (56.4) | | 376 (68.6) | | 63 (11.5) | | 59 (10.8) | |
| Age | | 12.5/0.001 | | 0.049/0.826 | | 0.102/0.75 | | | | 2.82/0.093 | | 4.305/0.038 |
| ≤14 y ($n$=506) | 394 (77.9) | | 420 (83.0) | | 331 (65.4) | | 413 (81.6) | 0.803/0.37 | 51 (10.1) | | 32 (6.3) | |
| >14 y ($n$=594) | 511 (86.0) | | 496 (83.5) | | 394 (66.3) | | 497 (83.7) | | 43 (7.2) | | 58 (9.8) | |
| Father's education | | 10.7/0.013 | | 12.28/0.006 | | 9.92/0.019 | | 10.09/0.018 | | 15.862/0.001 | | 2.65/0.448 |
| Primary ($n$=237) | 211 (89.0) | | 205 (86.5) | | 167 (70.5) | | 209 (88.2) | | 24 (10.1) | | 15 (6.3) | |
| Secondary ($n$=695) | 554 (79.7) | | 586 (84.3) | | 464 (66.8) | | 566 (81.4) | | 44 (6.3) | | 61 (8.8) | |
| Diploma/degree ($n$=45) | 38 (84.4) | | 32 (71.1) | | 26 (57.8) | | 32 (71.1) | | 8 (17.8) | | 2 (4.4) | |
| No formal education ($n$=123) | 102 (82.9) | | 93 (75.6) | | 68 (55.3) | | 103 (83.7) | | 18 (14.6) | | 1 2 (9.8) | |
| Mother's education | | 37.1/0.001 | | 4.078/0.253 | | 12.97/0.005 | | 17.88/0.001 | | 14.97/0.002 | | 0.161/0.984 |
| Primary ($n$=240) | 215 (89.6) | | 200 (83.3) | | 180 (75.0) | | 209 (87.1) | | 18 (7.5) | | 19 (7.9) | |
| Secondary ($n$=374) | 277 (74.1) | | 321 (85.8) | | 244 (65.2) | | 292 (78.1) | | 26 (7.1) | | 32 (8.6) | |
| Diploma/degree ($n$=10) | 5 (50.0) | | 7 (70.0) | | 5 (50.0) | | 5 (50.0) | | 4 (40.0) | | 1 (10.0) | |
| No formal education ($n$=476) | 408 (85.7) | | 388 (81.5) | | 296 (62.2) | | 404 (84.9) | | 46 (9.7) | | 38 (8.0) | |
| Father's occupation | | 37.6/0.001 | | 8.763/0.03 | | 7.055/0.07 | | 18.88/0.001 | | 6.266/0.099 | | 9.19/0.027 |
| Skilled ($n$=66) | 51 (77.3) | | 52 (78.8) | | 47 (71.2) | | 52 (78.8) | | 7 (10.6) | | 3 (4.5) | |
| Semiskilled ($n$=428) | 318 (74.3) | | 343 (80.1) | | 262 (61.2) | | 334 (78.0) | | 40 (9.3) | | 48 (11.2) | |
| Unskilled ($n$=600) | 532 (88.7) | | 517 (86.2) | | 412 (68.7) | | 521 (86.8) | | 45 (7.5) | | 39 (6.5) | |
| No employment ($n$=6) | 4 (66.7) | | 4 (66.7) | | 4 (66.7) | | 3 (50.0) | | 2 (33.3) | | 4 (66.7) | |
| Mother's occupation | | 0.002/0.968 | | 0.018/0.895 | | 2.917/0.08 | | 1.04/0.308 | | 0.53/0.82 | | 0.003/0.96 |
| Non-working ($n$=853) | 702 (82.3) | | 711 (83.4) | | 551 (64.6) | | 711 (83.4) | | 72 (8.4) | | 70 (8.2) | |
| Working ($n$ =247) | 203 (82.2) | | 205 (83.0) | | 174 (70.4) | | 199 (80.6) | | 22 (8.9) | | 20 (8.1) | |

Data are presented as $n$ (%). Behavioral patterns: The table presents data on unhealthy dietary behaviors (inadequate FV intake, junk food intake, and SSB intake), physical inactivity, tobacco use, and alcohol consumption among adolescents. Statistical measures: The table includes numbers ($n$) and percentages of adolescents engaging in unhealthy behaviors, along with chi-square ($\chi^2$) values and corresponding $p$-values indicating the statistical significance of observed differences across demographic categories (gender, school location, age, parental education, and parental occupation). A $p$-value less than 0.05 was considered to indicate statistical significance.

FV, fruit and vegetable; SSB, sugar-sweetened beverage; PA, physical activity.



phrp

education: $\chi^2 = 15.0$, $p < 0.001$).

### Predictors of Lifestyle Behaviors

Logistic regression analysis revealed that urban school location was a strong predictor of several unhealthy lifestyle behaviors, including junk food intake (adjusted OR [AOR], 5.20; $p < 0.001$), SSB consumption (AOR, 2.39; $p < 0.001$), and physical inactivity (AOR, 13.39; $p < 0.001$). Younger age (≤14 years) predicted inadequate FV intake (AOR, 1.63; $p = 0.007$). A maternal educational attainment of secondary school was also associated with increased risk relative to no formal education, particularly for inadequate FV intake (AOR, 1.59; $p = 0.023$), and junk food intake (AOR, 1.71; $p = 0.011$) (Table 4, Table S1).

### Clustering of Risk Behaviors

Table 5 highlights significant clustering of unhealthy lifestyle behaviors among adolescents. Physical inactivity frequently co-occurred with low FV intake (72%) and junk food consumption (73%). Low FV intake also co-occurred with tobacco use (5.8%) and alcohol consumption (5.6%). Co-occurrence of tobacco and alcohol use was also significant (1.82%). Adjusted analyses confirmed these associations, including those of low FV intake with physical inactivity (AOR, 0.24; 95% CI, 0.17–0.34), tobacco use (AOR, 2.01; 95% CI, 1.22–3.30), and alcohol consumption (AOR, 2.36; 95% CI, 1.43–3.89). Figure 1 complements Table 5 by illustrating the most prevalent co-occurrence patterns of lifestyle risk behaviors, with physical inactivity and junk food consumption showing the highest clustering among adolescents.

Urban adolescents were significantly more likely to exhibit clustered risk behaviors, with 19-fold higher odds of having ≥1 risk factor (AOR, 19.04) and 4-fold higher odds of having ≥2 risk factors (AOR, 4.06) compared with rural peers. Higher parental education, particularly father's education, was associated with a lower likelihood of risk factor clustering. Boys showed slightly more risk factors than girls, although the difference was not statistically significant (Table 6).

## Discussion

### Key Results

This study assessed the co-occurrence of NCD risk factors and their correlates among urban and rural school-going adolescents in Karnataka. Data from 1,100 adolescents aged 13–16 years showed a high prevalence of lifestyle-related risk behaviors, with significant urban–rural differences. Insufficient FV intake (96.7% and 67.7%, respectively) and physical inactivity (96.7% and 68.6%) were particularly common, whereas tobacco use (5.6% and 11.5%) and alcohol consumption (5.6% and 10.8%) were more prevalent among rural adolescents. These findings are consistent with other research reporting high rates of lifestyle-related risk factors among adolescents in LMIC contexts, reflecting greater exposure to unhealthy environments, with implications for early onset of NCDs and the urgent need for targeted preventive interventions [21,22]. Evidence also links these risk behaviors to psychological distress and reduced quality of life among adolescents [23], reinforcing the importance of early identification and intervention to mitigate the future burden of NCDs [23]. These patterns may be influenced by increased access to fast food outlets, limited integration of health education into school curricula, and greater digital exposure that promotes sedentary behavior and unhealthy dietary choices [23].

Differences in lifestyle-related risk factors between urban and rural adolescents were significant. Urban adolescents reported higher rates of insufficient FV intake, junk food and SSB consumption, and physical inactivity, whereas rural adolescents reported higher tobacco and alcohol use. These patterns are shaped by socioeconomic status, food accessibility, environmental factors, media exposure, and cultural norms. Evidence from India indicates that urban adolescents are more likely to have multiple risk factors than their rural counterparts [24], highlighting the need for targeted interventions in both settings. The association between urban school location and higher risk behaviors is consistent with findings from other studies [24,25].

Logistic regression analysis indicated that urban school location and younger age (≤14 years) significantly predicted unhealthy diet and lifestyle behaviors. Lower parental education, particularly maternal education, was also associated with higher risk. These findings are consistent with evidence identifying urban residence and lower parental education as strong predictors of multiple lifestyle-related risk factors. Boys more often exhibited multiple risk factors than girls, although the difference was not statistically significant. This pattern may reflect differences in pocket money, parental investment, and resilience and vulnerability profiles [26–28]. Urban adolescents had 19-fold higher odds of having ≥1 risk factor and 4-fold higher odds of having ≥2 risk factors than rural adolescents. This aligns with previous research highlighting the co-occurrence of unhealthy behaviors and the influence of demographic factors such as school location and parental education [29].

