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## Aims & Scope

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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.

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Editorial

# How we can prevent a resurgence this year

Jong-Koo Lee

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Signs of a resurgence in coronavirus disease 2019 (COVID-19) cases this autumn are being observed globally, with a notable increase in the Asia-Pacific region. The Republic of Korea, in particular, continues to report the highest number of patients worldwide, indicating a widespread prevalence of the disease. However, due to challenges in data collection, it is difficult to determine the exact statistics, so it cannot be conclusively stated that this increase is unique to the Republic of Korea. The World Health Organization (WHO) has stated that the currently reported cases may not accurately reflect the actual infection rates, given the global reduction in testing and reporting [1].

On June 1, the government reduced the alert level from "serious" (level 4) to "caution" (level 3) in the established alert system, which had been in place for 3 years and 4 months. Moreover, as of August 31, COVID-19 will be reclassified as a Class 4 infectious disease. This change will prompt a shift in testing protocols from mandatory to optional, with costs borne by the individual. This is akin to the approach taken with influenza, where only sentinel surveillance is conducted. The disease prevention system has now largely transitioned to a model based on recommendations and voluntary actions, with the exception of mandatory mask-wearing within medical facilities. These relaxed measures are a response to the reduced fatality rate of the disease, which has now reached the level of an endemic disease. To elaborate, according to the Korea Disease Control and Prevention Agency's press release on August 23, the fatality rate of COVID-19 in July was between 0.02% and 0.04%, a figure comparable to that of seasonal influenza (0.03% to 0.07% according to the WHO). Furthermore, the number of new confirmed cases, severe cases, and deaths have all shown a declining trend compared to the previous week, with the infection reproduction number (Rt) decreasing to 0.91. This marks the first time it has fallen below 1.0 in 8 weeks, since the third week of June. When compared to the 2 waves of the Omicron variant's prevalence in 2022, the recent fatality rate is lower: 0.10% during the predominance of the BA.1/2 variant and 0.07% during the predominance of the BA.5 variant [2].

Given the epidemiological characteristics of the severe acute respiratory syndrome coronavirus 2 virus, we anticipate an increase in cases this coming fall, making it challenging to predict how COVID-19 will progress. However, the potential for a resurgence due to the waning of humoral antibodies from vaccination is a cause for concern. It is essential to implement strategies that boost vaccination rates and prioritize protection for high-risk groups. Moreover, we need to make more proactive efforts to persuade the general population to increase their vaccination uptake rates. The goal of preventing hospitalizations and deaths among high-risk groups, such as those aged 65 and above and immunocompromised individuals, remains a significant focus. The push for nationwide free vaccination for individuals aged 12 and above

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in preparation for winter in October, despite COVID-19 being reclassified as a level 4 disease, is of great importance. Additionally, the introduction of the second-generation vaccine, which covers emerging sub-lineages like EG.5 and existing prevalent lineages like BA.4/5, is expected to be highly effective. However, a more nuanced approach is necessary, as the analysis of lower booster vaccination rate needs to address the association between vaccination and side effects. Prompt decisions regarding compensation for potential damages are also crucial. Furthermore, we need to review alternative solutions to reduce morbidity and mortality among chronic patients and high-risk groups, which were previously lacking. It is vital to develop comprehensive strategies that minimize collateral damage.

To ensure a coordinated and consistent response across various government departments for the protection of vulnerable high-risk groups and facilities, the COVID-19 crisis alert level will remain at the caution level (level 3). Additionally, specific measures designed to protect high-risk groups, including mandatory indoor mask-wearing and securing the hospital beds for critical patient care, should continue to be enforced.

The Republic of Korea's change in vaccination strategy this year does not significantly deviate from the essential immunization roadmap announced by the WHO's Strategic Advisory Group of Experts on Immunization in March, which includes the COVID-19 vaccination. However, the designation of the "elderly population" as individuals aged 65 and above seems to be derived from our own mortality data.

On May 11, the announcement was made to maintain a heightened alert status, even after the end of the public health emergency of international concern situation. This was in anticipation of a potential resurgence in the autumn. The decision was based on 7 temporary recommendations provided by the International Health Regulations (IHR). On August 5, 2023, "standing recommendations" were announced, which would be applicable from August 9, 2023, to April 30, 2025. These recommendations outline critical actions to assist States Parties in transitioning from an emergency response to COVID-19 to strengthened and integrated infectious disease prevention and control programs. The aim is to reduce the disease burden from COVID-19 and prepare for the possibility of a worsening situation due to new virus variants [3]. While each country is urged to comply with these recommendations, it is expected that more fundamental changes will be achieved through the revision of the IHR or the establishment of a pandemic prevention treaty.

We are now on the brink of an autumn resurgence. The articles featured in this issue present epidemiological research findings that scrutinize existing policies in anticipation of this resurgence. More specifically, these studies concentrate on cluster outbreaks, with a particular emphasis on schools and various other facilities. They also delve into epidemiological examinations of intra-family infections, as well as the management of adverse reactions to vaccination. These topics are both timely and pertinent.

## 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.

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Review Article

# Public health agencies' use of social media for communication during pandemics: a scoping review of the literature

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## ABSTRACT

Public health agencies (PHAs) have increasingly incorporated social media into their communication mix during successive pandemics in the 21st century. However, the quality, timing, and accuracy of their health messages have varied significantly, resulting in mixed outcomes for communication, audience engagement, and pandemic management. This study aimed to identify factors influencing the effectiveness of pandemic-related health messages shared by PHAs on social media and to report their impact on public engagement as documented in the literature. A scoping literature review was conducted following a predefined protocol. An electronic search of 7 relevant databases and 5 grey literature repositories yielded 9,714 papers published between January 2003 and November 2022. Seventy-three papers were deemed eligible and selected for review. The results underscored the insufficiency of social media guidance policies for PHAs. Six themes were identified: message source, message topic, message style, message timing, content credibility and reliability, and message recipient profile. These themes encompassed 20 variables that could inform PHAs' social media public health communication during pandemics. Additionally, the findings revealed potential interconnectedness among the variables, and this study concluded by proposing a conceptual model that expands upon existing theoretical foundations for developing and evaluating pandemic-related health messaging.

**Keywords:** Communicable disease control; Health communication; Pandemics; Public health administration; Social media

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## Introduction

Social media has introduced a new dimension to communication and interaction in

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today's world. Built on advanced Web 2.0 technology and applications, social media platforms enable real-time, multi-directional communication, interaction, and engagement among users, as well as the sharing of user-generated content [1]. Consequently, social media has revolutionized the way we communicate by fostering the continuous exchange of information and co-creation of user experiences. Messages can be targeted at a specific audience of followers without the need for an intermediary, which is typically required in traditional forms of communication. Additionally, feedback can be received directly from the audience.

Public health agencies (PHAs) have gradually embraced social media as an essential communication tool. This positive development is particularly important during pandemics when the public seeks regular, relevant updates and information. The 21st century has witnessed a series of pandemics, coinciding with the rise of social media [2,3]. Over time, PHAs have expanded their ability to use social media as one of the tools for managing pandemics.

A pandemic is a disease that simultaneously breaks out in multiple geographical locations worldwide, caused by a new and highly pathogenic microbe (or a variant thereof) to which humans have no prior immunological resistance [4]. A pandemic disease can easily cross international borders and spread within communities, constituting a public health emergency of international concern (PHEIC). Therefore, a swift and coordinated effort that focuses the attention and resources of governments and the public health community is always necessary to respond to and ultimately end a pandemic [4]. In the past 20 years, the World Health Organisation (WHO) has declared 6 diseases as constituting PHEICs (Table 1) [4–7]. Given the frequency of PHEIC declarations, global preparedness for managing another potential declaration in the future is crucial.

**HIGHLIGHTS**

- During pandemics, the public has a multitude of communication needs and expectations that public health agencies grapple with, as they face an avalanche of misinformation on social media.
- Public health agencies must uphold public trust in their social media communications, despite the initial knowledge gaps and constantly changing dynamics that are characteristic of pandemics.
- Effective audience engagement can be achieved by public health agencies sharing relevant, timely, and persuasive pandemic-related health messages on social media.
- Six overarching themes define how public health agencies can enhance the efficacy of their health messages through their social media accounts during pandemics.

One of the primary reasons that PHAs are established at all levels of government is to guide and coordinate efforts and initiatives aimed at preventing the spread of pandemics. Modern PHAs have evolved over 300 years, reflecting the growing sophistication of territories in managing diseases with the potential for rapid community transmission [8]. This crucial responsibility of PHAs is rooted in one of the most fundamental principles of public health: the control of

**Table 1.** Infectious diseases with their PHEIC and pandemic statuses

| Serial no. | Infectious diseases | PHEIC status | | | Pandemic status[a] |
|---|---|---|---|---|---|
| | | Considered | Announced | Duration (d) | |
| 1 | Poliomyelitis | Yes | Yes | 3,303 (ongoing) | No |
| 2 | COVID-19 | Yes | Yes | 1,192 | Yes |
| 3 | Ebola (first outbreak) | Yes | Yes | 600 | Yes |
| 4 | H1N1 influenza | Yes | Yes | 473 | Yes |
| 5 | Ebola (third outbreak) | Yes | Yes | 346 | No |
| 6 | Zika | Yes | Yes | 292 | Yes |
| 7 | Monkeypox | Yes | Yes | 293 | No |
| 8 | SARS[b] | No | No | - | Yes |
| 9 | MERS | Yes | No | - | Yes |
| 10 | Ebola (second outbreak) | Yes | No | - | No |
| 11 | Yellow fever | Yes | No | - | No |

PHEIC, public health emergency of international concern; SARS, severe acute respiratory syndrome; MERS, Middle East respiratory syndrome.
[a]The authors used the definition of Doshi [4] as a criterion. [b]SARS did not undergo a PHEIC evaluation as it predates the revised International Health Regulations policy of the World Health Organization. It was called "a worldwide health threat" instead.


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communicable infections [9]. Public health communication during pandemics is a core responsibility of PHAs [9,10]. The success of preparedness, response, and control measures for pandemics relies on the dissemination of accurate health messages that inform and empower individuals to make sound health decisions [11,12]. When misconceptions exist among the public, there is an increased risk of pandemic spread [13]. Effective communication fosters positive action from the population.

PHAs have increasingly incorporated the use of social media into their communication mix with each successive pandemic [14]. Pandemics typically involve significant uncertainty and knowledge gaps, which intensify the demand for accurate and reliable health information [15]. As individuals increasingly turn to social media for health-related information, PHAs have established social media accounts to address these needs [16]. The effectiveness of using social media to disseminate health message is demonstrated by increased reach [17] and interaction with the public [18]. However, social media communication during a pandemic presents unique challenges. Pandemics involve novel diseases that often necessitate continuously evolving messages from PHAs as the situation develops [19]. This complexity can be compounded by unscrupulous and unauthorized individuals and organizations spreading inaccurate health information, which can undermine and overshadow credible sources [20]. The number of followers on PHAs' social media accounts tends to increase significantly during pandemics [21]. However, followers may soon become dissatisfied with the level of engagement they receive due to conflicting messages from different agencies on the same topic within the same timeframe [22,23] or from a particular agency on the same issue at different times [22,24].

There is a growing body of research that evaluates and promotes the use of social media platforms by PHAs for communicating health messages during pandemics. However, it remains unclear whether these studies have comprehensively captured all the potential components of pandemic-related health messages by PHAs via their social media accounts that could foster effective public engagement and influence societal behavior [25–27]. This argument is based on the diverse contexts and research methodology used in studies [28,29], which limit the replicability of results. This scoping review aimed to synthesize the variables that influence the effectiveness of health messages from PHAs via their social media accounts during pandemics. To achieve this, we conducted a comprehensive overview of the existing research literature on PHAs' social media health communication during pandemics over the past 20 years.

## Materials and Methods

We conducted a scoping literature review to identify studies and documents relevant to our research scope. The scoping review methodology is well-suited for exploring a new field where evidence from previous research is scarce [30]. Therefore, the search for pertinent references in a scoping review encompasses both published journal articles and grey literature [30]. We followed the guidelines of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses Extension for Scoping Reviews (PRISMA-ScR) [31].

### Search Strategy and Selection

We searched 7 bibliographic databases (Sociological Abstracts, Medline, PsycInfo, Scopus, Health Business Elite, Health Policy Reference Centre, and Embase) for relevant peer-reviewed publications. These databases encompass reference sources for biomedical research, behavioral and sociological research, healthcare administration and policy issues, and related fields of interest. For grey literature searches, we consulted 5 sources: Bielefeld Academic Search Engine (BASE), WHO's Institutional Repository for Information Sharing (IRIS), and the .gov.au and .edu.au domains of the Google platform (each search limited to the first 5 pages).

We developed the search terms based on our research aim and in consultation with a healthcare specialist university research librarian, using the Sample-Phenomenon-of-Interest-Design-Evaluation-Research-type (SPIDER) framework [32]. We defined our sample (population of interest) as publicly funded health agencies at all levels of governance, and the phenomenon of interest as social media communication of public health messages during a pandemic. The design described the research methodologies used, while the evaluation focused on how members of the public engaged with and utilized the public health messages.

Following this process, we selected 3 key search terms: "social media", "healthcare communication", and "pandemic management". We then subjected the search terms to explosion and critical evaluation using Medical Subject Headings (MeSH) to generate keywords for the search strategy. Finally, we employed the resulting keywords for each database search. An example is provided in Table 2.