The study contributes to the growing evidence on clustering of unhealthy lifestyle risk factors among adolescents and the role of demographic characteristics, underscoring the need for multifaceted public health



https://doi.org/10.24171/j.phrp.2025.0204

https://doi.org/10.24171/j.phrp.2025.0204

**Table 4.** Predictors of non-communicable disease behavioral risk factors among adolescents: AORs

| Variable | Inadequate FV intake | | Unhealthy diet (junk) | | SSBs | | Physical inactivity | | Tobacco | | Alcohol | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | AOR (95% CI) | *p* | AOR (95% CI) | *p* | AOR (95% CI) | *p* | AOR (95% CI) | *p* | AOR (95% CI) | *p* | AOR (95% CI) | *p* |
| Gender | | | | | | | | | | | | |
| Boy | 0.97 (0.69–1.38) | 0.878 | 0.95 (0.68–1.33) | 0.761 | 0.91 (0.70–1.19) | 0.496 | 0.99 (0.70–1.40) | 0.963 | 1.21 (0.78–1.88) | 0.398 | 1.10 (0.71–1.71) | 0.674 |
| Girl (ref.) | 1 | | 1 | | 1 | | 1 | | 1 | | 1 | |
| School location | | | | | | | | | | | | |
| Urban area | 0.08 (0.05–0.14) | 0.001 | 5.20 (3.46–7.84) | 0.001 | 2.39 (1.89–3.19) | 0.001 | 13.39 (7.92–22.7) | 0.001 | 0.43 (0.26–0.71) | 0.001 | 0.55 (0.33–0.91) | 0.019 |
| Rural area (ref.) | 1 | | 1 | | 1 | | 1 | | 1 | | 1 | |
| Age (y) | | | | | | | | | | | | |
| ≤14 | 1.63 (1.14–2.32) | 0.007 | 0.99 (0.70–1.39) | 0.954 | 0.97 (0.74–1.26) | 0.810 | 1.00 (0.70–1.41) | 0.977 | 1.44 (0.92–2.26) | 0.110 | 0.58 (0.36–0.92) | 0.021 |
| >14 (ref.) | 1 | | 1 | | 1 | | 1 | | 1 | | 1 | |
| Father's education | | | | | | | | | | | | |
| Primary | 1.05 (0.52–2.13) | 0.886 | 1.67 (0.91–3.06) | 0.100 | 1.48 (0.92–2.39) | 0.108 | 0.96 (0.48–1.92) | 0.903 | 0.85 (0.42–1.72) | 0.656 | 0.65 (0.28–1.55) | 0.309 |
| Secondary | 1.09 (0.61–1.95) | 0.768 | 1.65 (0.99–2.76) | 0.055 | 1.44 (0.94–2.19) | 0.091 | 0.91 (0.51–1.63) | 0.746 | 0.41 (0.22–0.78) | 0.007 | 0.85 (0.42–1.71) | 0.647 |
| Diploma/degree | 0.41 (0.13–1.29) | 0.126 | 0.93 (0.39–2.22) | 0.862 | 1.08 (0.51–2.29) | 0.849 | 0.74 (0.29–1.92) | 0.539 | 0.98 (0.34–2.85) | 0.967 | 0.35 (0.07–1.80) | 0.208 |
| No formal education (ref.) | 1 | | 1 | | 1 | | 1 | | 1 | | 1 | |
| Mother's education | | | | | | | | | | | | |
| Primary | 0.86 (0.58–1.48) | 0.579 | 0.91 (0.58–1.44) | 0.695 | 1.62 (1.13–2.34) | 0.009 | 1.05 (0.63–1.75) | 0.854 | 0.96 (0.52–1.75) | 0.881 | 1.12 (0.61–2.05) | 0.714 |
| Secondary | 1.59 (1.07–2.37) | 0.023 | 1.71 (1.13–2.58) | 0.011 | 1.23 (0. 98–1.68) | 0.199 | 0.90 (0.61–1.35) | 0.617 | 0.77 (0.44–1.33) | 0.347 | 1.00 (0.59–1.71) | 0.995 |
| Diploma/degree | 4.42 (0.95–20.5) | 0.058 | 1.44 (0.31–6.76) | 0.648 | 0.78 (0.28–3.05) | 0.717 | 0.48 (0.11–2.05) | 0.318 | 2.79 (0.61–12.70) | 0.184 | 3.00 (0.36–30.4) | 0.353 |
| No formal education (ref.) | 1 | | 1 | | 1 | | 1 | | 1 | | 1 | |
| Father's occupation | | | | | | | | | | | | |
| Skilled | 1.64 (0.24–11.4) | 0.619 | 1.03 (0.16–6.85) | 0.972 | 0.92 (0.15–5.72) | 0.927 | 1.75 (0.29–10.50) | 0.541 | 0.32 (0.04–2.41) | 0.270 | 0.0 | |
| Semiskilled | 1.28 (0.20–8.08) | 0.797 | 1.39 (0.23–8.40) | 0.720 | 0.65 (0.11–3.76) | 0.628 | 2.17 (0.40–11.70) | 0.366 | 0.33 (0.05–2.15) | 0.248 | 0.0 | |
| Unskilled | 0.96 (0.15–6.12) | 0.963 | 1.27 (0.21–7.71) | 0.799 | 0.64 (0.11–3.74) | 0.621 | 1.92 (0.35–10.40) | 0.451 | 0.33 (0.05–2.14) | 0.244 | 0.0 | |
| No employment (ref.) | 1 | | 1 | | 1 | | 1 | | 1 | | 1 | |
| Mother's occupation | | | | | | | | | | | | |
| Non-working | 1.37 (0.90–2.09) | 0.142 | 1.01 (0.67–1.52) | 0.964 | 0.73 (0.53–1.01) | 0.058 | 1.00 (0.66–1.59) | 0.983 | 1.04 (0.60–1.77) | 0.894 | 0.95 (0.56–1.62) | 0.851 |
| Working (ref.) | 1 | | 1 | | 1 | | 1 | | 1 | | 1 | |

A *p*-value less than 0.05 was considered to indicate statistical significance. The table presents behavioral patterns among school-going adolescents and includes AORs, 95% CIs, and *p*-values across demographic categories (gender, school location, age, parental education, and parental occupation).

AOR, adjusted odds ratio; FV, fruit and vegetable; CI, confidence interval; SSB, sugar-sweetened beverage; ref., reference category.



phrp

**Table 5.** Prevalence of co-occurrence of behavioral non-communicable disease risk factors among school-going adolescents

| Combination of risk factors | Co-occurrence count (*n*) | Co-occurrence (%) = (co-occurrence/total)×100 | OR (95% CI) | AOR (95% CI) |
|---|---|---|---|---|
| Low FV intake and junk eating | 758 | 68.9 | 0.83 (0.56–1.23) | 1.35 (0.87–2.11) |
| Low FV intake and physical inactivity | 789 | 71.7 | 0.24 (0.17–0.34)[a)] | 0.24 (0.17–0.34)[a)] |
| Low FV intake and tobacco intake | 64 | 5.8 | 2.39 (1.50–3.80)[a)] | 2.01 (1.22–3.30)[a)] |
| Low FV intake and alcohol intake | 61 | 5.6 | 2.42 (1.56–3.88)[a)] | 2.36 (1.43–3.89)[a)] |
| Physical inactivity and junk eating | 801 | 72.8 | 0.21 (3.47–6.61)[a)] | 0.21 (0.15–0.30)[a)] |
| Physical inactivity and tobacco intake | 72 | 6.5 | 1.52 (0.92–2.53) | 1.52 (0.92–2.53) |
| Physical inactivity and alcohol intake | 75 | 6.8 | 0.95 (0.54–1.70) | 0.89 (0.49–1.66) |
| Tobacco use and junk eating | 76 | 6.9 | 1.20 (0.78–2.06) | 1.08 (0.61–1.91) |
| Alcohol intake and junk eating | 76 | 6.9 | 0.91 (0.50–1.65) | 0.92 (0.49–1.77) |
| Tobacco use and alcohol intake | 20 | 1.8 | 0.28 (0.16–0.48)[a)] | 0.31 (0.18–0.55)[a)] |

The table shows the prevalence of co-occurrence of behavioral risk factors among school-going adolescents. It includes co-occurrence counts (n) and percentages, as well as ORs, AORs, 95% CIs, and *p*-values. A *p*-value less than 0.05 was considered to indicate statistical significance.
OR, odds ratio; CI, confidence interval; AOR, adjusted odds ratio; FV, fruit and vegetable.
[a)]Statistically significant associations.

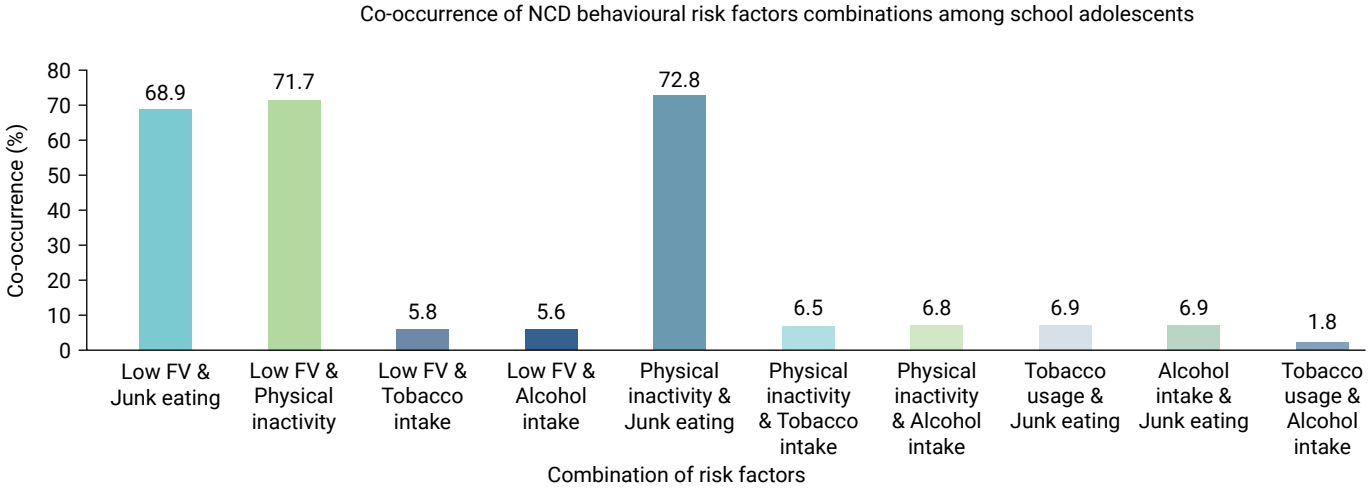



**Figure 1.** Co-occurrence patterns of NCD behavioral risk factors among school-going adolescents.
NCD, non-communicable disease; FV, fruit and vegetable.

strategies [30]. Educational institutions provide an ideal setting for promoting healthy behaviors during formative years [31,32]. Policy-level measures such as regulating food advertising to adolescents, mandating daily physical activity in schools, and implementing school-based screening programs are recommended. Emphasizing school-based interventions, leveraging parental influence, and addressing socioeconomic disparities may promote healthier choices and reduce NCD risk [31,32].