### Inclusion and Exclusion Criteria

The SPIDER framework facilitated the process of determining inclusion and exclusion criteria [32]. First, key search terms were defined. "Social media" referred to online platforms that utilize Web 2.0 technology to enable

**Table 2.** Example of search strategy: Sociological Abstracts

| | |
|---|---|
| 1 | AB = (("social media" OR "social networking site*" OR Facebook OR Twitter OR YouTube OR Weibo OR Instagram OR WeChat OR TikTok OR "online social network*") OR ti("social media" OR "social networking site*" OR Facebook OR Twitter OR YouTube OR Weibo OR Instagram OR WeChat OR TikTok OR "online social network*") OR if("social media" OR "social networking site*" OR Facebook OR Twitter OR YouTube OR Weibo OR Instagram OR WeChat OR TikTok OR "online social network*")) |
| 2 | AB = (("health messag*" OR "public health" OR "health policy" OR "health campaign" OR "health promotion" OR "health information" OR "false health information" OR misinformation OR disinformation OR "health behavio?r" OR "health literacy" OR "health communication") OR ti("health messag*" OR "public health" OR "health policy" OR "health campaign" OR "health promotion" OR "health information" OR "false health information" OR misinformation OR disinformation OR "health behavio?r" OR "health literacy" OR "health communication") OR if("health messag*" OR "public health" OR "health policy" OR "health campaign" OR "health promotion" OR "health information" OR "false health information" OR misinformation OR disinformation OR "health behavio?r" OR "health literacy" OR "health communication")) |
| 3 | AB = ((pandemic* OR MERS OR Zika OR SARS* OR H1N1 OR Ebola OR COVID* OR coronavirus OR "acute communicable disease*" OR "emerging communicable disease*" OR "acute infectious disease*" OR "acute communicable disease*") OR ti(pandemic* OR MERS OR Zika OR SARS* OR H1N1 OR Ebola OR COVID* OR coronavirus OR "acute communicable disease*" OR "emerging communicable disease*" OR "acute infectious disease*" OR "acute communicable disease*") OR if(pandemic* OR MERS OR Zika OR SARS* OR H1N1 OR Ebola OR COVID* OR coronavirus OR "acute communicable disease*" OR "emerging communicable disease*" OR "acute infectious disease*" OR "acute communicable disease*")) |
| 4 | 1 AND 2 AND 3 |

*, allows for different search term endings; ?, allows for both British and American spelling.

the creation and exchange of user-generated content across a variety of communication activities, supporting user interactions [1]. "Health communication" pertained to the dissemination of health messages aimed at influencing behavior change within the realm of health [33]. A "pandemic" was characterized as an emerging infectious disease with rapid international spread among humans, where no prior immunity existed [4]. Out of the 6 diseases declared as PHEICs in the past 20 years, poliomyelitis and monkeypox were excluded. These diseases did not meet the definition of a pandemic, as they were not new at the time of the outbreak and had existing vaccines [7,34,35]. The remaining 4 diseases—coronavirus disease 2019 (COVID-19), Ebola, H1N1 influenza, and Zika—met the definition of a pandemic. Middle East respiratory syndrome and severe acute respiratory syndrome (SARS) were also included in our list, despite not being declared as PHEICs by the WHO [7], because they met the definition of a pandemic (Table 1) [4]. The SARS outbreak occurred before the 2007 revision of the International Health Regulations by the WHO and the introduction of the "PHEIC" term [5]. Thus, the WHO termed SARS "a worldwide health threat" [36].

After finalizing our definitions, we established the following inclusion criteria: full-text publications in English, evaluations of health messages from PHAs posted on their social media accounts focusing on acute communicable diseases of pandemic proportions, and publications between January 2003 and August 2022. Our initial database searches yielded 4,208 non-duplicated papers. After applying the inclusion and exclusion criteria, 73 eligible papers were selected for the scoping review. The first author conducted the stepwise process, while the other 4 authors reviewed each step and addressed discrepancies. Figure 1 presents the flowchart in accordance with the PRISMA-ScR guidelines [31]. The first author served as the primary coder, extracting variables that influenced the effectiveness of PHAs' health messages on their social media accounts during pandemics from the full text of the 73 eligible papers. These variables were then integrated into sub-themes and further aggregated into themes. The second author independently coded 10% of the studies at random to ensure consistency. All remaining authors reviewed the codes to confirm reliability. Consequently, an iterative approach involving independent work and group discussions was employed to eliminate individual bias and enhance data validity.

## Results

### Characteristics of Included Studies

The resulting records included 71 peer-reviewed papers and 2 pieces of grey literature (Figure 1) [31]. Only 25% of the studies were published within the first 10 years of research output (Table 3). The remaining 75% were published in the last 3 years, coinciding with the COVID-19 pandemic. Three other pandemics covered by the studies were Ebola, Zika, and H1N1. The relative number of publications for each pandemic corresponded to the duration of their PHEIC status (Table 1) [4]. The publications originated from 18 countries, with approximately half coming from the United States of America (USA). China, Canada, and Singapore were other significant contributors, while countries from Africa, Europe, Oceania, and South America were less represented. These publications examined the social media public health communication activities of PHAs in 42 countries. The USA was the focus of 32 studies, either partially ($n$ = 5) or entirely ($n$ = 27), while 27 countries were each the subject of



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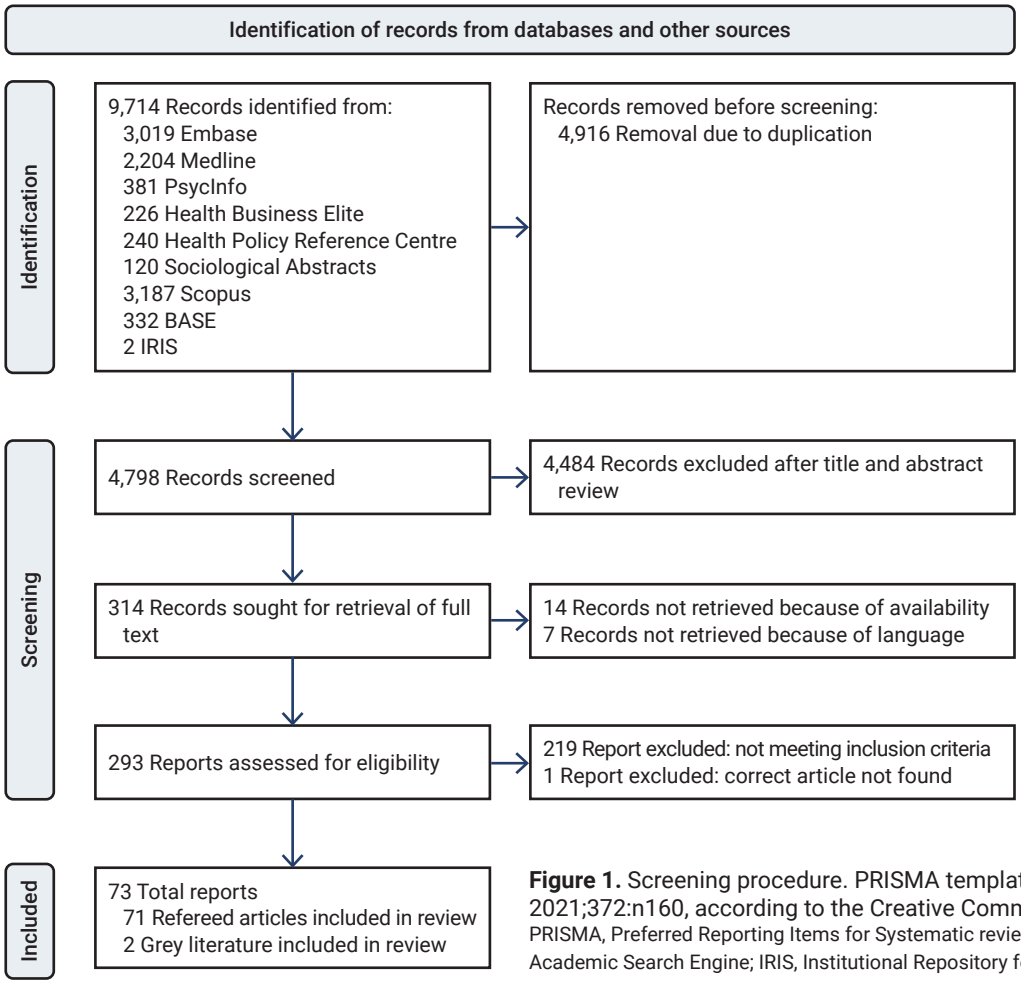


**Figure 1.** Screening procedure. PRISMA template adapted from Page et al. BMJ 2021;372:n160, according to the Creative Commons license [31].
PRISMA, Preferred Reporting Items for Systematic reviews and Meta-Analyses; BASE, Bielefeld Academic Search Engine; IRIS, Institutional Repository for Information Sharing.

no more than 1 study. The WHO was analyzed in 15 studies, and 12 studies compared multiple countries. Twitter and Facebook were the primary social media sources of research data, with 76% of the studies relying exclusively on one or the other. Twitter was included in all 7 studies that utilized data from multiple social media platforms. Single-method studies, either quantitative (42%) or qualitative (37%), were more common than mixed-method studies (21%). Of the 22 papers analyzed, 30% employed a theoretical framework or approach for their study, with the crisis and emergency risk communication (CERC) model being the most prominent (Table 4) [15,18,27,29,37–54].

A wide diversity is evident in the volume of social media data used in the studies (Table S1). Some studies analyzed only tens of health messages, while others examined thousands. The health messages studied ranged from low-media-styled posts (plain text) to high-media-styled posts (videos, infographics, and photos). Fifty-seven papers (78%) assessed PHAs at 1 of the following levels: global, national, state, or local (Figure 2). National-level PHAs were the most studied, with 52 papers in total; 38 of these focused solely on that level, and 14 compared them with PHAs belonging to other levels. Local-level PHAs were the least studied, involving 13 papers, 1 fewer than state-level PHAs. Only 4 papers examined PHAs' social media health messages across all tiers of government in a country. Thirty-one papers studied 1 PHA each, while 42 studied multiple PHAs; 12 of these papers focused on PHAs from multiple countries (Table 5). The United States' Centers for Disease Control and Prevention was the most studied PHA, followed by the WHO (Table S1). There was also a wide variety in the timeframe of social media data used in the studies (Figure 3). The most prevalent range was 2 to 4 months (28%), followed by 6 to 12 months (22%). Half of all the studies fell between both timeframes. Twenty-one studies (29%) based their timeframes on the period surrounding a PHEIC or national health emergency declaration. The assortment of PHAs studied, pandemics of interest, social media data volume, and data timeframe in the reviewed papers underscore the plurality of researchers' scope and attention.

**Table 3.** Characteristics of the reviewed papers ($n = 73$)

| Characteristic | No. of papers (%) |
|---|---|
| Publication year | |
| 2010–2014 | 2 (2.7) |
| 2015–2019 | 16 (21.9) |
| 2020–2022 | 55 (75.3) |
| Pandemic of focus | |
| COVID-19 | 54 (74.0) |
| Ebola | 9 (12.3) |
| Zika | 7 (9.6) |
| H1N1 | 3 (4.1) |
| SARS, MERS | 0 (0) |
| Country of study | |
| USA | 31 (42.5) |
| China | 9 (12.3) |
| Canada, Singapore | 5 (6.8) |
| India, Italy, Norway | 3 (4.1) |
| Saudi Arabia, Spain, UK | 2 (2.7) |
| Australia, Denmark, Finland, Israel, UAE, Philippines, Portugal, Romania | 1 (1.4) |
| Social media data source | |
| 66 Single sources (90%) | |
| Twitter | 26 (39.4) |
| Facebook | 25 (37.9) |
| Sina Weibo | 4 (6.1) |
| Instagram, WeChat, YouTube | 3 (4.5) |
| TikTok | 2 (3.0) |
| 7 Multiple sources (10%) | |
| Twitter | 7 (100) |
| Facebook | 5 (71.4) |
| Instagram, YouTube | 3 (42.9) |
| LinkedIn, Pinterest | 1 (14.3) |
| Study methodological approach/design | |
| Mixed | 15 (20.5) |
| Qualitative | 27 (37.0) |
| Quantitative | 31 (42.5) |
| Country of focus (multiple countries = 12) | |
| USA | 32 (43.8) |
| WHO | 15 (20.5) |
| China | 8 (11.0) |
| Singapore | 7 (9.6) |
| Canada | 6 (8.2) |
| Italy, England | 4 (5.5) |
| Norway, India | 3 (4.1) |
| Saudi Arabia, Denmark, Brazil, Australia, Nigeria, South Africa, New Zealand | 2 (2.7) |
| UAE, Spain, Romania, Philippines, Macao, Israel, Portugal, Sweden, Gambia, Chile, South Sudan, Namibia, Germany, Botswana, Ethiopia, Kenya, Liberia, Malawi, Rwanda, Sierra Leone, Zimbabwe, Sudan, Ghana, Tanzania, Uganda, Zambia, UK | 1 (1.4) |

SARS, severe acute respiratory syndrome; MERS, Middle East respiratory syndrome; USA, United States of America; UK, United Kingdom; UAE, United Arab Emirates; WHO, World Health Organization.

**Table 4.** Theoretical frameworks used for social media data analysis

| Theoretical frameworks used for data analysis | No. of studies |
|---|---|
| Crisis and emergency risk communication model [15,18,29,37–40] | 7 |
| Health belief model [41–45] | 5 |
| Media richness theory [46,47] | 2 |
| Social amplification of risks framework [48,49] | 2 |
| Agenda-setting theory [50] | 1 |
| Dialogic accounting framework [27] | 1 |
| Dialogic communication theory [46] | 1 |
| Disaster communication ecology framework [51] | 1 |
| Extended parallel process model [52] | 1 |
| Frame theory [53] | 1 |
| Mixed game model [54] | 1 |
| Public value theory [47] | 1 |
| Socially mediated crisis communication model [49] | 1 |
| Total | 25[a] |

[a]Three studies used 2 frameworks each for data analysis.

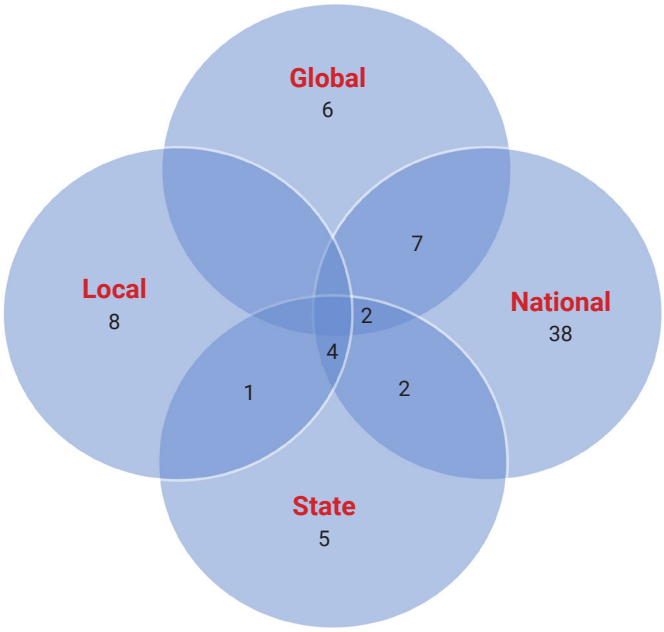


**Figure 2.** Distribution of the jurisdiction of public health agencies assessed by the reviewed papers.

**Table 5.** Jurisdiction of PHAs assessed by the reviewed papers

| Level of PHA | Focus of study | | |
|---|---|---|---|
| | Single PHA | Multiple PHAs (one country) | Multiple PHAs (multiple countries) |
| Global | 4 | 7 | 4 |
| National | 24 | 19 | 10 |
| State | 0 | 14 | 0 |
| Local | 3 | 10 | 0 |
| Total | 31 | 30 | 12 |

PHA, public health agency.



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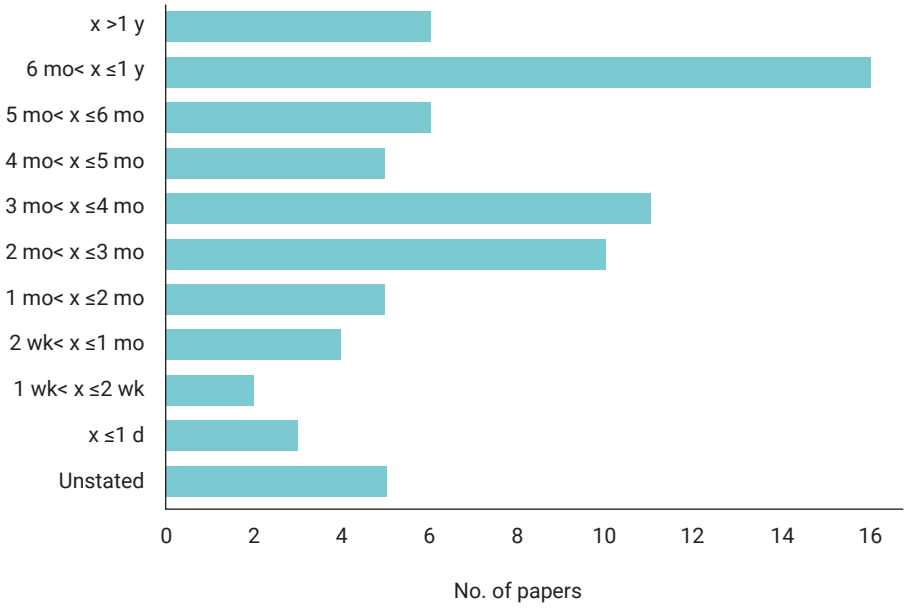


**Figure 3.** Time span of social media data used for analysis.

## Variables Influencing PHAs' Social Media Health Messaging during Pandemics

A total of 20 variables were identified as playing a role in the effectiveness of PHAs' use of their social media accounts to communicate relevant health messages during pandemics, based on the 73 reviewed studies. These variables were grouped under 6 broad themes: the origin of health information, the topic addressed, the semantics and style of messaging, the timing of messaging, the diversity of platforms and audience profile, and the credibility and reliability of message content (Table 6). The findings are further explained below, followed by a review of implications for practice and future research.

## Origin of Health Information

Sixty-two selected papers (85%) examined variables related to the reputation, internal players, and strategies of PHAs. Four sub-themes emerged under the sender of health information—namely, the status, tactics, policies, and personnel of PHAs.

The status of having a track record in pandemic management was found to be critical to a PHA's effectiveness when using social media to communicate health messages during a pandemic [55–59]. PHAs were perceived by the public as high-impact organizations that should serve as the primary source of health information during pandemics [60–62]. To ensure the effectiveness of social media health messages, there must be no ambiguity regarding which PHA in a country or territory is the authorized information source [63]. An absence of ambiguity enabled PHAs to act as agenda-setters on social media for both other PHAs and the public. These agenda-setters occupy strategic network positions, which amplify the reach of their health messages and generate widespread public engagement as other PHAs share the messages with their own followers [25,51]. PHAs that have earned public trust tend to be more effective in disseminating health messages during pandemics than those with a trust deficit [39,64,65]. Not only should PHAs be trustworthy, but they should also actively work to build mutual trust [47].

Nimble tactics also influenced PHAs' effectiveness. To increase their reach within their jurisdiction, PHAs adopted multilingual health messages [14,15,66]. They also utilized appropriate terminology in their messages [67] and offered advice using culturally fitting strategies [54,68]. PHAs featured diverse personalities as subjects or spokespersons on their social media channels, such as social media influencers [14,40,69], celebrities [70,71], medical personnel [72], political leaders [73], or victims sharing personal experiences [42,72]. Another tactic was "attribution of responsibility," which negatively labelled non-conforming members of the public [67,74]. At other times, PHAs sometimes opted for "ethical disengagement" [10] as a means of enhancing the effectiveness of its messages. PHAs also collaborated by sharing one another's health messages [25,51]. The tactics implemented by PHAs enabled them to disseminate their messages to various special populations and target audiences.

In-house social media policies providing guidelines have been shown to influence the characteristics and effectiveness of health messages shared by PHAs during pandemics [49,75]. Policy frameworks for PHAs were helpful in setting goals and strategies, as well as identifying the target audience

**Table 6.** Variables influencing PHAs' social media health messages during pandemics

| Serial no. | Themes/sub-themes (% of reported paper) | Description of sub-themes |
|---|---|---|
| 1 | Origin of health information (85) | |
| 1.1 | Status (59) | Experience and reputation of pandemic or public health crisis management |
| 1.2 | Tactics (59) | Granular approach adopted for social media communication |
| 1.3 | Policy (40) | Use of guidelines and regulation for social media communication |
| 1.4 | Personnel (12) | Those responsible for content creation and sharing, and resource management |
| 2 | Topical issues addressed (85) | |
| 2.1 | Education (73) | Public awareness about the pandemic and subsequent actions to take |
| 2.2 | Government efforts (37) | Communication of specific actions by (health) authorities |
| 2.3 | Collaboration (36) | Call for concerted support to tackle the pandemic |
| 2.4 | News update (34) | Highlights and breaking stories about the pandemic spread |
| 2.5 | Misinformation (33) | Communication addressing the menace of inaccurate information |
| 2.6 | Ancillary messages (29) | Non-pandemic related messages important for sustaining public health |
| 3 | Structure and style of messaging (75) | |
| 3.1 | Dialogue tools (63) | Incorporation of dialogic elements to trigger feedback and engagement |
| 3.2 | Media richness (44) | Incorporation of enriching elements to trigger feedback and engagement |
| 3.3 | Tone (23) | Incorporation of emotional tone to trigger feedback and engagement |
| 4 | Diversity of platforms and audience profile (68) | |
| 4.1 | Platforms (58) | Relevant summary attributes of social media platforms for health information |
| 4.2 | Community (53) | Followers, subscribers, and users of PHAs' social media accounts |
| 5 | Timeliness and relevance (67) | |
| 5.1 | Milestones and phases (66) | Messaging in accordance with specific pandemic events and stages |
| 5.2 | Frequency (10) | Regularity of messaging |
| 6 | Content credibility and reliability (62) | |
| 6.1 | Congruence (41) | Collaboration among PHAs to share similar messages |
| 6.2 | Consistency (16) | Coherence of a PHA's health messages to meet public information demands |
| 6.3 | Transparency (15) | Perceived openness and forthrightness in communication |

PHA, public health agency.

for its social media health communication. Twenty-nine studies discussed 17 guidelines that PHAs followed to create and share health messages on social media. Among these guidelines, the most prominent focused on emphasizing the transmission of health messages [17,26,69], fostering public interaction and engagement [10,37], and expressing empathy to those directly affected by pandemics [27,29]. PHAs were also encouraged to put risks into proper perspective [12,68], promote transparency of information and efforts [49,65], and be timely [38]. Utilizing multiple social media platforms was found to be valuable in effectively reaching a larger audience [18], while members of the public could be recognized as advocates and partners in the co-creation and dissemination of health messages [49,55]. If necessary, PHAs could discontinue further interaction with any member of the public [10,26]. However, Chen et al. [46] noted that adhering strictly to guidelines without flexibility could hinder effective social media messaging for PHAs.

Nine studies shed light on the impact that the personnel in charge of PHAs' social media accounts could have on the effectiveness of health messages shared during pandemics. Possessing expertise in areas such as journalism, public information management, or public health was associated with enhanced quality of PHAs' social media health messages [26,75,76]. These professionals demonstrated a greater aptitude for employing appropriate strategies to develop and distribute content on behalf of PHAs. However, disclosing the identity of these individuals could be detrimental if they have had a negative past with the public [24]. Alongside the personnel's ability to perform their jobs, emphasis was placed on providing them with the necessary digital tools and equipment [75].

## Topical Issues Addressed

Sixty-two selected papers (85%) examined variables related to the general message topics of PHAs. There was considerable diversity in how PHAs framed their social media health messages during pandemics [63,77]. The 6 categories within the subject of messages comprised education, government efforts, collaboration, news updates, misinformation, and supplementary messages.

Education dealt with PHAs' health messages that aimed to raise public awareness about the risks associated with pandemics [46,53,78]. These messages offered specific insights into disease mechanisms, as well as preventive and safety measures that individuals should adopt [44,79,80].



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Public consciousness was heightened regarding pandemic epidemiology, accompanied by recommendations on preventive strategies to prevent both community and hospital transmission [63,72]. This educational approach successfully captured public attention. Topics addressed included the use of personal protective equipment [24,52,63], vaccination and vaccine hesitancy [55,72], lockdowns, isolation, and physical distancing [45,51,73], personal sanitation [68,77], routine immunological testing [41,66], and contact tracing [29,73].

Government efforts to implement public health policies, enhance healthcare delivery, initiate or sponsor epidemiological studies, announce significant scientific breakthroughs, and modify the usual social and economic order comprise another category of health messages [27,29,52,53,59,67,68,77,81–83]. The extent to which this information was communicated impacted the effectiveness of these messages. Regular updates on government actions provided the public with incremental knowledge, offering reassurance during the uncertainties of pandemics [29,71]. These messages reflected the preparedness of governments at all levels [76]. Consequently, the public was eager to discuss and share these messages with other social media users [52,81]. Health messages of this nature maintained high public engagement throughout all stages of a pandemic [27,81,84].

PHAs' health messages also encouraged active public collaboration in efforts to combat pandemics by soliciting philanthropic donations of personal resources, including time, skills, and funds [50,79,81]. Utilizing local and international collaborations provided the solidarity PHAs needed to drive their narratives [12,44,68]. Other messages expressed appreciation to donors and contributors [37,82], with special mentions for healthcare workers [78,83], and construction workers [29]. PHAs' tendency to acknowledge the concerted efforts of the public during pandemics influenced the effectiveness of their health messages, as people were more likely to like and share the messages [27].

News updates were identified as another prominent feature of PHAs' social media health messages [14,78]. These messages aim to inform the public about the changing pandemic indices by providing real-time information on morbidity and mortality cases, as well as other related data [27,56,64] and the latest updates on hospital services [76,82]. Health messages often came in various forms, such as broadcasts of press conferences [37,63,76,81,85]. Framing health messages as news enables the public to gain situational awareness of a pandemic as it unfolds. However, not all PHAs utilized this approach, which may hinder the effectiveness of their health messages within their jurisdiction [76].

PHAs also shared health messages on their social media accounts to combat the spread of misinformation and fake news that incited panic among social media users [18,26,64,86]. They raised the public's awareness on how to avoid falling for misinformation [14,37] and corrected false information when necessary [10,87]. However, in many cases, inaccurate information from unverifiable sources was disseminated more widely by irresponsible social media users than the accurate health messages provided by PHAs [88]. In some instances, even reliable government sources inadvertently shared incorrect information [12]. The dedication of PHAs to addressing uncertainties and clarifying inaccurate health information played a major role in the effectiveness of their social media messaging during pandemics.

Finally, PHAs also posted messages unrelated to the ongoing pandemic [15,67,83]. Often, PHAs were slow to respond at the beginning of a pandemic, as evidenced by the predominance of non-pandemic messages in their social media communications [48,62,67,88]. However, when compared to messages not related to the pandemic, those addressing the pandemic were read by more people, and readers spent more time engaging with them [37,48,62]. It remains unclear why PHAs hesitated to increase their pandemic-related messaging in response to the public's growing information needs during outbreaks. It appears that PHAs may be uncertain about what information to share at the onset of pandemics [83].

### Structure and Style of Messaging

Fifty-five papers (75%) examined variables that focused on the structure, style, and supplementary elements of the messages of PHAs. The 3 resulting sub-themes were the dialogic tools, media richness, and message tone of PHAs.

Dialogic tools refer to elements incorporated into social media health messages that facilitate engagement and interaction between the sender and the audience [27]. The presence of dialogic tools in PHAs' health messages influenced the effectiveness of those messages. Hashtags and hyperlinks were the most commonly used dialogic tools by PHAs [39,41,62]. For example, the use of hashtags was associated with higher levels of public engagement while the opposite was true for hyperlinks [15,53]. When both were combined in a post, public engagement levels increased [76]. Health messages featuring multiple dialogic features tended to garner more engagement than those with a single feature [46]. Higher-level PHAs often used hyperlinks to direct their audience to their own websites for more information [41], but state-level PHAs preferred to send their audience to the websites of federal-level PHAs and other reputable organizations [42]. Although PHAs used dialogic tools in various ways, they generally used such tools to collaborate, which in turn reinforced

one another's messages [25,56,63,89]. This approach effectively demonstrated the coherence of the views of different PHAs on the same issue. Other dialogic tools used less frequently by PHAs included the @ mention function, question and exclamation marks, live chats, reply, forward, and quote functions [46,52,53,76,87]. These tools were effective to varying degrees in generating public engagement with health messages. The public's perception of the effectiveness of health messages is related to the degree to which 2-way communication is accommodated [60,90]. Two-way communication benefitted the public by promoting consensus building and mutual trust [10,27].

Media richness refers to the ability of a message to generate shared meanings and facilitate smooth interactions between the sender and receiver of the message [46]. Generally, health messages with high media richness were less likely to engage users on text-oriented platforms like Twitter and Sina Weibo [46]. However, combining images with plain text can increase public attention [56]. Infographics and pictures were the commonest media enrichment tools used by PHAs [56,68,70]. The current pandemic phase at the time of infographic development influenced their design and layout [91]. Factors such as the choice of background colors, the language used, and the personality presented in the image were all subtle but influential elements of graphics and pictures incorporated into PHAs' health messages [40,92]. Higher-level PHAs further enriched their health messages (e.g., by using videos) more frequently than lower-level PHAs [92]. As with infographics, PHAs had different options for creative video styles to adopt for their health messages, ranging from animations to live-action videos [63,89]. More creative videos were more effective. Factors such as video duration, tone, and title length significantly influence the effectiveness of health messages in generating public engagement [14,63,84]. However, engagement levels with videos were lower than with plain text on text-oriented social media platforms such as Twitter [15], WeChat [82], and Sina Weibo [46].

The choice of message tone was another sub-theme. As the language used on social media tends to be more similar to spoken communication rather than written, the effectiveness of PHAs' health messages was related to the extent to which the messages exhibited a conversational tone [38,39,47]. PHAs, however, typically adopted either an authoritative formal tone or an interactive informal tone [47,54]. PHAs were more likely to use a formal tone in their social media messaging when emphasizing guidelines, instructions, and warnings [68]. Although the public often perceived PHAs' formality negatively as mere grandstanding, certain situations, such as addressing misinformation, made the formal stance non-negotiable [10,18]. Conversely, when informality, cordiality, and humor were incorporated into health messages, public engagement increased with more views and reactions [69]. In the same vein, PHAs may choose to convey positive, negative, or both tones in their messaging. Positive messages tend to focus on solutions, while negative messages can dampen public morale [56,72]. The more positive a health message is, the more engaging it becomes. Message tone also involves communicating emotion-laden cues to which the public responds [67,84]. The emotional valence of PHAs' health messages influences their effectiveness in triggering public sentiments, emotional support, diffusion, and engagement [58,67,84,93].