The current findings are consistent with global studies reporting co-occurring behavioral risk factors among adolescents. Studies in developed nations have similarly documented clustering of physical inactivity, poor dietary intake, tobacco use, and alcohol consumption [33,34]. In rural contexts, such co-occurrence may be driven by limited health awareness and the societal normalization of tobacco and alcohol use, where these behaviors are often culturally accepted and less regulated [35].

Parental education emerged as a key determinant of adolescent habits, consistent with the literature on parental influence in health education [36–38]. Parents with higher educational attainment may have greater health literacy and more resources to support healthier choices. Interventions that engage both parents and adolescents may therefore be pivotal in reducing risk behaviors [39–42].

Overall, our findings emphasize the need for tailored public health approaches that consider the socioeconomic and cultural contexts of urban and rural adolescents. While urban adolescents face greater challenges related to diet and physical inactivity, rural adolescents are more likely to


https://doi.org/10.24171/j.phrp.2025.0204

**Table 6.** Association between co-occurrence of behavioral risk factors and demographic variables

| Variable | Reference group | ≥1 Risk factor (*n* = 1,047; 95%) | ≥2 Risk factors (*n* = 943; 86%) | ≥3 Risk factors (*n* = 765; 70%) | ≥4 Risk factors (*n* = 143; 13%) | Five or 6 risk factors (*n* = 32; 3%) |
|---|---|---|---|---|---|---|
| Gender | Boy (ref.: girl) | 0.59 (0.34–1.04) | 1.07 (0.75–1.53) | 1.05 (0.81–1.373) | 0.91 (0.63–1.29) | 1.46 (0.70–3.06) |
| School location | Urban area (ref.: rural area) | 19.04 (5.95–61.51)[a] | 4.06 (2.74–6.02)[a] | 1.99 (1.52–2.61)[a] | 0.41 (0.28–0.59)[a] | 0.35 (0.16–0.87)[a] |
| Age (y) | ≤14 (ref.: >14) | 0.97 (0.54–1.77) | 1.33 (0.93–1.89) | 0.96 (0.74–1.26) | 1.15 (0.80–1.65) | 1.17 (0.56–2.46) |
| Father's education | (ref: no formal education) | | | | | |
| | Primary | 0.67 (0.21–2.18) | 2.02 (1.08–3.84) | 1.46 (0.91–2.33) | 1.05 (0.54–2.06) | 0.59 (0.17–2.05) |
| | Secondary | 0.72 (0.26–1.99) | 1.72 (1.05–2.84) | 1.55 (1.03–2.32) | 1.01 (0.57–1.79) | 0.44 (0.16–1.18) |
| | Diploma/degree | 0.37 (0.09–1.50) | 1.34 (0.56–3.21) | 0.87 (0.43–1.75) | 0.61 (0.19–1.97) | 1.10 (0.20–5.99) |
| Mother's education | (Ref.: no formal education) | | | | | |
| | Primary | 0.83 (0.49–1.74) | 1.16 (0.71–1.91) | 1.35 (0.94–1.94) | 1.19 (0.72–1.98) | 0.66 (0.21–2.12) |
| | Secondary | 1.82 (0.93–3.56) | 1.48 (0.97–2.26) | 1.27 (0.92–1.75) | 1.25 (0.81–1.93) | 0.81 (0.34–1.93) |
| | Diploma/degree | 1.22 (0.15–10.27) | 3.04 (0.34–26.91) | 2.10 (0.49–9.02) | 1.98 (0.34–11.59) | 0.00 |
| Father's occupation | (ref: no employment) | | | | | |
| | Skilled | 2.31 (0.19–28.7) | 2.11 (0.39–14.83) | 1.28 (0.20–8.08) | 0.32 (0.05–2.10) | - |
| | Semiskilled | 2.78 (0.27–28.25) | 2.18 (0.35–13.58) | 0.92 (0.16–5.39) | 0.52 (0.09–2.87) | - |
| | Unskilled | 2.39 (0.23–24.73) | 1.84 (0.29–11.53) | 0.93 (0.16–5.46) | 0.33 (0.06–1.87) | - |
| Mother's occupation | Homeworker (ref.: no employment) | 1.04 (0.52–2.09) | 0.91 (0.59–1.41) | 0.79 (0.57–1.09) | 1.21 (0.77–1.89) | 1.14 (0.45–2.88) |

The table presents the co-occurrence of combinations of behavioral risk factors and their associations with demographic factors among school-going adolescents. It includes adjusted odds ratios, 95% confidence intervals, and p-values across demographic categories. A *p*-value less than 0.05 was considered to indicate statistical significance.

Ref., reference; -, not estimable due to zero cell count or insufficient sample size.

[a]Statistically significant associations.

engage in tobacco and alcohol use. These differences support the need for context-specific implementation strategies. Integrating behavior change communication within schools and communities may enhance the effectiveness of interventions [39–43].

### Strengths

This study has multiple strengths. It employed a robust design and a large sample size and provides a comprehensive analysis of lifestyle risk factors and their co-occurrence in Karnataka. The focus on adolescents and the potential to inform school-based interventions align with the United Nations Sustainable Development Goals, particularly efforts to reduce premature NCD mortality.

### Limitations

The cross-sectional design provides only a snapshot of behaviors, limiting causal inference. Self-reported data may have introduced bias, as participants could have underreported or overreported behaviors due to recall errors. Social desirability bias may also have influenced responses, particularly regarding tobacco and alcohol use. In addition, the data did not fully capture parental influences such as parenting styles and family dynamics.

## Conclusion

This study highlights the prevalence and clustering of NCD-related lifestyle risk factors among school-going adolescents in Karnataka, with urban school location and low parental education emerging as strong predictors. Addressing these multiple interrelated behaviors early is critical to reducing premature NCD morbidity and mortality.

Based on the findings, recommended actionable strategies include integrating school-based physical activity modules into daily timetables, embedding health education within curricula, strengthening parental engagement—particularly among mothers—through structured involvement programs, and leveraging digital behavior-change tools tailored for adolescents. Teacher-led health promotion initiatives grounded in social cognitive theory may further enhance self-efficacy, model healthy behaviors, and promote supportive environments. These strategies can be implemented within schools and reinforced by

families, providing a practical foundation for sustainable behavior change. Future research should consider using a longitudinal design to assess the long-term impact of such interventions, thereby informing evidence-based policies and programs for effective NCD prevention and control among adolescents.

## Supplementary Material

**Supplementary Material 1.** Detailed data analysis methods; **Table S1.** Predictors of non-communicable disease behavioral risk factors among adolescents: unadjusted ORs (additional information for Table 4). Supplementary data are available at https://doi.org/10.24171/j.phrp.2025.0204.

## Notes

### Ethics Approval

This study was approved by the institutional ethics committee of Ramaiah Medical College prior to study initiation (Ref no: MSRMC/EC/AP-02/11-2022). The study was conducted in accordance with the principles of the Declaration of Helsinki. Written informed consent was obtained from participants and their parents/guardians.

### Conflicts of Interest

The authors have no conflicts of interest to declare.

### Funding

None.

### Availability of Data

The datasets generated and analyzed during the present study are not publicly available but are available from the corresponding author upon reasonable request. Due to ethical considerations and institutional policies, access to the raw data is restricted to authorized researchers who meet applicable confidentiality and regulatory requirements.

### Authors' Contributions

Conceptualization: TBD; Methodology: TBD, SNS, KJ; Data curation: TBD; Formal analysis: TBD, SNS, KJ; Investigation: TBD; Project administration: SS; Visualization: SS; Supervision: KJ, SCN; Writing–original draft: TBD; Writing–review & editing: all authors. All authors read and approved the final manuscript.

### Acknowledgements

Artificial intelligence was not used for concept development or analysis for this manuscript.

## References

1. World Health Organization (WHO) (CH). Non-communicable diseases key facts by WHO [Internet]. WHO; 2025 [cited 2023 Jun 1]. Available from: https://www.who.int/news-room/fact-sheets/detail/noncommunicable-diseases.
2. United Nations International Children's Emergency Fund (UNICEF) (US). Non-communicable diseases [Internet]. UNICEF; 2021 [cited 2023 Aug 14]. Available from: https://data.unicef.org/topic/child-health/noncommunicable-diseases/.
3. Akseer N, Mehta S, Wigle J, et al. Non-communicable diseases among adolescents: current status, determinants, interventions and policies. BMC Public Health 2020;20:1908.
4. Marathe A, Mane S, Agarkhedkar S. Risk-factors of non-communicable diseases in urban adolescents in Western India. World J Adv Res Rev 2020;8:064–71.
5. Darukaradhya TB. An alarming non-communicable diseases burden: time for adolescent health investment. Int J Community Med Public Health 2024;11:590–3.
6. Shinde S, Harling G, Assefa N, et al. Counting adolescents in: the development of an adolescent health indicator framework for population-based settings. EClinicalMedicine 2023;61:102067.
7. Ali D, Shah S, Nazir M, et al. Assessment of the magnitude of behavioural risk factors among school going adolescents of Kashmir Valley: a cross sectional study. Int J Community Med Public Health 2023;10:1156–60.
8. Patton GC, Sawyer SM, Santelli JS, et al. Our future: a Lancet commission on adolescent health and wellbeing. Lancet 2016;387:2423–78.
9. Jangid AK. Healthcare inequality: bridging the gap in rural and urban areas in India. IOSR J Nurs Heal Sci 2025;14:5–6.
10. Viner RM, Ozer EM, Denny S, et al. Adolescence and the social determinants of health. Lancet 2012;379:1641–52.
11. Abinayaa M. Social media addiction and its impact on mental health among adolescents. Int J Psychol 2023;11:2484–90.
12. Podiya JK, Navaneetham J, Bhola P. Influences of school climate on emotional health and academic achievement of school-going adolescents in India: a systematic review. BMC Public Health 2025;25:54.
13. Mathur P, Kulothungan V, Leburu S, et al. Baseline risk factor prevalence among adolescents aged 15-17 years old: findings from National Non-communicable Disease Monitoring Survey (NNMS) of India. BMJ Open 2021;11:e044066.
14. Shayo FK. Co-occurrence of risk factors for non-communicable diseases among in-school adolescents in Tanzania: an example of a low-income setting of sub-Saharan Africa for adolescence health policy actions. BMC Public Health 2019;19:972.
15. Sunitha S, Gururaj G. Health behaviours & problems among young people in India: cause for concern & call for action. Indian J Med Res 2014;140:185–208.
16. Dorle AS, Mallapur AA, Mannapur BS, et al. A school based intervention model to promote healthy life style among school children for prevention of risk factors for cardiovascular disease in Bagalkot, Karnataka: a quasi experimental study. Med Innov 2017;6:24–30.
17. Shaikh NI, Frediani JK, Ramakrishnan U, et al. Development and evaluation of a nutrition transition-FFQ for adolescents in South India. Public Health Nutr 2017;20:1162–72.
18. World Health Organization (WHO) (CH). Noncommunicable disease surveillance, monitoring and reporting [Internet]. WHO; 2025

[cited 2025 Sep 22]. Available from: https://www.who.int/teams/noncommunicable-diseases/surveillance/systems-tools/global-school-based-student-health-survey.

19. World Health Organization (WHO) (CH). Noncommunicable disease surveillance, monitoring and reporting [Internet]. WHO; 2024 [cited 2024 Sep 21]. Available from: https://www.who.int/teams/noncommunicable-diseases/surveillance/systems-tools/global-youth-tobacco-survey/questionnaire.
20. World Health Organization (WHO) (CH). Noncommunicable disease surveillance, monitoring and reporting [Internet]. WHO; 2024 [cited 2024 May 21]. Available from: https://www.who.int/teams/noncommunicable-diseases/surveillance/systems-tools/steps/instrument.
21. Pati MK, Swaroop N, Kar A, et al. A narrative review of gaps in the provision of integrated care for noncommunicable diseases in India. Public Health Rev 2020;41:8.
22. Li X, Dessie Y, Mwanyika-Sando M, et al. Co-occurrence of and factors associated with health risk behaviors among adolescents: a multi-center study in sub-Saharan Africa, China, and India. EClinicalMedicine 2024;70:102525.
23. Champion KE, Chapman C, Gardner LA, et al. Lifestyle risks for chronic disease among Australian adolescents: a cross-sectional survey. Med J Aust 2022;216:156–7.
24. Panda A, Parida J, Jena S, et al. Prevalence and associated risk factors of overweight and obesity among adolescent population of India: a scoping review. BMC Nutr 2025;11:110.
25. Wattelez G, Frayon S, Caillaud C, et al. Physical activity in adolescents living in rural and urban New Caledonia: the role of socioenvironmental factors and the association with weight status. Front Public Health 2021;9:623685.
26. Lozza E, Jarach CM, Sesini G, et al. Should I give kids money?: the role of pocket money on at-risk behaviors in Italian adolescents. Ann Ist Super Sanita 2023;59:37–42.
27. Barcellos SH, Carvalho LS, Lleras-Muney A. Child gender and parental investments in India: are boys and girls treated differently? Am Econ J Appl Econ 2014;6:157–89.
28. Mawarni DP, Safira L, Aprilia CA. Association between pocket money availability and frequency of fast-food consumption toward overnutrition case among junior high school student, South Jakarta. In: ICPH 2020: Proceedings of the 7th International Conference on Public Health; 2020 Nov 18-19; Surakarta, ID. Masters Program in Public Health, Universitas Sebelas Maret; 2020. p. 128–34.
29. Song Y, Liu J, Zhao Y, et al. Unhealthy lifestyles and clusters status among 3637 adolescents aged 11-23 years: a school-based cross-sectional study in China. BMC Public Health 2023;23:1279.
30. Darukaradhya TB, Krishnamurthy J. Modifying non-communicable disease behaviours through effective health communication and behaviour change: a systematic review. Prev Med Res Rev 2025;2:24–39.
31. Jayanna K. Integrative approach to lifestyle management: implications for public health research & practice in the context of SDG-3. J Ayurveda Integr Med 2023;14:100796.
32. Kar A, Jayanna K. Using mixed-methods approach in an implementation research project to design a comprehensive urban primary health care intervention for management of diabetes and hypertension. SAGE Res Methods Cases 2021 Jan 11 [Epub]. https://doi.org/10.4135/9781529764239.
33. Lioret S, Touvier M, Lafay L, et al. Dietary and physical activity patterns in French children are related to overweight and socioeconomic status. J Nutr 2008;138:101–7.
34. Jago R, Fox KR, Page AS, et al. Physical activity and sedentary behaviour typologies of 10-11 year olds. Int J Behav Nutr Phys Act 2010;7:59.
35. Mudgal SK, Patidar V, Sharma SK, et al. Tobacco and alcohol use among adolescents and young adults in aspirational districts in India: NFHS-5 based secondary analysis. Pan Afr Med J 2025;51:17.
36. Munoz-Galiano IM, Connor JD, Gomez-Ruano MA, et al. Influence of the parental educational level on physical activity in schoolchildren. Sustainability 2020;12:3920.
37. Yanez AM, Bennasar-Veny M, Leiva A, et al. Implications of personality and parental education on healthy lifestyles among adolescents. Sci Rep 2020;10:7911.
38. Moral-Garcia JE, Urchaga-Litago JD, Ramos-Morcillo AJ, et al. Relationship of parental support on healthy habits, school motivations and academic performance in adolescents. Int J Environ Res Public Health 2020;17:882.
39. Decker MJ, Gutmann-Gonzalez A, Saphir M, et al. Integrated theory-based health and development interventions for young people: a global scoping review. Health Educ Behav 2024;51:82–93.
40. Champion KE, Hunter E, Gardner LA, et al. Parental information needs and intervention preferences for preventing multiple lifestyle risk behaviors among adolescents: cross-sectional survey among parents. JMIR Pediatr Parent 2023;6:e42272.
41. Ho YL, Mahirah D, Ho CZ, et al. The role of the family in health promotion: a scoping review of models and mechanisms. Health Promot Int 2022;37:daac119.
42. Sampaio F, Nystrand C, Feldman I, et al. Evidence for investing in parenting interventions aiming to improve child health: a systematic review of economic evaluations. Eur Child Adolesc Psychiatry 2024;33:323–55.
43. Darukaradhya T, Jayanna K. Development of a health promotion intervention in managing behavioral risk factors for non-communicable diseases in adolescents: an intervention mapping approach. J Epidemiol Found India 2024;2:56–65.

phrp
OSONG PUBLIC HEALTH AND RESEARCH PERSPECTIVES

# Instruction for authors

Enacted: January 1, 2010
Last revision: June 1, 2024
Partial revision: October 21, 2025

*Osong Public Health and Research Perspectives* (PHRP) is the international bimonthly (published at the end of February, April, June, August, October, and December) journal founded in 2010 by the Korea Disease Control and Prevention Agency (KDCA). With the mission of the KDCA, to create a disease-free world, PHRP encourages sharing medical information and knowledge in the areas of public health. PHRP publishes original articles, review articles, guidelines, data profiles (including cohort profiles), special articles, short communications, viewpoints, editorials and correspondence, with a focus on the following areas of expertise: emerging infectious diseases, vaccinology, zoonotic diseases, non-communicable diseases, intractable and rare diseases, and human genomics.

Before submitting a manuscript, authors should carefully read and follow the instructions for writing an article for PHRP. For issues not addressed in these instructions, authors should refer to the Recommendations for the Conduct, Reporting, Editing, and Publication of Scholarly Work in Medical Journals (http://www.icmje.org/recommendations/) from the International Committee of Medical Journal Editors (ICMJE). Manuscripts submitted to PHRP that do not follow these instructions will be returned to the authors without further review.

### Contact Us

**Editorial Office:** Korea Disease Control and Prevention Agency
National Center for Medical Information and Knowledge, 202 Osongsengmyung 2nd street, Osong-eup, Heungdeok-gu, Cheongju 28159, Korea
E-mail: ophrp@korea.kr

## Table of Contents

ARTICLE PROCESSING CHARGES
RESEARCH AND PUBLICATION ETHICS
EDITORIAL POLICY
SUBMISSION & PEER REVIEW PROCESS
MANUSCRIPT PREPARATION
FINAL PREPARATION FOR PUBLICATION

## ARTICLE PROCESSING CHARGES

The author does not have pay publication charges for open access. The KDCA will pay to make the article open access.