### Diversity of Platforms and Audience Profile

Fifty selected papers (68%) examined variables related to the reach of PHAs' health messages to the public, with an emphasis on the subscribers and followers of the social media accounts of PHAs. This theme was consolidated from 2 sub-themes: community and platforms.

During pandemics, the followership of PHAs' social media channels consistently increased as people sought health messages from authentic sources [18,26,42,57,62]. Higher-level PHAs with broader jurisdictional coverage tended to attract more followers than lower-level PHAs [48]. PHAs established social media accounts on platforms where their target audience was most likely to be found [83,91]. The geographic location of a PHA played a role in distinguishing its audience characteristics from those of other PHAs [10,14,42]. However, each PHA had to contend with diverse audience profiles in terms of demographic features [17,38,39,57,63,64]. PHAs tailored their health messages to specific target audience profiles and social media channels [40,49,56,70,94]. The engagement patterns of the audience also tended to influence subsequent messaging from PHAs [44,48,63,95].

Accessibility to social media platforms within a PHA's jurisdiction encourages users to engage with the PHA's social media channels. The most popular social media accounts for PHAs were found on Facebook, followed by Twitter, across various regions and countries, including Anglophone Africa [14], the USA [42,48,57,65,71], Italy [27,70], Canada [38,39,62], New Zealand [27], the United Kingdom [27,71], Denmark, Norway, and Sweden [10], Singapore [71], and for the WHO [55,65]. Twitter provided the most connections to PHAs' social media accounts in India [73]. Sina Weibo was the most popular in China, followed by TikTok [46,53,82,84]. Despite YouTube's ubiquity, few users connected with PHAs' social media accounts on the platform [14,63,89]. Channel popularity did not always correlate with PHA usage. For example, while a large Facebook following prompted health



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communication by PHAs in Singapore and Macao [49,81], the less popular Twitter was more frequently used by PHAs in the USA [49,57,78,88] and Africa [14]. Nevertheless, PHAs often used multiple platforms to share their health messages [56,85], as each social media platform exhibited unique characteristics [15,81,94] and [14] supported public engagement differently [41,85,94].

### Timeliness and Relevance

Forty-nine selected papers (67%) investigated variables associated with the relevance of health messages from PHAs at the time of delivery. This theme encompassed 2 sub-themes: pandemic milestones and phases, as well as message frequency.

PHAs recognized certain milestones or new developments during a pandemic, such as the announcement of a PHEIC, during which health information demand is highest [37,45]. Notwithstanding, while some PHAs posted the preponderance of their pandemic-related health messages around these landmark events [52,60,70,94], others shared a disproportionately small volume of information [42]. When PHAs trended together with pandemic-related events, their health messages were highly effective in attracting public engagement [43,62,71] and generating diverse emotional reactions from the public [67]. Conversely, Madvig et al. [26] and Lwin et al. [29] reported no consistent relationship between PHAs' health message volume during landmark pandemic-related events and the level of public engagement.

The pandemic phase during which PHAs shared health messages could influence the effectiveness of messaging [81]. Pandemics can be segmented into phases based on the disease progression in the community. However, there was no shared basis for this segmentation in the literature, and the number of phases was presented as 5 [15,29,37], 4 [51,59,81,83] or 3 [65]. Ahmed et al. [79] and Radwan and Mousa [68] restricted the segmentation to the lockdown period only. PHAs' pandemic-related health messages varied with pandemic phases, irrespective of the segmentation type adopted [15,83]. The volume of messages and the range of topical issues addressed were lowest during the prodromal phase, but rose significantly when the first pandemic cases were reported [14,15,59,63,81,83,88]. However, despite the higher volume of messages, certain population groups were often not targeted [96]. Batova [24] attributed this apparent oversight to PHAs' limited knowledge about pandemics during the early stages of an outbreak.

Early messaging from PHAs following an outbreak was helpful in guiding the public [41,62], although such messaging was often delayed until a sharp increase in cases occurred [14,76,78]. Frequently, the content of these health messages did not meet the public's information needs [59,80,83], which evolved with the different phases of the pandemic [29]. There were instances when the messaging from PHAs did not align with the rate of disease spread, rendering the messages less relevant to the audience [88,97]. Within the same pandemic phase, individual PHAs shared health messages on topics they deemed appropriate [79] or established common ground with other PHAs [51]. The posting of conflicting messages from different PHAs was widespread during the early phases of pandemics, but coherence and collaboration gradually became more evident as pandemics progressed [77]. With social media, PHAs could communicate at the public's most preferred times of the day [64,76,98], resulting in a wider reach for well-timed communication strategies. Similarly, maintaining a regular frequency of health messaging [37,56] allowed the public to build trust and confidence in the activities of PHAs.

### Content Credibility and Reliability

Forty-five selected papers (62%) investigated variables related to the credibility and reliability of health messages conveyed by PHAs. Within these studies, 3 sub-themes were identified: congruence, transparency, and consistency of the messages.

Congruence refers to the extent to which PHAs display consistency in content and context within their pandemic-related health messages. This is particularly crucial for PHAs operating within the same jurisdiction or catering to the same audience. Incongruence among PHAs is not uncommon during pandemics, as situations continually evolve [65,77,91]. Instances of incongruence have been observed in message volume, the selection of topics addressed, and the timeliness of addressing issues by different PHAs [14,27,40,47,65,79,89,95–98]. For example, PHAs' health messages addressed misinformation differently during the COVID-19 pandemic [71]. Incongruence can lead to varying levels of public emotional diffusion across PHAs [93]. Dissonance among PHAs negatively affects the public's response to conflicting health messages, while congruence has the opposite effect [77]. Sharing health messages with similar themes at comparable times and frequencies, as well as referencing one another, indicated coordination and collaboration among PHAs [25,51].

Health messages from PHAs could be perceived to be insufficiently transparent and objective [74,91]. The transparency of PHAs was called into question when they faced a deficit in public trust, as evidenced by fear-inducing health messages that suggested hidden motives related to financial gain, corruption, conspiracy [24,58,60,85]

or political interference [26]. Health messages that are perceived as non-transparent often prompt public responses calling for PHAs to be more forthright. However, message transparency could be hindered by the public's level of scientific literacy [72]. The public frequently associates transparency with the jurisdictional level of PHAs [50,53]. Nevertheless, PHAs at all levels have the potential to exhibit transparency, which can influence the effectiveness of their pandemic-related health messages [98].

The consistency of opinions expressed in PHAs' pandemic-related health messages was another influential factor. Perceived inconsistency diminished the relevance of PHAs' health messages to the public [18,24,26,39,77]. Inconsistency and ambiguity in PHAs' communication of pandemic-related risks arose when successive health messages continually shifted, leading to public anger and criticism [18,24,77,86]. This caused some individuals to become more anxious, while others downplayed the risks [48]. Since PHAs' health messages did not consistently address the public's concerns, the resulting demand-supply mismatch undermined the effectiveness of their health messages [37,47,59,80,83].

## Discussion

This review examined the evidence in the literature concerning PHAs' use of social media for disseminating public health messages during a pandemic and assessed the resulting public engagement. Twenty key factors were identified for PHAs to consider when using social media for health communication during a pandemic. These 20 factors (sub-themes) were then grouped into 6 overarching themes. The review highlighted the interconnections between the themes and sub-themes, which work together to enhance effective public engagement via PHAs' social media accounts. This ecosystem is encapsulated in a conceptual model, which is displayed in Figure 4.

Even though pandemics have different courses (Table 1) [4], this literature review has identified general criteria that can guide PHAs in crafting pandemic-related health messages for their social media accounts. PHAs create and disseminate messages on diverse topics, tailored to audiences with differing locations, demographics, engagement profiles, and health literacy levels. In developing these messages, PHAs rely on their inherent factors, such as trust capital, social media policies, tactics, and skilled personnel, to fulfill their communication responsibilities. For example, the absence of internal social media policies for PHAs impeded effective health communication activities on social media during the pandemic [67,75]. However, PHAs' intrinsic factors were not the sole determinants of effective messaging, as they were also influenced by other variables within the ecosystem. For instance, a recipient could be a contributor, promoter,

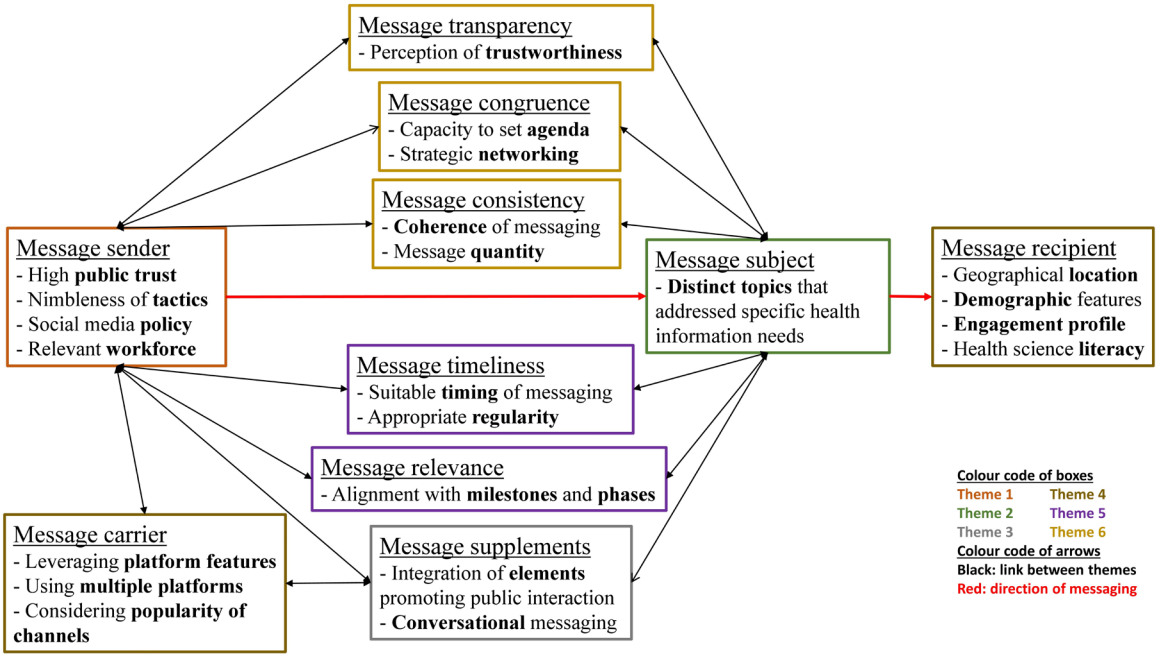


**Figure 4.** A conceptual model of social media communication by public health agencies during pandemics.


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or champion. Contributors frequently interacted with PHAs' health messages, often as detractors, while champions engaged less frequently but typically as advocates and partners of PHAs [48,55]. Each category of recipient perceived pandemic-related health messages differently and engaged accordingly [50,73]. They evaluated the messages based on relevance, transparency, congruence, consistency, timeliness, and tone [40,47,52,82,92]. The public experienced various stages and milestones during pandemics, which continually affected the communication strategies of PHAs and the content of their health messages [15,29,37,59,65,68,81,83]. Consequently, PHAs needed to learn from the public's engagement with previous messages before moving forward with new ones.

### Contribution to Theory and Practice

The grounding of public health communication science and practice in social media theory is still in its early stages. This literature review discovered that only 22 studies (30%) employed a theoretical approach or framework for critical data analysis. Thirteen distinct theoretical frameworks were utilized, with the CERC model being the most prominent. The variety of theories applied indicates that they are still being tested in health communication research. This finding supports the arguments made by Hannawa et al. [99] and Hannawa et al. [100], who posited that empirical research in health communication lacked theoretical rigor and a clear epistemological approach, which are 2 essential components for framing practical solutions in the field.

Only 1 study, by Vijaykumar et al. [49], discussed a framework. This framework, risk amplification through media spread (RAMS), was conceptualized as a potential tool to guide future public health communication activities of PHAs during pandemics. However, the framework was designed for the entire health communication spectrum, not social media only. Liu and Kim [67] called for further investigation into viable communication frameworks during pandemics. Pandemics and their associated effects typically last longer than most crises, which tend to be acute and have a more limited geographical spread. Conversely, Vijaykumar et al. [49] emphasized the importance of evaluating the ways in which social media efforts impact societal behavior during pandemics. It is not enough for PHAs to simply post health messages on social media; the influence on societal behavior should also be monitored and measured. This literature review proposes a conceptual model (Figure 4) that could serve as a foundation for additional research into social media health communication by PHAs during a pandemic.

### Research Gaps: Directions for Future Research

Each successive pandemic of the 21st century has increasingly exposed the gaps in social media health messaging by PHAs [14]. The year 2003 marked the beginning of the social media revolution as we know it today [3]. SARS, the first pandemic recorded in the social media era [2], occurred the same year [36]. This scoping review found no evidence that any PHA used social media platforms for relevant communication during SARS. As social media was still in its infancy [3], PHAs would not have considered it as an option for their public health communication. The next pandemic, H1N1 [5,7], presented a different narrative. Three studies [49,67,75] revealed that PHAs utilized their social media channels to communicate pertinent health messages about the pandemic. However, these studies focused solely on the USA. By the time of the most recent pandemic, COVID-19, studies have covered 42 countries to varying extents (Table 3). Consequently, there is a gap in knowledge about the situation in many countries during a pandemic. Likewise, there are gaps in understanding how social media platforms can be effectively used. This literature review identified 7 social media platforms that were used for study purposes. However, there are over a hundred other social media platforms where the public gathers and health communication circulates. PHAs cannot afford to overlook such platforms.

## Conclusion

This scoping literature review aimed to identify and synthesize the variables that influence the effectiveness of PHAs health messages on their social media accounts during pandemics. Our review categorized these variables into 6 themes: origin of health information, topical issues discussed, structure and style of messaging, timeliness and relevance, content credibility and reliability, and diversity of platforms and audience profiles. These factors can be considered by PHAs when using their social media accounts for effective pandemic-related health communication. However, we identified a significant research gap in determining the relative importance of these variables. Furthermore, the existing theoretical frameworks in the studies examined were insufficient in addressing this gap. We have proposed a conceptual model to hypothesize the interconnectedness of these variables and advocate for more research to provide insight, as PHAs need to be better equipped in health communication for potential future pandemics.

## Supplementary Material

**Table S1.** Description and analysis of included articles (in order of period of the social media data studied). Supplementary data are available at https://doi.org/10.24171/j.phrp.2023.0095.

## Notes

**Ethics Approval**
Not applicable.

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

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**Availability of Data**
All data generated and analyzed during this study are included in this published article. Other data may be requested through the corresponding author.