## RESEARCH AND PUBLICATION ETHICS

The journal adheres to the guidelines and best practices published by professional organizations, including the ICMJE Recommendations and the Principles of Transparency and Best Practice in Scholarly Publishing (joint statement by the Committee on Publication Ethics [COPE], Directory of Open Access Journals [DOAJ], World Association of Medical Editors [WAME], and Open Access Scholarly Publishers Association [OASPA]; https://doaj.org/bestpractice). Furthermore, all processes of handling research and publication misconduct shall follow the applicable COPE guidances (https://publicationethics.org/)

### Human and Animal Rights

Clinical research should be conducted in accordance with the World Medical Association's Declaration of Helsinki (https://www.wma.net/what-we-do/medical-ethics/declaration-of-helsinki/) and approved by the Institutional Review Board (IRB) of the institution where the experiment was performed. Animal experiments should also be reviewed by an appropriate committee (Institutional Animal Care and Use Committee [IACUC]) for the care and use of animals. Studies involving pathogens requiring a high degree of biosafety should pass review of a relevant committee (Institutional Biosafety Committee [IBC]). Clinical studies that do not meet the Helsinki Declaration will not be considered for publication.

### Statement of Informed Consent and Institutional Approval

The editor of PHRP may request submission of copies of informed consent forms from human subjects in all studies and IRB approval documents. For articles involving human subjects who can be identified through descriptions, photographs, or pedigrees, a signed informed consent statement must be provided. This consent must be obtained from each identifiable participant, or from a parent or legal guardian if the participant is unable to provide consent. The statement should explicitly permit the publication of the relevant descriptions, photographs, and pedigrees in both print and online formats. Articles describing the use of animals in experiments must be approved by the relevant authorities.


© 2026 Korea Disease Control and Prevention Agency

### Protection of privacy and confidentiality

Patients have a right to privacy that must not be violated without informed consent. Identifying information, such as names, initials, or hospital numbers, should not be published unless essential for scientific purposes and with written informed consent from the patient (or parent or guardian). Nonessential identifying details should be omitted. If there is any doubt about maintaining anonymity, informed consent is necessary, as masking the eye region in photographs is inadequate. If identifying characteristics are deidentified, authors must assure, and editors must confirm, that these changes do not distort scientific meaning.

### Originality

Manuscripts are considered with the understanding that no part of the work has been published previously in print or electronic format and the paper is not under consideration by another publication or electronic medium.

### Secondary Publication

It is possible to republish manuscripts if the manuscripts satisfy the conditions for secondary publication as described in the ICMJE Recommendations (http://www.icmje.org/icmje-recommendations.pdf).

### Plagiarism and Duplicate Publication

Attempting to publish substantially similar work more than once without attribution of the original source(s) is considered a redundant publication. The definition of "substantially similar" is as follows: (1) at least one of the authors is common to all reports (it is likely to be plagiarism if there are no common authors); (2) the subject or study populations are the same or similar; (3) the methodology is typically identical or nearly so and; (4) the results and interpretation vary little or not at all.

If all or part of the subject population has been reported previously, it should be declared in the Materials and Methods and must be appropriately referenced. In cases where authors are concerned with any potential overlap with published manuscripts or manuscripts being reviewed, the authors must include a letter explaining how the manuscript submitted to PHRP significantly differs from other materials. For more information, please refer to ICMJE Recommendation (available at: http://www.icmje.org/recommendations/).

### Authorship and the Author's Responsibilities

Authorship credit must be based on (1) substantial contributions to conception and design, acquisition of data, or analysis and interpretation of data; (2) drafting the article or revising it critically for important intellectual content; (3) final approval of the version to be published; and (4) agreeing to be accountable for all aspects of the work in ensuring that the questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The authors should meet these 4 conditions. If the number of authors exceeds 3, the specific role(s) of authors should be described at the end of the main text.

- Correction of authorship: Any requests for changes in authorship (adding author(s), removing author(s), or re-arranging the order of authors) after the initial manuscript submission and before publication should be explained in writing to the editor in a letter or e-mail from all authors. This letter must be signed by all authors of the paper. A copyright assignment must be completed by every author.
- Role of the corresponding author: The corresponding author takes primary responsibility for communication with the journal during the manuscript submission, peer review, and publication process. The corresponding author typically ensures that all of the journal's administrative requirements, such as providing the details of authorship, ethics committee approval, clinical trial registration documentation, and conflict of interest forms and statements, are properly completed, although these duties may be delegated to one or more coauthors. The corresponding author should be available throughout the submission and peer review process to respond to editorial queries in a timely manner, and after publication, should be available to respond to critiques of the work and cooperate with any requests from the journal for data or additional information or questions about the article.
- Contributors: Any researcher who does not meet all 4 ICMJE criteria for authorship discussed above but contributes substantively to the study in terms of idea development, manuscript writing, conducting research, data analysis, and financial support should have their contributions listed in the Notes section of the article.
- Recommendations for working with people with personal connections: Authors who intend to include minors (under the age of 19) or their family members (such as spouse, children, and relatives) in their research, including when publishing or presenting papers jointly with them, should clearly indicate this in the cover letter. For further information, please refer to the "Guidelines

for Preventing Illegitimate Authorship" by the National Research Foundation of Korea (https://www.nrf.re.kr/eng/).

### Conflict of Interest Statement

The corresponding author must inform the editor of any potential conflicts of interest that could influence the authors' interpretation of the data. Potential conflicts should be reported even if the authors believe they were not influenced in preparing the manuscript. All authors must disclose i.e., (1) financial relationships (such as employment, consultancies, stock ownership, honoraria, paid expert testimony), (2) personal relationship, (3) academic competition, and (4) intellectual passion. These disclosures should be included on the title page.

### Role of the Funding Source

The author is requested to identify who provided financial support for the conduct of the research and/or preparation of the article and to briefly describe the role of the sponsor (s), if any, in study design; in the collection, analysis and interpretation of data; in the writing of the report; and in the decision to submit the article for publication. If the funding source(s) had no such involvement, then this should be stated.

### Inclusive Language

Authors are encouraged to use inclusive language that acknowledges diversity, respects all individuals, and promotes equal opportunities. Avoid assumptions about the reader's beliefs or identities, and refrain from language that implies superiority based on factors such as age, gender, race, ethnicity, culture, sexual orientation, disability, or health condition. Writing should be free of bias, stereotypes, and cultural assumptions. Gender neutrality is encouraged by using plural nouns (e.g., "patients") instead of gendered pronouns ("he/she"). Descriptors of personal attributes should only be used if relevant and valid.

### Process for Managing Research and Publication Misconduct

When the journal faces suspected cases of research and publication misconduct such as redundant (duplicate) publication, plagiarism, fraudulent or fabricated data, changes in authorship, an undisclosed conflict of interest, ethical problems with a submitted manuscript, a reviewer who has appropriated an author's idea or data, complaints against editors, and so on, the resolution process will follow the guidances provided by the COPE (https://publicationethics.org/guidance). The editorial boards of PHRP will carry out the discussion and decision for suspected cases. We will not hesitate to publish errata, corrigenda, clarifications, retractions, and apologies when needed.

### Complaints and Appeals Policy

The policies of PHRP are principally intended to protect the authors, reviewers, editors, and the publisher of the journal. The process of handling complaints and appeals follows the guidances of COPE (https://publicationethics.org/guidance).

### Editorial Responsibilities

The Editorial Board will continuously work to monitor and safeguard publication ethics, including guidelines for retracting articles; maintenance of the integrity of the academic record; preclusion of business needs from compromising intellectual and ethical standards; publishing corrections, clarifications, retractions, and apologies when needed; and excluding plagiarism and fraudulent data. The editors maintain the following responsibilities: responsibility and authority to reject and accept articles; avoiding any conflict of interest with respect to articles they reject or accept; promoting publication of corrections or retractions when errors are found; and preservation of the anonymity of reviewers.

## EDITORIAL POLICY

### Copyright

The Korea Disease Control and Prevention Agency (publisher) holds the copyright on all submitted materials and the right to publish, transmit, sell, and distribute them in the journal or other media. The publisher applies the Creative Commons Attribution license to works it publishes. Under this license, although the publisher retains ownership of the copyright for content, it allows anyone to download, reuse, reprint, distribute, and/or copy the content for non-commercial purposes.

### Open Access License

Every article appearing in this journal will be published as open-access. Articles are distributed under the terms of the Creative Commons Attribution-Non Commercial-No Derives (http://creativecommons.org/licenses/by-nc-nd/4.0/), which permits unrestricted non-commercial use, distribution, and reproduction in any medium, provided the original work is properly cited. Author(s) do not need to

permission to use tables or figures published in PHRP in other journals, books, or media for scholarly and educational purposes.

## Article Sharing (Author Self-Archiving) Policy

PHRP is an open access journal, which means that authors who publish with us are able to freely share their research in various ways, including preprint servers, social media platforms, conferences, and educational materials, in accordance with our open access policy.

**• Accepted version**
The accepted version, which incorporates all peer review amendments prior to final publication, may be shared on non-commercial websites and repositories. Authors who previously uploaded their article to a preprint server should update the preprint with the accepted manuscript following peer review.

**• Published version**
The final, published version can be shared immediately upon publication. Under the CC BY-NC 4.0 license, this version permits unrestricted non-commercial use, distribution, and reproduction in any medium, provided the original work is properly cited.

## Data Sharing Policy

To foster transparency, we encourage authors to state the availability of their data in your submission.
Subject to ethical and legal considerations, authors are encouraged to:

- Upload research data during the submission process; otherwise, share research data in a relevant public data repository with DOI for the data location.
- Include a data availability statement linking to the data. If it is not possible to share the data, use the statement to confirm why it cannot be shared.