**Authors' Contributions**
Conceptualization: all authors, AH; Design: all authors; Methodology: all authors; Supervision: AH, NK, LY, MA; Literature review: BAB, AH; Validation: all authors; Visualization: BAB; Writing–original draft: BAB; Writing–review & editing: all authors. All authors read and approved the final manuscript.

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Original Article

# Risk factors for transmission in a COVID-19 cluster infection in a high school in the Republic of Korea

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## ABSTRACT

**Objectives:** This study aimed to examine the scale, characteristics, risk factors, and modes of transmission in a coronavirus disease 2019 (COVID-19) outbreak at a high school in Seoul, Republic of Korea.

**Methods:** An epidemiological survey was conducted of 1,118 confirmed cases and close contacts from a COVID-19 outbreak at an educational facility starting on May 31, 2021. In-depth interviews, online questionnaires, flow evaluations, and CCTV analyses were used to devise infection prevention measures. Behavioral and spatial risk factors were identified, and statistical significance was tested.

**Results:** Among 3rd-year students, there were 33 confirmed COVID-19 cases (9.6%). Students who used a study room in the annex building showed a statistically significant 4.3-fold elevation in their relative risk for infection compared to those who did not use the study room. Moreover, CCTV facial recognition analysis confirmed that 17.8% of 3rd-year students did not wear masks and had the lowest percentage of mask-wearers by grade. The air epidemiological survey conducted in the study room in the annex, which met the 3 criteria for a closed space, confirmed that there was only 10% natural ventilation due to the poor ventilation system.

**Conclusion:** To prevent and manage the spread of COVID-19 in educational facilities, advance measures that consider the size, operation, and resources of each school are crucial. In addition, various survey methodologies should be used in future studies to quickly analyze a wider range of data that can inform an evidence-based quarantine response.

**Keywords:** COVID-19; Epidemiology; Risk factors; Surveys and questionnaires; Video analysis

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## Introduction

Coronavirus disease 2019 (COVID-19) is spread primarily by droplets expelled from the respiratory tract of infected individuals in closed, crowded, and close-contact environments, and transmission can occur by touching a surface contaminated with the virus and then touching the mouth, eyes, or nasal mucosa without washing one's hands [1,2]. Among the various living environments encountered in daily life, educational facilities pose a high risk of infection (3 risk factors: enclosed, crowded, and close contact) because many students are in close contact for extended periods of time, such as during classes, meals, and sports activities [1].

At the beginning of the COVID-19 pandemic, many schools worldwide closed or were only partially operated to prevent the further transmission of the disease [3–5]. Educational facilities have suggested infection control measures such as wearing masks in schools, checking body temperature and respiratory symptoms, practicing hand sanitization, and not allowing students with symptoms to attend classes to reduce the risk of infection [6]. In May 2021, educational facilities in the Republic of Korea provided in-person or online classes according to the social distancing stages by region during the COVID-19 pandemic [7].

Following a cluster of 33 COVID-19 cases at a high school in Seoul, a large-scale epidemiological investigation was conducted from May 21 to May 31, covering a total of 1,118 people, which included both cases and contacts. All of the cases belonged to the same grade (3rd-year students), enabling an online survey, CCTV video analysis, and aerodynamic experiments to be conducted with 3rd-year students only ($n$=343) to investigate the outbreak pattern and key risk factors.

The existing literature on risk factor survey methods for COVID-19 prevention is diverse. This study was the first to use multiple survey methods to identify risk factors for rapid prevention in educational settings where there is a high risk of infection.

### HIGHLIGHTS

- The study utilized various research techniques to examine the scale, characteristics, risk factors, and modes of transmission in a COVID-19 outbreak in a high school in the Republic of Korea.
- In-depth interviews, online surveys, on-site aerodynamic testing, and CCTV analysis were used to identify risk factors for the spread of COVID-19.
- The identified risk factors included not wearing masks and using the annex study room, which was an enclosed space. This information can be used to devise effective infection prevention measures at schools.
- Utilizing various survey techniques facilitated the identification of risk factors and enabled the development of comprehensive, evidence-based guidelines for preventing the future spread of infectious diseases.

## Materials and Methods

### Participants

This was a cross-sectional study. The sample included 1,118 high school students and staff from the high school. All infections were in 3rd-year students. Therefore, to analyze the behavioral characteristics of 3rd-year high school students related to COVID-19 infection, we conducted an online survey of 343 3rd-year students and analyzed the mask-wearing rate by grade among the entire school population of 1,118 participants. Given the COVID-19 incubation period, we defined cases as individuals who tested positive for severe acute respiratory syndrome coronavirus 2 genetic material in an upper respiratory tract specimen using reverse transcription-polymerase chain reaction testing according to the test criteria in the diagnostic assay between May 30, 2021, which was the date the first case was confirmed, and June 13, 2021.

### Epidemiological Investigation

Based on the date of onset of symptoms of the index patient (May 23, 2021), the incidence rate was determined by calculating the proportion of confirmed COVID-19 cases among 3rd-year students within the incubation period. For symptomatic patients, the incidence rate was determined based on the date of symptom occurrence according to an individual basic epidemiological survey and an in-depth epidemiological survey conducted by the public health center in the jurisdiction of the confirmed patient's area of residence related to the cluster infection. In cooperation with the school principal, we collected a list of students who attended classes and users of the annex self-study room.

### Risk Factor Analysis

#### Online questionnaire

The survey was designed to identify significant differences in the behavioral characteristics of students with and without confirmed COVID-19 infections at the study school in order to devise strategies to prevent future infections.

The survey was conducted online using Google Forms with the condition that no personal information would be included. Participants were informed about the purpose of the survey, the conditions of participant consent for information collection, the legal basis for the study, and the planned destruction of participant data after analysis. The survey totaled 25 questions across 6 categories, focusing on behaviors that could cause vulnerability to infection, such as whether individuals were previously infected with COVID-19, whether they switched classes, their food intake history, and whether they wore masks, performed hand sanitization, and talked with classmates (online survey: https://forms.gle/ZF2HqMrc5DTVaKE99) (Supplementary Material 1). With the permission of the person in charge of the school and parents, the study was conducted only with the 343 third-year students, regardless of their COVID-19 infection status. We asked students to respond about their in-school behaviors between May 21 and May 31, 2021, and conducted an online survey on June 1. Among the 343 students, 266 responded. The collected survey data were extracted and organized in Excel ver. 2016 (Microsoft Corp.). Basic statistics, the t-test, and the Pearson chi-square test were conducted using STATA ver. 17.0 (StataCorp LLC). Based on a reference study that conducted a survey about COVID-19, statistical significance was set at $p < 0.05$ [8].

### Investigation of the environment

The floor plans of the main and annex buildings of the high school were obtained to confirm the routes of transmission of the cluster infection. We verified that the school administration complied with the school quarantine management regulations. Interviews and on-site surveys were conducted with the school's facilities manager to determine whether features to improve ventilation, such as windows and air conditioners, were installed in the annex self-study room.

### Video analysis

In order to prevent school violence and ensure a safe learning environment in schools, as covered by Article 2 of the Elementary and Secondary Education Act, the school principal must follow the Standard Guidelines for Installation and Operation of Video Information Processing Devices in Schools created by the Ministry of Education by installing a CCTV system. Therefore, we analyzed the students' movements and mask-wearing rates by grade during the exposure period (May 20 to May 31) using CCTVs installed in the schools.

The CCTV footage was collected in accordance with the Ministry of Education's Personal Information Processing Policy and Article 18, Paragraph 3, of the Constitution of the Republic of Korea (Act on the Prevention and Control of Infectious Diseases) on the legal grounds that information disclosure requests and submission of documents necessary for epidemiological investigations, respectively, can be requested. For CCTV analysis, we used BriefCAM Investigator software ver. 5.4 (BriefCAM Investigator), which is currently used by the Korean National Police Agency for investigations requiring extensive information analysis. The program filters out all faces identified in the footage. Filtering was performed using artificial intelligence (AI) for face detection, during which the face resolution, face image quality, and face pose were identified. The filtered faces were then removed via alarm triggers for objects with low quality or when no face was detected. The faces, extracted using AI, were automatically mosaicked and categorized according to whether the subject was wearing a mask, not wearing a mask, or wearing a mask across the chin only. The program was run on a laptop registered as the property of the Gyeonggi Southern Police Agency. The laptop was protected by physical and digital security systems and could not be connected to the Internet. Therefore, information leakage was impossible. Furthermore, the analysis was performed by an investigator affiliated with the police department. At the end of the analysis, all data were permanently deleted.

### Field experiment on aerodynamics

The epidemiological investigation confirmed that the index case and additional cases all occurred among students who had used the annex study room, which is a closed, densely packed, and close-contact environment. Therefore, we investigated the movement of infectious disease droplets in the annex room. First, we divided the area into 10 zones. The concentration distribution for ventilation and airflow and the change in droplet particle concentration in the selected areas were measured with the windows both closed and opened. The concentration of contaminants in each area was measured with a smoke generator, oil vapor generator, indoor air quality sensor, and particle imaging velocimeter system to evaluate the possible horizontal spread of droplet-type particles in the target building space.

## Ethics Approval

This study was approved by the Institutional Review Board of the Korea Disease Control and Prevention Agency (2022-10-01-PE-A) and performed in accordance with the principles of the Declaration of Helsinki.


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## Results

### General Characteristics of the Confirmed Cases

Outbreak pattern of all confirmed cases in the school: The school was an all-boys school, and the infected students and contacts were all male. A total of 33 confirmed cases of COVID-19 were identified among the students, with no confirmed cases among faculty members. The incidence rate was the highest in class 11, with 9 infected students (30%), while there were no confirmed cases in class 2 (Table 1). Twenty-eight patients (84.8%) responded that they had clinical symptoms of COVID-19, while 5 students (15.2%) were asymptomatic. Among the students with symptoms, 16 (23.2%) had a sore throat, 12 (17.4%) had a headache, and 11 (15.9%) had a fever (Figure 1).

Outbreak pattern of confirmed cases according to the use of the self-study room in the annex: A total of 21 out of the 33 confirmed cases (63.6%) involved those who used the study room. Among the students who tested negative, 144 (46.5%) used the study room. Therefore, the relative risk of patients who used the study room compared to those who did not was 2.2 (95% confidence interval, 1.12–4.37) (Table 2).

### Trends of the Epidemic

Of the 33 high school students with confirmed COVID-19 infections, 14 used the annex self-study room, which is

**Table 1.** Prevalence of symptoms and incidence of COVID-19 infection by high school class

| Class | No. of students | Infected | | | Non-infected | Infection rate (%) |
|---|---|---|---|---|---|---|
| | | Total | Symptomatic | Asymptomatic | | |
| Total | 343 (100.0) | 33 (100.0) | 28 (100.0) | 5 (100.0) | 310 (100.0) | 9.6 |
| 3rd-year students | | | | | | |
| Class 1 | 33 (9.6) | 1 (3.0) | 1 (3.6) | 0 (0) | 32 (10.3) | 3.0 |
| Class 2 | 34 (9.9) | 0 (0) | 0 (0) | 0 (0) | 34 (11.0) | 0.0 |
| Class 3 | 32 (9.3) | 1 (3.0) | 1 (3.6) | 0 (0) | 31 (10.0) | 3.1 |
| Class 4 | 31 (9.0) | 6 (18.2) | 6 (21.4) | 0 (0) | 25 (8.1) | 19.4 |
| Class 5 | 30 (8.7) | 1 (3.0) | 1 (3.6) | 0 (0) | 29 (9.4) | 3.3 |
| Class 6 | 30 (8.7) | 2 (6.1) | 2 (7.1) | 0 (0) | 28 (9.0) | 6.7 |
| Class 7 | 32 (9.3) | 5 (15.2) | 3 (10.7) | 2 (40.0) | 27 (8.7) | 15.6 |
| Class 8 | 31 (9.0) | 3 (9.1) | 3 (10.7) | 0 (0) | 28 (9.0) | 9.7 |
| Class 9 | 30 (8.7) | 3 (9.1) | 3 (10.7) | 0 (0) | 27 (8.7) | 10.0 |
| Class 10 | 30 (8.7) | 2 (6.1) | 2 (7.1) | 0 (0) | 28 (9.0) | 6.7 |
| Class 11 | 30 (8.7) | 9 (27.3) | 6 (21.4) | 3 (60.0) | 21 (6.8) | 30.0 |

Data are presented as *n* (%).

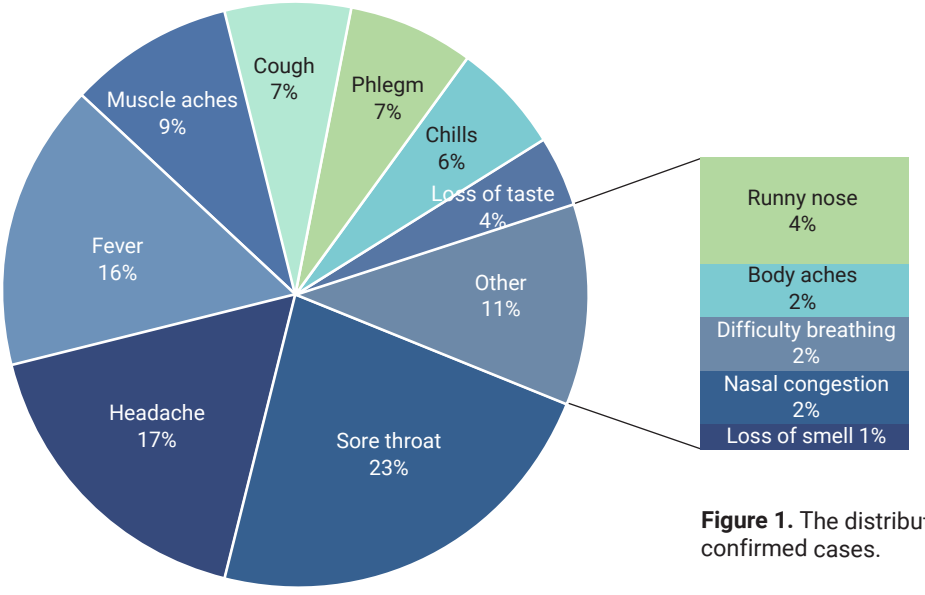


**Figure 1.** The distribution of clinical symptoms in COVID-19 confirmed cases.

**Table 2.** The relative risk of COVID-19 infection among 3rd-year high school students according to whether they used the self-study room

| School annex self-study room | Positive (*n* = 33) | Negative (*n* = 310) | Total (*n* = 343) | RR (95% CI) | *p* |
|---|---|---|---|---|---|
| Used | 21 (63.6) | 144 (46.5) | 135 (39.4) | 2.2 (1.12–4.37) | 0.018 |
| Not used | 12 (36.4) | 197 (63.5) | 208 (60.6) | Ref. | |

Data are presented as *n* (%) or RR (95% CI).
RR, relative risk; CI, confidence interval; ref., reference.