**Clinical Trials:** PHRP accepts the ICMJE Recommendations for data sharing statement policies. Authors may refer to the editorial, "Data Sharing Statements for Clinical Trials: A Requirement of the International Committee of Medical Journal Editors," in the Journal of Korean Medical Science (https://dx.doi.org/10.3346/jkms.2017.32.7.1051).

## Archiving Policy

PHRP provides electronic backup and preservation of access to the journal content in the event the journal is no longer published by archiving the journal content in National Library of Korea and PubMed Central (https://www.ncbi.nlm.nih.gov/pmc/journals/2151/) from the first volume, 2010.

## Preprint Policy

A preprint can be defined as a version of a scholarly paper that precedes formal peer review and publication in a peer-reviewed scholarly journal. PHRP allows authors to submit the preprint to the journal. It is not treated as duplicate submission or duplicate publication. PHRP recommend authors to disclose it with DOI in the letter to the editor during the submission process. Otherwise, it may be screened from the plagiarism check program—Similarity Check (Crosscheck) or Copy Killer. Preprint submission will be processed through the same peer-review process with a usual submission. If the preprint is accepted for publication, authors are recommended to update the info at the preprint with a link to the published article in PHRP, including DOI at PHRP. It is strongly recommended that authors cite the article in PHRP instead of the preprint at their next submission to journals.

## Use of Artificial Intelligence (AI)-Assisted Technologies

The journal has adopted policies, as specified by the ICMJE, regarding the use of AI in the preparation of materials intended for publication in the journal. Generative AI, including language models, chatbots, image creators, machine learning, or similar technologies, may be employed to enhance readability and language accuracy in scientific writing. However, chatbots or other AI-assisted technologies cannot be listed as authors.

**Generative AI images:** We do not permit the use of generative AI or AI-assisted tools for creating or altering images in submitted manuscripts. Adjustments like brightness, contrast, or color balance are acceptable if they don't obscure original information. Exceptions apply if AI is integral to the research design or methods, in which case details must be provided in the methods section. Authors should adhere to AI software policies and may be asked for pre-AI-adjusted versions of images for editorial review.

**Declaration of AI and AI-assisted technologies in the writing process:** Authors are required to disclose whether AI-assisted technologies were used in the production of the submitted work at the time of manuscript submission.

It must be clearly reported in a dedicated section of the Methods, or in the Acknowledgements section for article types lacking a Methods section. This disclosure should provide details about the specific tools used, including the model name, version, and manufacturer, along with an explanation of the capacity in which they were utilized. Authors should affirm that there is no plagiarism of text or images in materials produced by AI. It is not acceptable to cite AI-generated material as a primary source.

### Peer Review Policy

All papers, including those invited by the editor, are subject to peer review. PHRP has adopted a double-blind peer review policy, where the author identities remain anonymous to the reviewers, and vice versa, and the identities of the reviewers and authors are visible to (decision-making) the editor throughout the peer review process. The Editorial Board selects reviewers based on expertise, publication history, and past reviews. During the peer review process, reviewers can interact directly or exchange information (e.g., via submission systems or email) with only an editor, which is known as "independent review." An initial decision will normally be made within 4–6 weeks after the reviewers agree to review a manuscript. No information about the review process or editorial decision process is published on the article page.

- AI use by peer reviewers: Generative AI tools can lack up-to-date knowledge and may produce nonsensical, biased or false information. Manuscripts may also include sensitive or proprietary information that should not be shared outside the peer review process. For these reasons we ask that, while the journal explores providing our peer reviewers with access to safe AI tools, peer reviewers do not upload manuscripts into generative AI tools. If any part of the evaluation of the claims made in the manuscript was in any way supported by an AI tool, we ask peer reviewers to declare the use of such tools transparently in the peer review report.

## SUBMISSION & PEER REVIEW PROCESS

### Online Submission

All manuscripts should be submitted online at https://mc04.manuscriptcentral.com/osongphrp (PHRP online submission system: ScholarOne). The entire process of manuscript submission, peer-review, and resubmission to PHRP is done through the online system.

Manuscripts submitted to PHRP will be preliminarily reviewed by the Editorial Office. Manuscripts not conforming to the instructions will be returned to the corresponding authors without being considered for publication. Submitted manuscripts are also screened for possible plagiarism or duplicate publication using Crossref Similarity Check. If a paper that might be regarded as duplicate or redundant had already been published in another journal or submitted for publication, the author should notify the fact in advance at the time of submission.

Any inquiry concerning manuscript submission should be directed to the editorial office at ophrp@korea.kr.

### Peer Review Process

This journal operates a **double-blind** review process. All contributions will be initially assessed by the editor for suitability for the journal. Papers deemed suitable are then typically sent to a minimum of 2 independent expert reviewers to assess the scientific quality of the paper. The Editor is responsible for the final decision regarding acceptance or rejection of articles. The Editor's decision is final. The detailed review process is as follows.

- The Editorial Office of PHRP receives and reviews all submitted manuscripts, and all submitted manuscripts are considered confidential. The submitted manuscripts are initially screened for formatting. Once the manuscript is provisionally accepted, it is sent to the 2 most relevant reviewers for review.
- The reviewers are selected by the editor from the Editorial Board's database or the board members' recommendation. The reviewers are then requested to evaluate the manuscript based on originality, validity, presentation, and importance and interest, and, when considered necessary, statistics.
- Acceptance of a manuscript depends on the evaluation, critiques, and recommended decision made by the reviewers. A reviewer may recommend "accept," "minor revision," "major revision," and "reject." If there are conflicting decisions between reviewers, or between the author and reviewer(s), the Editor-in-Chief has the full right to decide whether the manuscript will be published in the journal. Three repeated decisions of "major revisions" are equivalent to rejection, and rejected papers will not be considered further.
- The reviewed manuscript with comments, recommendations, and revisions is returned to the corresponding author. The corresponding author is to submit the revised manuscript

accompanied by point-to-point replies to the comments given by the editor and how the revisions have been made. There should be a reasonable explanation for any noncompliance with the recommendations. In cases where references, tables, or figures are moved, added, or deleted during the revision process, renumbering must be done so that all references, tables, and figures are cited in numeric order. If the revised paper is not received within 2 months of decision, the manuscript is considered to have been withdrawn.

- When the final decision on the acceptance of the manuscript is made, the Editorial Office notifies the corresponding author. The peer-review process takes approximately 8–12 weeks.

### Submission by Editors

Final decisions regarding manuscript publication are made by the editor-in-chief or a designated editor who does not have any relevant conflicts of interest. In the event that an editor has a conflict of interest with a submitted manuscript or with the authors, the manuscript will be handled by one of the other editors who does not have a conflict with the review and who is not at the same institution as the submitting editor. In such circumstances, full masking of the process will be ensured so that the anonymity of the peer reviewers is maintained.

## MANUSCRIPT PREPARATION

### General Requirements

- All manuscripts must be in grammatically correct English and should be created using MS Word. The manuscript must be double-spaced and written in an A4 page format. Do not leave a space between paragraphs. Only a single font (preferably Times New Roman) should be used in 11 point with margins of 2.5 cm.
- All pages should be paginated consecutively.
- All numbers should be written in Arabic numerals throughout the manuscript except for the first word of the sentence. Texts should be justified on both sides and not hyphenated and headings should be in bold letters, aligned in the center. If possible, avoid using abbreviated words at the beginning of sentences.
- Abbreviations: Where a term/definition is repeatedly referred to (i.e., 3 times in the text), it is written in full when it first appears, followed by the subsequent abbreviation in parentheses (even if it was previously defined in the abstract); thereafter, the abbreviation is used.
- Gene nomenclature: Current standard international nomenclature for genes should be adhered to. Genes should be typed in italic font and include the accession number. For human genes, use the genetic notation and symbols approved by the HUGO Gene Nomenclature Committee (http://www.genenames.org/) or refer to PubMed (http://www.ncbi.nlm.nih.gov/sites/entrez).
- Units: Système International (SI) units must be used, with the exception of blood pressure values, which are to be reported in mmHg. Please use the metric system for expressions of length, area, mass, and volume. There should be a space between the numerals and the unit symbol. When indicating time, the 24-hour system is to be used.
- Math formulae: Present simple formulae in the line of normal text where possible and use the solidus (/) instead of a horizontal line for small fractional terms, e.g., X/Y. In principle, variables are to be presented in italics. Powers of e are often more conveniently denoted by "exp." Number consecutively any equations that have to be displayed separately from the text (if referred to explicitly in the text).

### Reporting Guidelines for Specific Study Designs

For specific study designs, such as randomized control studies, studies of diagnostic accuracy, meta-analyses, observational studies, and non-randomized studies, authors should adhere the reporting guidelines relevant to their specific research design and submit a checklist. A good source of reporting guidelines is the EQUATOR Network (https://www.equator-network.org/) and NLM (https://www.nlm.nih.gov/services/research_report_guide.html).

### Manuscript Types

PHPR publishes editorials, original articles, review articles, guidelines, data profiles (including cohort profiles), special articles, short communications, viewpoints, editorials, commentaries, and correspondence, and book reviews, and perspectives.

- **Original articles** are papers containing results of basic and clinical investigations, which are sufficiently well documented to be acceptable to critical readers. These articles should be written in the following format: title page; abstract and keywords; main body (introduction, materials and methods, results, discussion, conclusion [if any]); references; and tables and figure legends. Manuscript limitations are 5,000 words, excluding the abstract, references, and tables and figure legends.