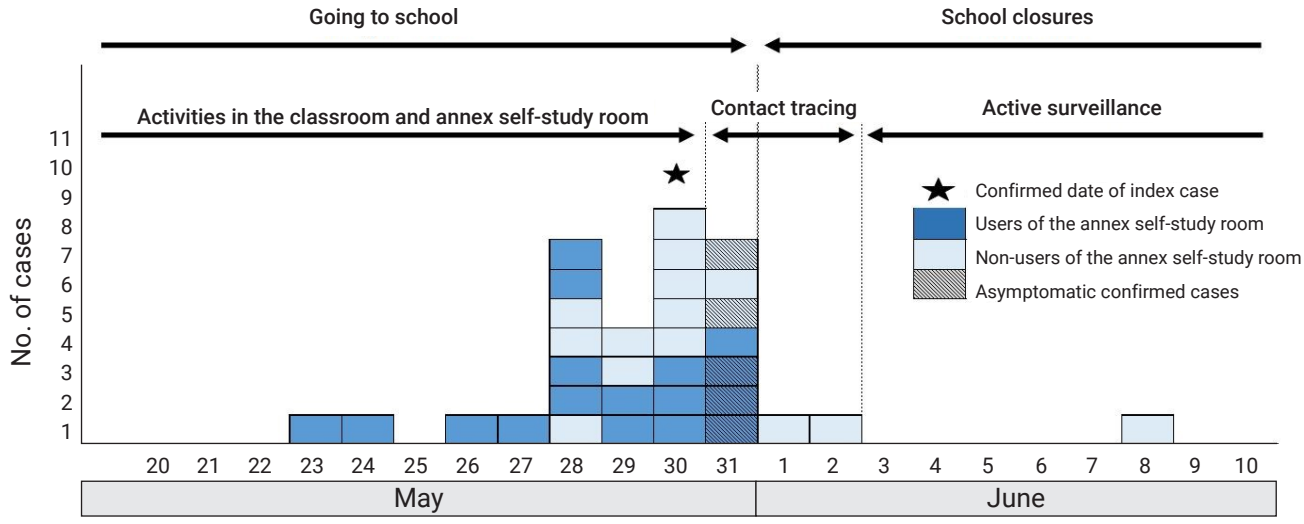


**Figure 2.** Epidemic curve for the characteristics of the COVID-19 outbreak in schools from May 20 to June 20, 2021, and the presence of symptoms.

exclusively for 3rd-year students. It is speculated that secondary transmission occurred in each class after the initial transmission in the annex self-study room, considering that users of the room spent more time at school than non-users and the room was not well-ventilated (Figure 2).

## Personal Preventive Behavior

Using the results of the survey to identify behavioral risk factors, 266 of the 3rd-year students who participated in the survey were asked about their preventive behaviors in the classroom. Of the 28 students with confirmed infections, 17 (60.7%) always wore masks in the classroom and 10 (35.7%) often wore them. Of the 238 non-cases, 141 (59.2%) always wore a mask and 91 (38.2%) often wore a mask. In addition, 220 students (82.7%) took off their masks while drinking water, and 19 (7.1%) and 3 (1.1%) students took off their masks while talking to friends and giving presentations, respectively.

Personal precautions when using the study room: Of the 33 students with confirmed infections, 21 (63.6%) used the study room and 12 (36.4%) did not. Of the total participants, 135 (50.4%) answered that they had used the study room. Among them, most used it 4 times a week (40.7%), followed by 5 or more times (34.1%). The average duration of use was more than 3 hours (87.4%). Overall, 37.8% of the students answered that they often wore a mask, while 3.7% (5 students) reported that they never wore a mask (Table 3).

Relationship between mask-wearing and confirmed COVID-19 infections when using the annex self-study room: There was a significant difference in the frequency of mask-wearing in the self-study room between students who tested positive for COVID-19 and those who did not, confirming that wearing a mask was effective ($p = 0.003$) (Table 3).

## Mask-Wearing Rate Based on CCTV Analysis

An in-depth analysis of footage from the CCTV system installed in the main building of the high school was conducted to assess the routes of transmission and quarantine compliance. The school had 12 CCTVs, with 3 to 4 installed on each floor. The rate at which students did not wear masks by grade was analyzed using video data for 12 days from May 20 to May 31, 2021, which was considered the transmission period. Individuals for whom it could not be determined whether they wore a mask through facial recognition during the time period were excluded (Figure 3). After collecting 17,693 data


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**Table 3.** Survey results on the frequency of the use of the annex self-study room and personal preventive behaviors

| Characteristic | Total | Positive | Negative | *p* |
|---|---|---|---|---|
| Total | 135 (100.0) | 21 (100.0) | 114 (100.0) | |
| No. of times students used the annex self-study room in a week (time) | | | | 0.439 |
| 1 | 9 (6.7) | 1 (4.8) | 8 (7.0) | |
| 2 | 7 (5.2) | 1 (4.8) | 6 (5.3) | |
| 3 | 18 (13.3) | 2 (9.5) | 16 (14.0) | |
| 4 | 55 (40.7) | 6 (28.6) | 49 (43.0) | |
| ≥5 | 46 (34.1) | 11 (52.4) | 35 (30.7) | |
| Average hours of use of the annex self-study room (h) | | | | 0.498 |
| <1 | 3 (2.2) | 0 (0) | 3 (2.6) | |
| 1–2 | 2 (1.5) | 1 (4.8) | 1 (0.9) | |
| 2–3 | 12 (8.9) | 2 (9.5) | 10 (8.8) | |
| >3 | 118 (87.4) | 18 (85.7) | 100 (87.7) | |
| Frequency of mask-wearing in the annex self-study room | | | | 0.009 |
| Always | 47 (34.8) | 3 (14.3) | 44 (38.6) | |
| Often | 51 (37.8) | 8 (38.1) | 43 (37.7) | |
| Sometimes | 32 (23.7) | 7 (33.3) | 25 (21.9) | |
| Never | 5 (3.7) | 3 (14.3) | 2 (1.8) | |
| Frequency of hand sanitization in the annex self-study room | | | | 0.369 |
| Always | 5 (3.7) | 1 (4.8) | 4 (3.5) | |
| Often | 20 (14.8) | 2 (9.5) | 18 (15.8) | |
| Sometimes | 49 (36.3) | 5 (23.8) | 44 (38.6) | |
| Never | 61 (45.2) | 13 (61.9) | 48 (42.1) | |
| Activities performed in the annex self-study room | | | | 0.726 |
| Discussion | 43 (31.9) | 6 (28.6) | 37 (32.5) | |
| Self-guided learning | 92 (68.1) | 15 (71.4) | 77 (67.5) | |
| Whether the student wore a mask in the annex self-study room | | | | 0.003 |
| Yes | 100 (74.1) | 10 (47.6) | 90 (79.0) | |
| No | 35 (25.9) | 11 (52.4) | 24 (21.0) | |
| Whether the student used mobile learning in the annex self-study room | | | | 0.028 |
| Yes | 121 (89.6) | 16 (76.2) | 105 (92.1) | |
| No | 14 (10.4) | 5 (23.8) | 9 (7.9) | |
| Whether the student ate in the annex self-study room | | | | 0.103 |
| Yes | 97 (71.9) | 12 (57.1) | 85 (74.6) | |
| No | 38 (28.1) | 9 (42.9) | 29 (25.4) | |

Data are presented as *n* (%).

points on 1st-year students, 16,883 data points on 2nd-year students, and 27,603 data points on 3rd-year students, we were able to determine whether individuals wore a mask (Table 4). Among the identifiable individuals, 3rd-year students were most likely to not wear a mask, at a rate of 17.8%, followed by 2nd-year students at 11.0% and 1st-year students at 9.6%. Based on this, the rate at which students on the 2nd floor, where the 3rd-year classroom was located, did not wear masks was found to be approximately 2% to 3% higher than that of students on other floors. In addition, frequent contact occurred between students in the hallway and bathroom, which were infection control blind spots where the infection control supervisor was absent.

## Aerodynamic Investigation in the Annex Self-study Room

When the air conditioner was operated with the windows closed, the air diffused faster to the 16th and 17th positions with high ceilings, and the highest droplet concentration (30%) was maintained even after 1 hour of diffusion in the room because of the airflow from the inlet and outlet of the air conditioner. In addition, when natural ventilation was not used, the use of the air conditioner greatly increased the diffusion in the room. However, when the air conditioner was used with the window partially (one-third) open, the horizontal movement increased with the direction of the external airflow. In addition, due to the effect of natural ventilation using a window, the concentration after 1 hour was approximately 10% of the highest

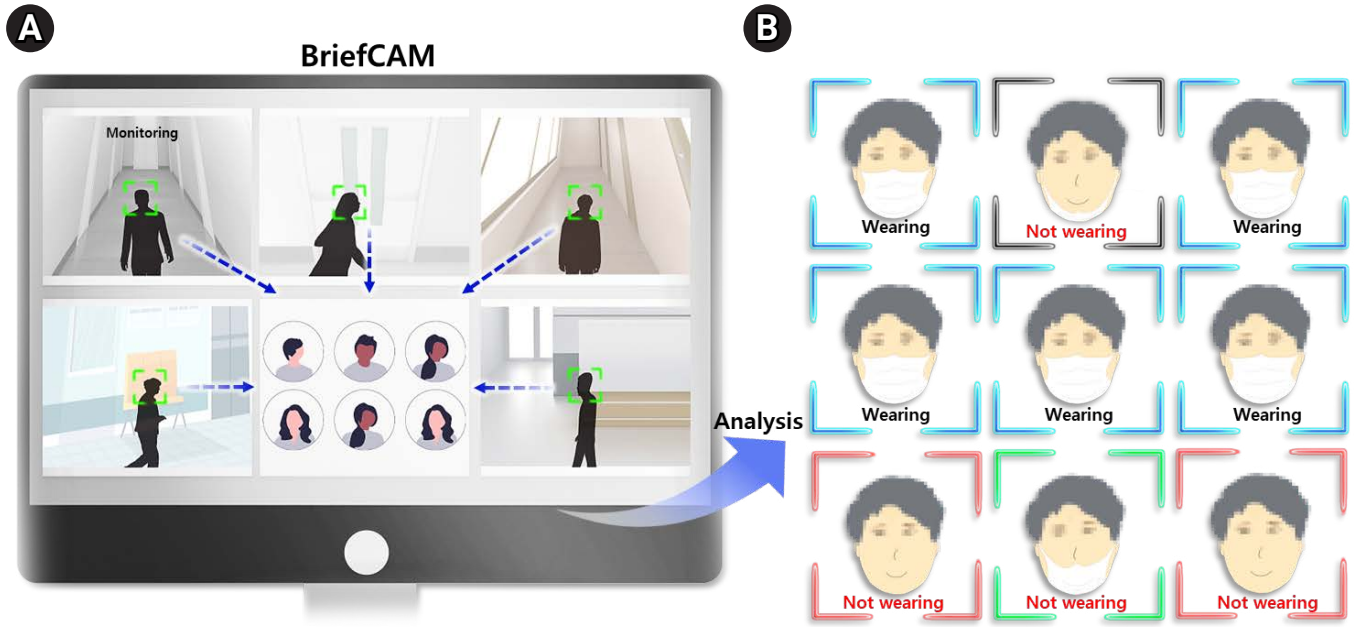


**Figure 3.** CCTV face recognition analysis using BriefCAM Investigator.
(A) Recognition of people in the video. (B) Extraction of the face of the recognized person, and then mosaic processing of the extracted person.

**Table 4.** Percentage of students who wore masks in the hallways of each floor by grade

| Grade | Total | Unidentifiable faces[a] | No. of identifiable students | No. of students not wearing masks | Students who did not wear masks (%) |
|---|---|---|---|---|---|
| 1st-year | 59,857 (100.0) | 40,468 (67.6) | 17,693 (29.6) | 1,696 (2.8) | 9.6 |
| 2nd-year | 53,485 (100.0) | 34,741 (65.0) | 16,883 (31.6) | 1,861 (3.5) | 11.0 |
| 3rd-year | 84,023 (100.0) | 51,505 (61.3) | 27,603 (32.9) | 4,915 (5.8) | 17.8 |
| Total | 197,365 (100.0) | 126,714 (64.2) | 62,179 (31.5) | 8,472 (4.3) | 13.6 |

Data are presented as *n* (%) unless otherwise specified.
[a]Objects with low quality or no detectable faces were removed.

concentration. Regarding natural ventilation using a window at the target facility, projection windows were installed at the bottom of the room; therefore, the effect of natural ventilation was relatively insignificant compared to other facilities (Figure 4).

## Discussion

In the present study, the epidemiological investigation and risk factor analysis revealed that quarantine management protocols, such as checking students' temperatures before entering classrooms, thorough classroom education on infection prevention, hand sanitization, mask-wearing, and ventilation, were fully implemented by teachers. Classroom teachers and school nurses were appointed as infection control managers according to the Korean government's Guidelines for Prevention and Management of COVID-19 in elementary, middle, high, and special schools (5th edition, July 19, 2021). However, our results showed that the spread of infectious diseases occurred due to multiple risk factors, such as not wearing a mask during recess or operating air conditioners in closed rooms with no open windows, such as in the annex self-study room, where natural ventilation is unlikely.

Video analysis of CCTV footage using the BriefCAM Investigator program, which is commonly used in police investigations, allowed us to track objects and detect abnormal behavior and events using CCTV images [9]. The results confirmed a low mask-wearing rate among the students, despite education on personal hygiene and social distancing measures in the school, indicating that compliance with COVID-19 rules was insufficient.