- **Review articles** provide concise reviews of subjects important to medical researchers, and can be written by an invited medical expert. These have the same format as original articles, but the details may be more flexible depending on the content. Manuscript limitations are 6,500 words from introduction to conclusion, 100 references, 10 figures and 10 tables. The abstract should not exceed 200 words, and must be written as one unstructured paragraph.
- **Systematic reviews** should adhere to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines. The template for systematic reviews can be downloaded from https://ophrp.org/file/PHRP_Systematic%20Review_PRISMA.docx.
- **Guidelines** are similar to original articles, but provide evidence-based recommendations expected to impact clinical research and practice. This category can include consensus-based statements of reporting standards or clinical practice guidelines.
- **Data Profiles (including Cohort Profiles)** present large data sets from specific populations that could be analyzed in epidemiological studies. Data Profiles should be structured with the following headings in the main text: Introduction, Collection, Data Resource Use, Strengths and Weaknesses, and Access. Cohort Profiles present up-to-date information about large population-based cohorts for which long-term data collection is planned. Data Profiles should be structured with the following headings in the main text: Introduction, Study Participants, Measurements, Key Findings, Strengths and Weaknesses, and Access. The main text of Data and Cohort Profiles is limited to 4,000 words, with an unstructured abstract of up to 200 words, a maximum of 7 tables and figures, and no more than 40 references.
- **Special Articles** deal with topics or issues that are relevant to public health, but without following a traditional study format. For example, articles in this category may address scientific methodology, wide-ranging ethical and social issues, scientific methodology, or other scholarly topics. Reports from consensus committees and working groups can be published as Special Articles. This category has a main text limit of 3,500 words, with an unstructured abstract of no more than 200 words, a maximum of 7 tables and figures, and no more than 40 references.
- **Brief reports** deal with issues of importance to biomedical researchers and follow the general guidelines for original articles. The manuscript should not exceed 2,000 words, excluding references, tables and figures, and must include a structured abstract of no more than 250 words.
- **Short communications** follow the general guidelines for original articles but present original research and/or preliminary findings in a more concise format with fewer details. The manuscript should not exceed 3,000 words, excluding references, tables, and figures, and must include a structured abstract of no more than 250 words.
- **Viewpoints** may deal with almost any topic deemed to be important in the fields of public health, ethics, health law, prevention, or health policy, and are not typically written in response to a specific article. Viewpoints should have a clear focus and present material in a well-organized and scholarly manner, but should not contain novel research findings or previously unpublished data. Although we welcome unsolicited viewpoint contributions, we request that authors contact the Editorial Office (ophrp@korea.kr) prior to submission to confirm that the proposed topic is suitable for the journal. The main text of Viewpoints is limited to 3,000 words, with an unstructured abstract of up to 150 words, a maximum of 4 tables and figures, and no more than 30 references.
- **Editorials** provide invited perspective on an area of PHRP, dealing with very active fields of research, current interests, fresh insights, and debates. An abstract is not required and a brief unstructured text should be prepared. Although editorials are normally invited or written by an editor, unsolicited editorials may be submitted. Manuscript limitations are 1,000 words and 20 references.
- **Commentaries** are brief articles with a narrow focus. The journal commissions most commentaries, but unsolicited commentaries will also be considered. Commentaries may undergo peer review. The length of commentaries should be limited to 500 words, 10 references, and 2 figure or small table.
- **Correspondence** is a comment from readers regarding a published article with a reply from the authors of the article. Manuscript limitations are 500 words, 2 tables/figures, and 5 references.
- **Book reviews** may be published. Please dispatch a book to the editorial office if you think the book is essential to public health personnel.
- **Perspectives** should present a viewpoint on current advances and future directions in a specific field of research. These articles are intended to provide scholarly and focused discussions rather than to report original research findings, and authors are advised not to primarily discuss their own previous work. Manuscripts should not exceed 1,500 words in length and may include up to 20 references. An abstract is not required. A maximum of

3 tables and figures combined is allowed. Authorship is generally limited to 1–2, and these articles are often commissioned by the Editorial Board.

Key features and limits of articles are summarized in Table 1 below.

**Table 1.** Key features and limits of articles

| Type of article | Abstract (words) | Text (words)* | References | Tables and figures |
|---|---|---|---|---|
| Original article | Structured, 250 | 5,000 | - | - |
| Review article | 200 | 6,500 | 100 | 10 Tables<br>10 Figures |
| Data profile | 200 | 4,000 | 40 | 7 |
| Special article | 200 | 3,500 | 40 | 7 |
| Brief report | Structured, 250 | 2,000 | - | - |
| Short communication | Structured, 250 | 3,000 | - | - |
| Viewpoint | 150 | 3,000 | 30 | 4 |
| Editorial | Not required | 1,000 | 20 | - |
| Commentary | Not required | 500 | 10 | 2 |
| Correspondence | Not required | 500 | - | 2 |
| Perspective | Not required | 1,500 | 20 | 3 |

*Excluding abstract, references, tables, and figure legends.

## Title Page

Title page should include (1) the title of the article (less than 50 words); (2) name of the authors (first name, middle initial, last name in capitals) and institutional affiliation including the name of department(s) and institution(s) of each author; (3) name, full address (including the postal code) of the institutional affiliation, telephone and e-mail address of the corresponding author; (4) a running title of 50 characters or less including blank spaces; and (5) notes (disclaimers). Notes include ethics approval and consent to participate, conflict of interest, funding, availability of data, authors' contributions according to the CRediT taxonomy (https://credit.niso.org/), additional contributions, and ORCID of all authors. All contributors who do not meet the criteria for authorship as defined above should be listed in an additional contribution section. Examples of those who might be acknowledged include a person who provided purely technical help, writing assistance, or a department chair who provided only general support. Authors should disclose whether they had any writing assistance and identify the entity that paid for this assistance.

## Abstract and Keywords

An abstract and 3–6 relevant keywords (in alphabetical order) are required. Abstracts should be no more than 250 words in length. Abstracts should be structured, with the following section headings: Objectives, Methods, Results, Conclusion. For selecting keywords, refer to the MeSH browser (http://www.ncbi.nlm.nih.gov/mesh).

## Highlights

All papers must include 3–5 short sentences presenting short summary or findings in the next of title page. The highlight section should be no more than 100 words, including spaces.

## Main Body

- **Introduction** should provide concise yet sufficient background information about the study to provide the readers with a better understanding of the study, avoiding a detailed literature survey or a summary of the results.
- **Materials and methods** should contain detailed procedures of the study or experiment including investigation period, methods of subject selection, and information on subjects such as age, sex or gender, and other significant features, in order to enable the experiment to be repeated. A procedure that has been already published or standardized should be described only briefly using literature citations. Clinical trials or experiments involving laboratory animals or pathogens must elaborate on the animal care and use and experimental protocols, in addition to mentioning approval from the relevant committees. The sources of special equipment and chemicals must be stated with the name of the manufacturer. All statistical procedures used in the study and criteria for determining significance levels must be described. Ensure correct use of the terms "sex" (when reporting biological factors) and "gender" (identity, psychosocial or cultural factors). Unless inappropriate, report the sex and/or gender of study participants, the sex of animals or cells, and describe the methods used to determine sex or gender. If the study involved an exclusive population (only one sex, for example), authors should justify why, except in obvious cases (e.g., prostate cancer). Authors should define how they determined race or ethnicity, and justify its relevance. Institutional Review Board approval and informed consent procedures can be described as follows: The study protocol was approved by the Institutional Review Board of OOO (IRB No: OO-OO-OO). Informed consent was obtained by all participants (or the participant's legal guardian) / Informed consent was waived by the IRB.
- **Results** should be presented in logical sequence. Only the most important observations should be emphasized or summarized, and the main or the most important

findings should be mentioned first. Tables and figures must be numbered in the order they are cited in the text, kept to a minimum, and should not be repeated. Supplementary materials and other details can be separately presented in an appendix. The authors should state the statistical method used to analyze the results (statistical significance of differences) with the probability values given in parentheses.

- **Discussion** should contain an interpretation and explanation of the results and important aspects of the study, followed by the conclusions drawn from them. Information already mentioned in the Introduction or Results sections should not be repeated and the main conclusions of the study may be presented in the discussion.
- **Conclusion** (if any) must be linked with the purpose of the study stated in the abstract, and clearly supported by the data produced in the study. New hypotheses may be stated when warranted, but must be clearly labeled.

## References

Authors are responsible for the accuracy and completeness of their references and for correct text citations.

- References are presented with [ ] following a surname in the main text, such as Kim [1] and Kim et al. [2]. When a reference is cited within the content, it is shown as [3] or [4,5] at the end. References should be searchable online.
- The last names and initials of all the authors (up to 3) should be included. For articles with more than 3 authors, list the first 3 authors only followed by "et al."
- When citing organizations that are national bodies such as government agencies, if a nationality is not part of the name, place the country in parentheses after the name, using the two-letter ISO country code.
- References cited in tables or figure legends should be included in sequence at the point where the table or figure is first mentioned in the main text.
- Do not cite abstracts unless they are the only available reference to an important concept.
- Uncompleted work or work that has not yet been accepted for publication (i.e., an "unpublished observation" or "personal communication" should not be cited as a reference). In the references list, references should be limited to those cited in the text and listed in the order in which they appear in the text. The journals should be abbreviated according to the style used in the list of journals indexed in the NLM Journal Catalog (http://www.ncbi.nlm.nih.gov/nlmcatalog/journals).
- Use of DOI is highly encouraged. Note that missing data will be highlighted at the proof stage for the author to correct.
- Other types of references not described below should follow the ICMJE Recommendations (https://www.nlm.nih.gov/bsd/uniform_requirements.html).

Please refer to the following examples.

- **Journal articles**
  1. Park AK, Kim IH, Kim J, et al. Genomic surveillance of SARS-CoV-2: distribution of clades in the Republic of Korea in 2020. Osong Public Health Res Perspect 2021; 12:37-43.
  2. Hyun J, Lee JH, Park Y, et al. Interim epidemiological and clinical characteristic of COVID-19 28 cases in South Korea. Public Health Wkly Rep 2020;13:464-74. Korean.
  3. Gultekin V, Allmer J. Novel perspectives for SARS-CoV-2 genome browsing. J Integr Bioinform 2021 Mar 15 [Epub]. https://doi.org/10.1515/jib-2021-0001.
- **Books**
  1. Riffenburgh RH, Gillen DL. Statistics in medicine. 4th ed. Academic Press; 2020.
  2. Miller DD. Minerals. In: Damodaran S, Parkin KL, editors. Fennema's food chemistry. 5th ed. CRC Press; 2017. p. 627-80.
  3. Ministry of Employment and Labor (KR). Statistics on occupational injuries and illnesses, 2008. Ministry of Employment and Labor; 2009. Korean.
- **Websites**
  1. World Health Organization (WHO) (CH). COVID-19 vaccines [Internet]. WHO; 2021 [cited 2021 Mar 15]. Available from: https://www.who.int/emergencies/diseases/novel-coronavirus-2019/covid-19-vaccines.
- **Conference papers**
  1. Christensen S, Oppacher F. An analysis of Koza's computational effort statistic for genetic programming. In: EuroGP 2002: Proceedings of the 5th European Conference on Genetic Programming; 2002 Apr 3-5; Kinsdale, IE. Springer; 2002. p. 182-91.
- **Dissertation**
  1. Park HY. The role of the thrombomodulin gene in the development of myocardial infarction [dissertation]. Yonsei University; 2000.

## Tables and Figures

Tables should be simple, self-explanatory, and supplemental, and should not duplicate the text or figures. Each table must be on a separate page, not exceeding 1 page when printed, and have a concise and informative title. The tables should be numbered with Arabic numerals in consecutive order.

Each column should be appropriately headed with units in parentheses if numerical measures are given. All units of measurements and concentrations must be indicated. Footnotes are followed by the source notes, other general notes, abbreviation, notes on specific parts of the table ([a], [b], [c], [d]...), and notes on level of probability (*, **, *** for *p*).

Figures should be numbered with Arabic numerals consecutively in figure legends. The figures must not be interfered and must be clearly seen. The legend for each light microscopic image should include name of the stain and magnification. Electron microscopic images should contain an internal scale marker. All figures may be altered in size by the editor. The legends should briefly describe the data shown, explain abbreviations or reference points, and identify all units, mathematical expressions, abscissas, ordinates, and symbols.

Figures that are drawn or photographed professionally should be sent as JPG or PPT files. However, if an article receives approval for publication, files must be submitted as .tiff or .pdf. Each figure must have a caption explaining the figure. The preferred size of the images is 8 × 8 cm but 16.5 cm in width × 8 cm in length is also acceptable. It is authors' full responsibility to submit images of sufficient quality for accurate reproduction and to approve the final color galley proof. All images must be correctly exposed, sharply focused, and prepared in files of 500 dpi or more.

When tables and figures are mentioned together in the text, they should be presented in parentheses as follows: (Table 1; Figure 1), (Tables 1, 2; Figures 1–3).

### Appendix and Supplemental Data

If any materials are not enough to be included in the main text such as questionnaires, they can be listed in the Appendix. Any supplementary materials that help the understanding of readers or contain too great an amount of data to be included in the main text may be placed as supplementary data. Not only a recording of the abstract, text, audio or video files, but also data files should be added here.

## FINAL PREPARATION FOR PUBLICATION

### Final Version

After the paper has been accepted for publication, the author(s) should submit the final version of the manuscript. The names and affiliations of the authors should be double-checked, and if the originally submitted image files were of poor resolution, higher-resolution image files should be submitted at this time. Symbols (e.g., circles, triangles, squares), letters (e.g., words, abbreviations), and numbers should be large enough to be legible on reduction to the journal's column widths. All symbols must be defined in the figure caption. If references, tables, or figures are moved, added, or deleted during the revision process, renumber them to reflect such changes so that all tables, references, and figures are cited in numeric order.

### Manuscript Corrections

Before publication, the manuscript editor will correct the manuscript such that it meets the standard publication format. The author (s) must respond within 48 hours when the manuscript editor contacts the corresponding author for revisions. If the response is delayed, the manuscript's publication may be postponed to the next issue.

### Proofs and Reprints

The author(s) will receive the final version of the manuscript as a PDF file. Upon receipt, the author(s) must notify the editorial office of any errors found in the file within 48 hours. Any errors found after this time are the responsibility of the author(s) and will have to be corrected as an erratum.

### Correction

To correct errors in published articles, the corresponding author should contact the journal's editorial office with a detailed description of the proposed correction. Corrections that profoundly affect the interpretation or conclusions of the article will be reviewed by the editors. Corrections will be published as author correction or publisher correction in a later issue of the journal.

Minor errors will be corrected directly in the online version of the article. An indication of the correction, along with the date it was made, will be added to the article information in both the HTML and PDF versions. A separate correction note will not be published.

**NOTICE:** These recently revised instructions for authors will be applied beginning with the January 2025 issue.

phrp
OSONG PUBLIC HEALTH AND RESEARCH PERSPECTIVES

# Author's checklist

## General Requirements

- ▫ The corresponding author (or the representative author of the co-corresponding authors) is the submitter of this manuscript.
- ▫ All manuscripts should be written in English.
- ▫ The main document with manuscript text and tables should be prepared in an MS Word (docx) or RTF file format.
- ▫ Manuscripts should be double-spaced in A4-size pages.
- ▫ Manuscripts should include line numbers.
- ▫ All pages should be numbered consecutively, starting with the abstract.

## Title Page

- ▫ The title page and the rest of the manuscript text are prepared separately in two files (not combined together).
- ▫ The title page is arranged in the following order: article title, authors' full name(s), affiliation(s), and corresponding author's information, running title (less than 50 characters), notes.
- ▫ The notes section including (1) ethics approval and consent to participate, (2) conflicts of interest, (3) funding, (4) availability of data, (5) author contributions, (6) additional contributions, and ORCID is in title page, not in the manuscript.

## Abstract

- ▫ The abstract does not exceed 250 words (Objectives, Methods, Results, Conclusion) for original articles and 200 words for reviews. Up to 3–6 keywords are listed at the bottom of the abstract.

## Main Text

- ▫ The manuscript is organized according to following sequence: Title page, Abstract and keywords, Main text, References, Tables, and Figure legends.

## Tables and Figures

- ▫ All tables and figures are numbered in the order of their appearance in a main text.
- ▫ Tables are included at the end of the manuscript as editable text and not as images.
- ▫ Figures are as separate files, in jpg, ppt, tiff, or pdf format.

## References

- ▫ References are listed in proper format.
- ▫ All references listed in the reference section are cited in the text and vice versa.


© 2026 Korea Disease Control and Prevention Agency

phrp
OSONG PUBLIC HEALTH AND RESEARCH PERSPECTIVES



## Copyright Transfer and Conflict of Interest Disclosure Form

**Title of the paper:** _____

_____

**I. Copyright Transfer Form**

The authors hereby transfer all copyrights in and to the manuscript named above in all forms and media, now or hereafter known, to the Korea Disease Control and Prevention Agency effective if and when the paper is accepted for publication in the *Osong Public Health and Research Perspectives*. The authors reserve all proprietary right other than copyright, such as patent rights.
Everyone who is listed as an author in this article should have made a substantial, direct, intellectual contribution to the work and should take public responsibility for it.
This paper contains works that have not previously published or not under consideration for publication in other journals.

**II. Conflict of Interest Disclosure Form**

All authors are responsible for recognizing any conflict of interest that could bias their work in the acknowledgments, disclosing all financial support and any other personal connections.

Please check the appropriate box below:

▫ No author of this paper has a conflict of interest, including specific financial interests, relationships, and/or affiliations relevant to the subject matter or materials included in this manuscript.

OR

▫ The authors certify that all conflicts of interest, as applicable to each author, including specific financial interests, relationships, and/or affiliations relevant to the subject matter or materials are disclosed in the manuscript.
(Please describe in detail about these interests.)

_____

_____

_____

These interests may include one or more of the following: employment; consultancy within the past two years; ownership interests – including stock options – in a start-up company, the stock of which is not publicly traded; ownership interest - including stock options but excluding indirect investments through mutual funds and the like - in a publicly traded company; research funding; honoraria directly received from an entity; paid expert testimony within the past two years; any other financial relationship (e.g., receiving royalties); membership on another entity's Board of Directors or its advisory committees (whether for profit or not for profit).

▫ All authors certify that the work followed the research ethics and have approved the submission of the manuscript for publication.

© 2026 Korea Disease Control and Prevention Agency

phrp
OSONG PUBLIC HEALTH
AND RESEARCH PERSPECTIVES

| | | | |
|---|---|---|---|
| Corresponding author: | _____ Name | _____ Signature | _____ Date |
| Authors: | _____ Name | _____ Signature | _____ Date |
| | _____ Name | _____ Signature | _____ Date |
| | _____ Name | _____ Signature | _____ Date |
| | _____ Name | _____ Signature | _____ Date |
| | _____ Name | _____ Signature | _____ Date |
| | _____ Name | _____ Signature | _____ Date |
| | _____ Name | _____ Signature | _____ Date |
| | _____ Name | _____ Signature | _____ Date |
| | _____ Name | _____ Signature | _____ Date |
| | _____ Name | _____ Signature | _____ Date |
| | _____ Name | _____ Signature | _____ Date |

(This form must be signed by all authors in an order as appeared in the article, and should be returned to the editorial office.)


© 2026 Korea Disease Control and Prevention Agency