One strength of this study is that, while most previous case-control and cohort studies of infectious diseases


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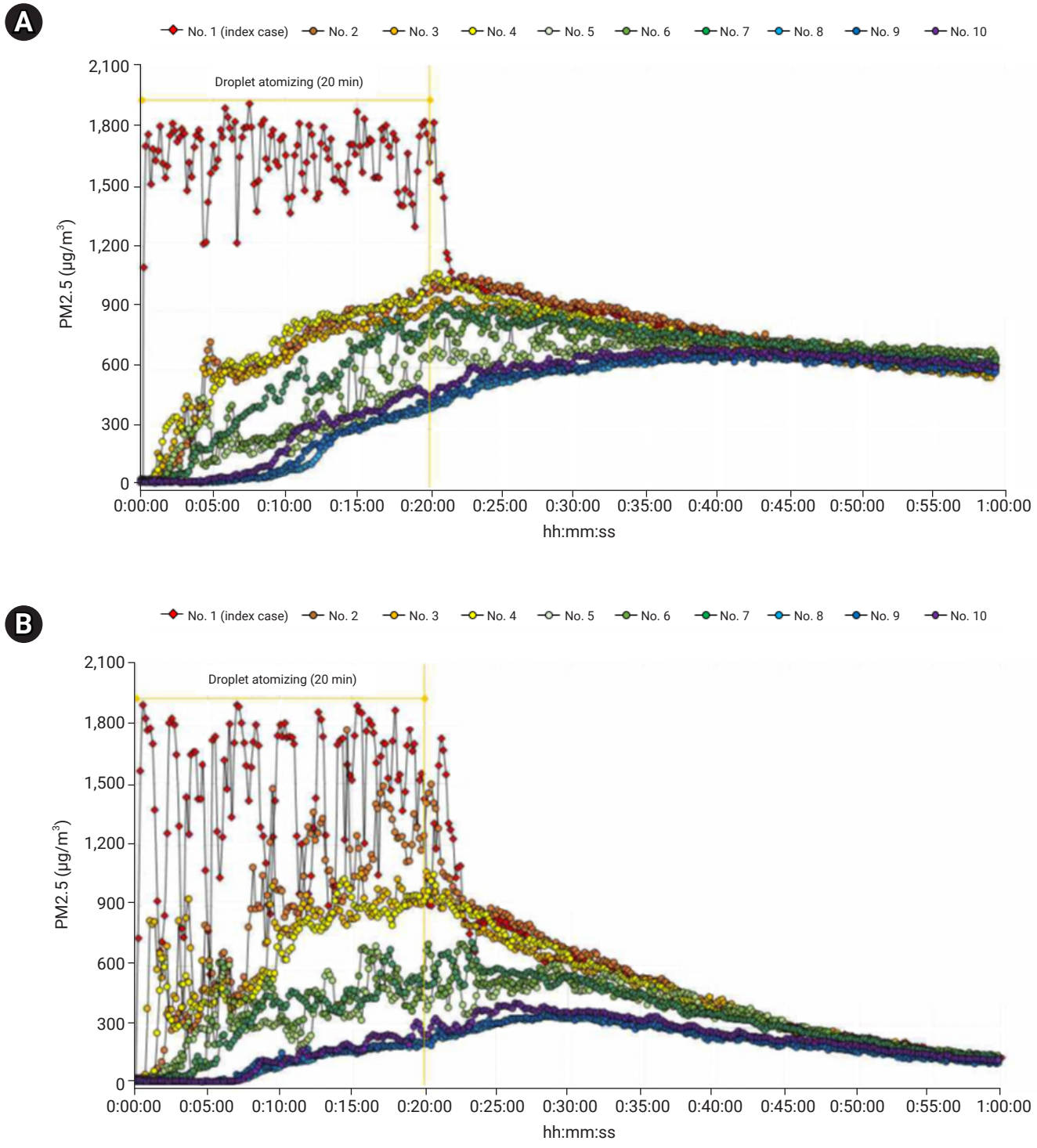


**Figure 4.** Droplet concentrations in the annex self-study room with and without natural ventilation at 10 locations.
(A) Air conditioning on and windows not open. (B) Air conditioning on and windows open.

have conducted 1 or 2 epidemiological investigations, we attempted to use multiple techniques that allowed us to identify and assess risk factors comprehensively [10–15]. Considering the size of the sample and the rapid epidemiological investigation, our results are consistent with those of previous studies that emphasized the importance of convenience and speed in infectious disease investigations [16,17].

As the importance of social distancing has been highlighted by the COVID-19 pandemic, software that uses AI and algorithms has been developed to monitor the spread of infectious diseases, eliminating constraints in terms of manpower and time and enabling rapid and efficient monitoring [8,18]. However, the use of personal or biometric information remains a controversial legal issue. Therefore, it was necessary to inform participants about the purpose of the study before it was used and to take specific measures for the collection, storage, use, and deletion of data [19,20]. By addressing the above issues, this tool can be effective in preventing the further spread of infectious diseases.

Ventilation is another preventive measure against COVID-19 infection [21,22]. In addition, the main areas where students spend their time at school are classrooms and self-study labs. The windows in the self-study room in the annex were closed while the air conditioner and air purifier were running, which inhibited effective ventilation. The artificial droplet experiment showed that the effect of ventilation in the study room was insignificant. This was because of the high ceiling in the building and the types of windows installed at the bottom of the room. In other words, since the room was not sufficiently ventilated, the viral droplets expelled from the student with the first confirmed infection remained in the air for hours. This result is similar to that of a previous simulation study that examined the effect of ventilation according to window opening area [23]. Finally, overcrowding was another risk factor identified in this study, since the annex self-study room was designed for 164 students with 80 seats and could have been overcrowded.

This study has several limitations. First, the study identified several infection control blind spots in the school, such as rooms with poor ventilation, and the results may have been biased since aerodynamic tests were not conducted in all areas. Therefore, if there are blind spots for infection control in each school, preventive measures should be designed and implemented that are tailored to the operation and structure of each school. Second, this study was conducted only at a school and did not investigate risk factors outside of schools; therefore, the study may not have identified all possible risk factors that outside of a school setting.

Our findings suggest a need to manage and supervise mask-wearing during classes and breaks and to maintain an appropriate distance between students when using the restroom. Intensive quarantine management in enclosed spaces, such as study rooms outside of classrooms, is also needed. Frequent and proper ventilation should be encouraged, and guidelines for creating proper ventilation conditions are critical.

## Conclusion

This was the first study in the Republic of Korea to perform risk factor analysis for a school outbreak using multiple epidemiological techniques. Our findings suggest effective strategies to minimize further transmission in the event of an outbreak of novel respiratory infections, such as COVID-19, in schools.

In our study, the patient with the earliest onset of symptoms (May 23) was thought to be the source of the initial transmission in the annex study room, leading to the secondary transmission to other students at the school. Immediate countermeasures were needed to prevent further infection and to reduce anxiety among teachers, students, and parents. Detailed countermeasures for encouraging preventive behaviors, such as mask-wearing, should be recommended in schools.

To prevent and stop future outbreaks in schools, it is necessary to identify the relevant variables, such as the size, operation, and resources of each school, to establish COVID-19 prevention and control measures and facility management plans. Adequate ventilation and exhaust systems for building structures and natural ventilation measures, such as opening windows, should also be emphasized. In addition, prevention efforts should focus on how to implement various investigative techniques to quickly analyze a wide range of information and rapidly implement an active, evidence-based prevention response. These techniques can be used to investigate infection control blind spots not monitored by on-site surveillance systems or quarantine personnel in high-risk facilities, including schools and community living facilities.

## Supplementary Material

**Supplementary Material 1.** Survey on the outbreak at a high school in Gangbuk-gu Seoul. Supplementary data are available at https://doi.org/10.24171/j.phrp.2023.0125.


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## Notes

### Ethics Approval
This study was approved by the Institutional Review Board of the Korea Disease Control and Prevention Agency (2022-10-01-PE-A) and performed in accordance with the principles of the Declaration of Helsinki.

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

### Funding
This work was supported by funding from the Korea Disease Control and Prevention Agency (2023, 6231-335-210-01).

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

### Authors' Contributions
Conceptualization: JHJ, SEL, YJP; Data curation: JHJ, SJK, SJJ; Formal analysis: JHJ, SJK, SJJ, HCJ; Funding acquisition: SEL; Investigation: JHJ, SJK, HCJ; Methodology: JHJ, SJK, SJJ, HCJ; Project administration: JHJ; Resources: JHJ; Software: JHJ; Supervision: SEL; Validation: SEL; Visualization: JHJ, HCJ; Writing–original draft: JHJ; Writing–review & editing: all authors. All authors read and approved the final manuscript.

### Additional Contributions
We thank all of the local government (Gangbuk Health Center, Seoul Metropolitan) infectious disease managers.

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Original Article

# Household secondary attack rates and risk factors during periods of SARS-CoV-2 Delta and Omicron variant predominance in the Republic of Korea

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## ABSTRACT

**Objectives:** The household secondary attack rate (SAR) of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is an important indicator for community transmission. This study aimed to characterize transmission by comparing household SARs and identifying risk factors during the periods of Delta and Omicron variant predominance in Republic of Korea.
**Methods:** We defined the period of Delta variant predominance (Delta period) as July 25, 2021 to January 15, 2022, and the period of Omicron variant predominance (Omicron period) as February 7 to September 3, 2022. The number of index cases included was 214,229 for the Delta period and 5,521,393 for the Omicron period. To identify the household SARs and risk factors for each period, logistic regression was performed to determine the adjusted odds ratio (aOR).
**Results:** The SAR was 35.2% for the Delta period and 43.1% for the Omicron period. The aOR of infection was higher in 2 groups, those aged 0 to 18 years and ≥75 years, compared to those aged 19 to 49 years. Unvaccinated individuals (vs. vaccinated individuals) and individuals experiencing initial infection (vs. individuals experiencing a second or third infection) had an increased risk of infection with SARS-CoV-2.
**Conclusion:** This study analyzed the household SARs and risk factors. We hope that the results can help develop age-specific immunization plans and responses to reduce the SAR in preparation for emerging infectious diseases or potential new variants of SARS-CoV-2.

**Keywords:** COVID-19; Epidemiology; Risk factors; SARS-CoV-2 variants

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## Introduction

Coronavirus disease 2019 (COVID-19) is an infectious disease caused by severe acute

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respiratory syndrome coronavirus 2 (SARS-CoV-2), which has been prevalent worldwide since January 2020, with more than 640 million confirmed cases and 6.64 million deaths as of December 28, 2022. In the Republic of Korea (hereinafter, Korea), as of December 28, 2022 the number of confirmed COVID-19 cases was 28.6 million, with 31,774 deaths [1]. The COVID-19 epidemic in Korea is classified into 4 periods according to the circulation of SARS-CoV-2 variants of concern (VOCs), based on the detection of a relative share of more than 50% by whole-genome sequencing: pre-Delta variant predominance (January 20, 2020 to July 24, 2021), Delta variant predominance (July 25, 2021 to January 15, 2022), Omicron BA.1/BA.2 subvariant predominance (January 16 to July 23, 2022), and Omicron BA.5 subvariant predominance (July 24 to September 3, 2022) (Figure 1) [2]. Before the period of Delta variant predominance, other VOCs such as the Beta and Gamma variants were introduced into Korea, but the transmissibility of these variants was relatively low, with detection rates of less than 50% [3].

After the introduction of new VOCs such as Delta and Omicron into Korea, the characteristics of community transmission of COVID-19 changed. Because those 2 variants were more transmissible than previous VOCs, several sporadic outbreaks were reported in the community with rapid surges of newly confirmed COVID-19 cases [4,5]; the same trend was reported worldwide [6]. Thus, the rate of transmissibility was shown to differ depending on the emergence of new SARS-CoV-2 VOCs. The secondary attack rate (SAR) is an important indicator for estimating community transmission. In the United Kingdom (UK), the household SAR of Delta variant cases was 1.7 times higher than that of Alpha variant cases [7]. In Norway, the household contacts of Omicron variant cases showed a SAR 1.3 times higher than that of Delta variant cases [8]. A Korean study also demonstrated a SAR 1.08 times higher for the Omicron variant than for the Delta variant [9]. In this regard, the household SAR for specific SARS-CoV-2 variants can be a significant indicator for measuring characteristics of community transmission of COVID-19 [10]. However, a study on household SARs across different periods of variant predominance has been difficult to undertake with a large dataset until recently. The current study aimed to characterize transmission patterns by comparing the household SARs and identifying risk factors during the periods of Delta and Omicron variant predominance in Korea.

### HIGHLIGHTS

- This study analyzed the household secondary attack rates (SAR) of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) and identified risk factors during the periods of Delta and Omicron variant predominance in the Republic of Korea.
- The SAR was 35.2% for the Delta period and 43.1% for the Omicron period. Persons aged 0 to 18 years and ≥75 years, unvaccinated individuals, and individuals experiencing initial infection had an increased risk of infection with SARS-CoV-2.

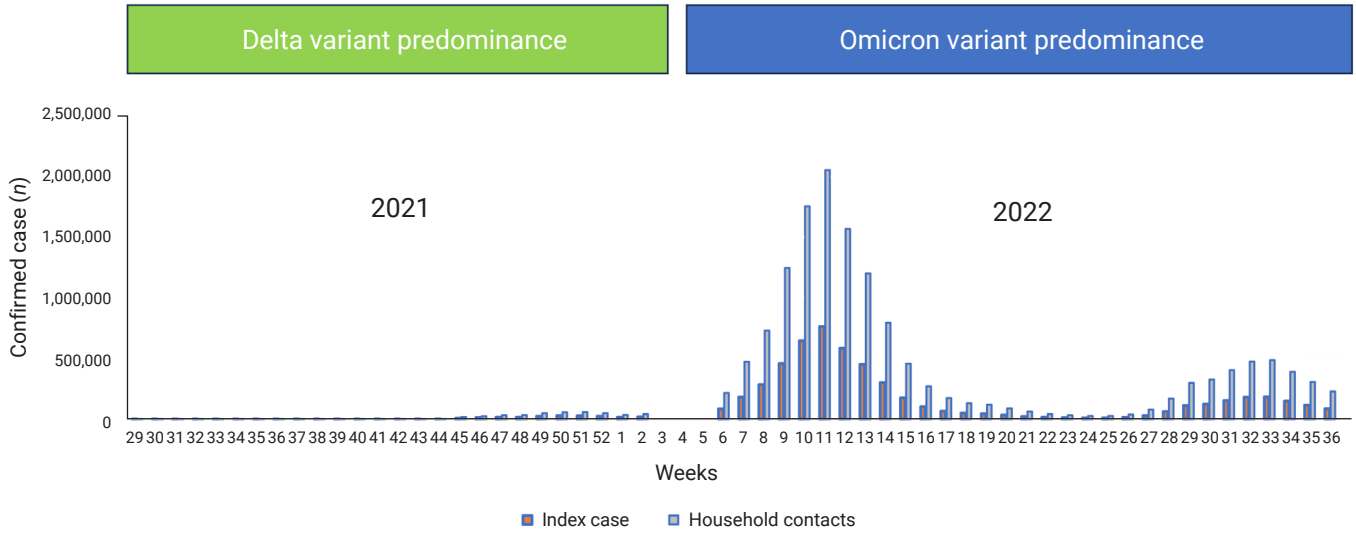


**Figure 1.** Numbers of index cases and household contacts during the periods of Delta and Omicron variant predominance, Republic of Korea.



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## Materials and Methods

### Study Population

Data were analyzed from confirmed COVID-19 cases and household contacts that were reported to the COVID-19 Information Management System (CIMS, https://covid19.kdca.go.kr), managed by Korea Disease Control and Prevention Agency (KDCA) as per the Infectious Disease Control and Prevention Act. We defined the period of Delta variant predominance (Delta period) from July 25, 2021 to January 15, 2022, and the period of Omicron variant predominance (Omicron period) from January 16 to September 3, 2022 [2]; for the Omicron period, data reporting began on February 7, 2022, when the KDCA introduced a mobile-based self-reporting form for epidemiological investigation [11]. During the Delta period, contacts of confirmed COVID-19 cases were enrolled in the CIMS and required to undergo polymerase chain reaction tests with 14 days of home quarantine [12]. During the Omicron period, contacts of confirmed cases were advised to monitor their health conditions, and public health centers provided all household contacts with education regarding home quarantine guidelines [13].

The CIMS confirmed a total number of 516,024 cases for the Delta period and 22,995,023 cases for the Omicron period. Of these, cases without information on epidemiological surveys and household members were excluded from our analysis: 313,057 and 14,054,210 cases for the Delta and Omicron periods, respectively. The first case with the earliest confirmed date of COVID-19 infection within a single household was defined as an index case. The numbers of index cases and household contacts selected in this study were 214,229 and 431,174, respectively, for the Delta period, and 5,521,393 and 14,650,810, respectively, for the Omicron period (Figure 2).

### Data Sources

Data on confirmed COVID-19 cases were retrieved from the CIMS. Information on household contacts was collected from the Epidemiological Investigation System. COVID-19 vaccination information was retrieved from the COVID-19 Vaccination Management System. The COVID-19 infection status such as second infection was assessed based on the definition used in the National Guidelines for Response to COVID-19 [12,13].

### Statistical Analysis

Descriptive statistical analysis was performed to estimate the SARs during the Delta and Omicron periods, and the SARs were compared by sex, age, vaccination status, and infection status. Logistic regression was conducted to identify risk factors and to determine their adjusted odds ratios (aORs) and 95% confidence intervals (CIs). All analyses were conducted using SAS ver. 9.4 (SAS Institute).

### Ethical Considerations

Information about all study participants was obtained

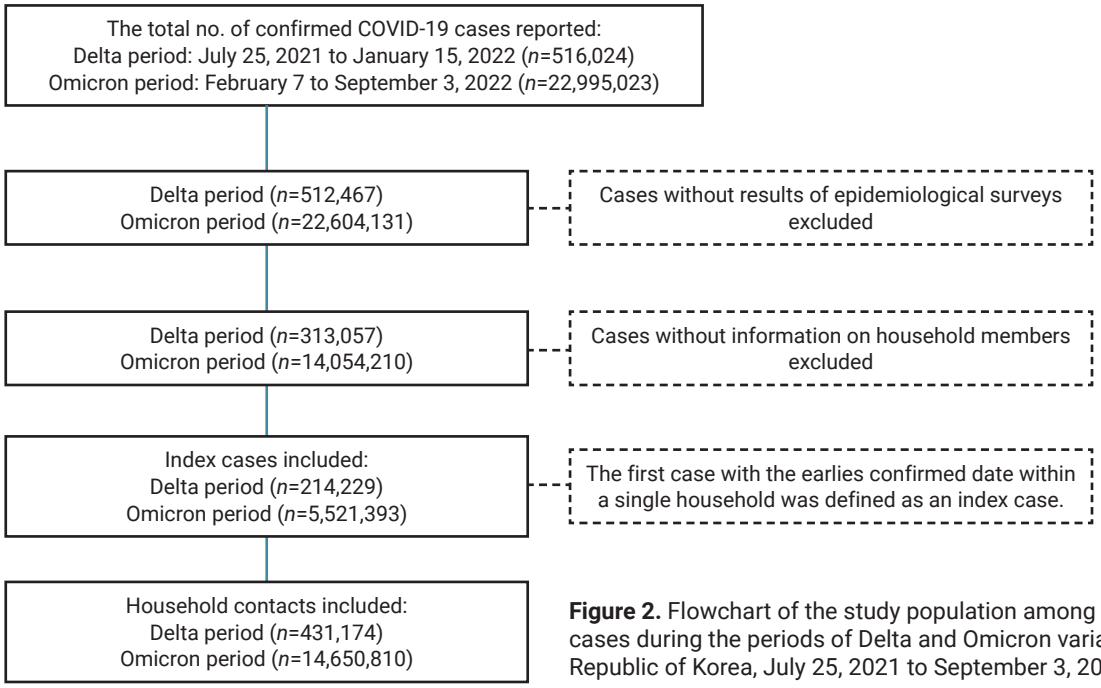


**Figure 2.** Flowchart of the study population among confirmed COVID-19 cases during the periods of Delta and Omicron variant predominance, Republic of Korea, July 25, 2021 to September 3, 2022.

after obtaining consent, in accordance with the Infectious Diseases Control and Prevention Act. The study was exempted from review by the Public Institutional Review Board designated by the Ministry of Health and Welfare (No. P01-202305-01-020).

## Results

The total numbers of index cases and household contacts during the Delta period were 214,229 and 431,174, respectively. Of these, 151,627 cases were confirmed, with a SAR of 35.2%. Among both index cases and household contacts, the proportion was higher in males than in females. By age group, the largest proportions were those aged 0 to 18 years (23.5%) among index cases, 19 to 49 years (37.7%) among household contacts, and 19 to 49 years (35.3%) among confirmed cases. Slightly over half of the study population had received a second vaccine dose, and the vast majority had experienced only an initial infection (Table 1).

During the Omicron period, the total numbers of index cases and household contacts were 5,521,393 and 14,650,810, respectively, of which 6,313,476 were confirmed cases. The SAR was 43.1%. Among both index cases and household contacts, the proportion of females was higher than that of males. By age group, the largest proportions were those aged 19 to 49 years (48.7%) among index cases, 19 to 49 years (47.8%) among household contacts, and 0 to 18 years (43.8%) among confirmed cases. A plurality of the study population had received a third vaccine dose, and the vast majority had experienced only an initial infection (Table 2).

The SAR among individuals aged ≥75 years (41.2%) was the highest during the Delta period, followed by individuals aged 0 to 18 years (37.8%). Unvaccinated individuals had the highest SAR (38.2%), and those experiencing an initial infection (35.2%) showed a higher SAR than those with a second infection (34.9%). The aOR of infection was 1.50 (95% CI, 1.46–1.54) in those aged 0 to 18 years and 1.17 (95% CI, 1.12–1.21) in those aged ≥75 years, compared to those aged 19 to 49 years. The aOR of infection according to vaccination status was 0.85 (95% CI, 0.81–0.88) after dose 1, 0.88 (95% CI, 0.86–0.90) after dose 2, and 0.65 (95% CI, 0.53–0.80) after dose 3, compared to unvaccinated individuals. The aOR of infection for individuals with a second infection was 0.96 (95% CI, 0.90–1.01) compared to those with an initial infection (Table 3; Figure 3).

During the Omicron period, the SAR in males (44.4%) was higher than that in females (41.8%). By age group, those aged 0 to 18 years (50.1%) had the highest SAR, followed by the group aged ≥75 years (47.0%). The SARs for unvaccinated individuals and those experiencing an initial infection were the highest, accounting for 55.7% and 43.7%, respectively. The aOR of infection among those aged ≥75 years was 1.45 (95% CI, 1.44–1.47) compared to those aged 19 to 49 years. The aOR of infection by vaccination status was 0.83 (95% CI, 0.82–0.84) after dose 1, 0.72 (95% CI, 0.72–0.73) after dose 2, and 0.55 (95% CI, 0.55–0.55) after dose 3, compared to unvaccinated individuals. The aOR of infection for individuals with a second infection was 0.19 (95% CI, 0.19–0.20) and for a third infection was 0.16 (95% CI, 0.15–0.18), compared to an initial infection (Table 4; Figure 4).

**Table 1.** Characteristics of index cases and household contacts, Republic of Korea, July 25, 2021 to January 15, 2022

| Characteristic | Index case | Household contacts | |
|---|---|---|---|
| | | Total | Confirmed |
| Total | 214,229 (100) | 431,174 (100) | 151,627 (100) |
| Sex | | | |
| Male | 108,848 (50.8) | 220,239 (51.1) | 77,294 (51.0) |
| Female | 105,381 (49.2) | 210,935 (48.9) | 74,333 (49.0) |
| Age (y) | | | |
| 0–18 | 50,388 (23.5) | 127,540 (29.6) | 48,248 (31.8) |
| 19–49 | 78,967 (36.9) | 162,673 (37.7) | 53,516 (35.3) |
| 50–74 | 72,336 (33.7) | 121,760 (28.2) | 41,945 (27.7) |
| ≥75 | 12,538 (5.9) | 19,201 (4.5) | 7,918 (5.2) |
| Vaccination status | | | |
| Unvaccinated | 75,569 (35.3) | 170,625 (39.6) | 65,155 (43.0) |
| Dose 1 | 12,072 (5.6) | 23,986 (5.6) | 7,966 (5.3) |
| Dose 2 | 126,174 (58.9) | 235,803 (54.7) | 78,278 (51.6) |
| Dose 3 | 414 (0.2) | 760 (0.2) | 228 (0.2) |
| Infection status | | | |
| Initial infection | 213,825 (99.8) | 430,282 (99.8) | 151,305 (99.8) |
| Second infection | 402 (0.2) | 887 (0.2) | 310 (0.2) |
| Third infection | 2 (0.0) | 5 (0.0) | 0 (0.0) |

Data are presented as *n* (%).

## Discussion

Our study estimated the household SARs of index cases during the periods of Delta and Omicron predominance in Korea in terms of specific risk factors. Other studies reported SARs of 35% to 36% for the Delta variant and 49% to 53% for the Omicron variant, respectively [14,15]; our study found a similar SAR for the Delta variant (35.2%) but a slightly lower SAR for the Omicron variant (43.1%). The SAR of the Omicron period was 1.2 times higher than that of the Delta period in our study, which is consistent with the previous finding that reported a SAR 1.4 times higher for the Omicron variant [8,16]. This increase in SAR can be attributed to the improvement in diagnostic procedures and tools, which enabled people to have easy access to the tests over time [17].

Compared to individuals aged 19 to 49 years, the aOR



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**Table 2.** Characteristics of index cases and household contacts, Republic of Korea, February 7 to September 3, 2022

| Characteristic | Index case | Household contacts | |
|---|---|---|---|
| | | Total | Confirmed |
| Total | 5,521,393 (100) | 14,650,810 (100) | 6,313,476 (100) |
| Sex | | | |
| Male | 2,635,574 (47.7) | 6,984,169 (47.7) | 3,102,479 (49.1) |
| Female | 2,885,819 (52.3) | 7,666,641 (52.3) | 3,210,997 (50.9) |
| Age (y) | | | |
| 0–18 | 1,967,334 (35.6) | 5,513,330 (37.6) | 2,763,475 (43.8) |
| 19–49 | 2,688,792 (48.7) | 7,006,612 (47.8) | 2,721,171 (43.1) |
| 50–74 | 812,725 (14.7) | 1,996,017 (13.6) | 765,442 (12.1) |
| ≥75 | 52,542 (1.0) | 134,851 (0.9) | 63,388 (1.0) |
| Vaccination status | | | |
| Unvaccinated | 1,609,916 (29.2) | 4,475,483 (30.5) | 2,481,707 (39.3) |
| Dose 1 | 49,129 (0.9) | 130,043 (0.9) | 54,891 (0.9) |
| Dose 2 | 1,525,210 (27.6) | 4,021,101 (27.4) | 1,561,224 (24.7) |
| Dose 3 | 2,309,849 (41.8) | 5,957,861 (40.7) | 2,183,216 (34.6) |
| Dose 4 | 27,289 (0.5) | 66,322 (0.5) | 21,681 (0.3) |
| Infection status | | | |
| Initial infection | 5,392,691 (97.7) | 14,288,683 (97.5) | 6,251,758 (99.0) |
| Second infection | 128,517 (2.3) | 361,610 (2.5) | 57,489 (0.9) |
| Third infection | 185 (0.0) | 517 (0.0) | 70 (0.0) |

Data are presented as *n* (%).

**Table 3.** Adjusted odds ratios by sex, age, vaccination status, and reinfection status of index cases, Republic of Korea, July 25, 2021 to January 15, 2022

| Index | SAR (%) | cOR (95% CI) | aOR (95% CI) |
|---|---|---|---|
| Total | 35.2 | | |
| Sex | | | |
| Male | 35.1 | 1.00 | 1.00 |
| Female | 35.2 | 1.00 (0.98–1.01) | 0.98 (0.97–1.00) |
| Age (y) | | | |
| 0–18 | 37.8 | 1.64 (1.60–1.68) | 1.50 (1.46–1.54) |
| 19–49 | 32.8 | 1.00 | 1.00 |
| 50–74 | 34.4 | 0.92 (0.90–0.94) | 0.94 (0.92–0.96) |
| ≥75 | 41.2 | 1.15 (1.11–1.20) | 1.17 (1.12–1.21) |
| Vaccination status | | | |
| Unvaccinated | 38.2 | 1.00 | 1.00 |
| Dose 1 | 33.2 | 0.68 (0.66–0.71) | 0.85 (0.81–0.88) |
| Dose 2 | 33.2 | 0.67 (0.66–0.68) | 0.88 (0.86–0.90) |
| Dose 3 | 30.0 | 0.51 (0.42–0.62) | 0.65 (0.53–0.80) |
| Infection status | | | |
| Initial infection | 35.2 | 1.00 | 1.00 |
| Second infection | 34.9 | 0.93 (0.88–0.99) | 0.96 (0.90–1.01) |
| Third infection | 0 | 0 | 0 |

SAR, secondary attack rate; cOR, crude odds ratio; CI, confidence interval; aOR, adjusted odds ratio.

of infection was 1.50 times higher in those aged 0 to 18 years and 1.17 times higher in those aged ≥75 years during the Delta period, and 1.45 times higher in those aged ≥75 years during the Omicron period. These results agreed with studies conducted in other countries; unvaccinated individuals aged ≤19 years had a risk of infection 1.3 times higher compared to individuals aged 20 to 59 years in Japan [18,19]. Furthermore, individuals in the UK aged ≥75 years had a risk of infection 1.61 times higher compared to those aged 30 to 39 years [16]. This may be because children aged 0 to 11 years and older adults aged ≥75 years are more likely to spend time with family compared to other age groups; similarly, a Japanese study reported that the higher risk of infection for individuals aged ≤19 years owes to various factors such as spending longer periods of time with household members [18,19]. In Korea, COVID-19 vaccination was not yet authorized for children and adolescents aged 0–17 years during the Delta period [20–23]. Furthermore, older individuals lose vaccine-induced immunity more rapidly than younger individuals, although they are likely to have better vaccine coverage [24,25].

This study confirmed, similar to previous findings, that the SAR of unvaccinated groups was higher than that of vaccinated groups during both the Delta and Omicron periods [14,16]. Other countries reported a risk of infection 1.4 to 2.5 times higher among unvaccinated groups [8,16,18,19], which agrees with a study that showed a higher risk of infection among unvaccinated Koreans [9]. Additionally, a study conducted in Spain reported that COVID-19 vaccination was effective during the Delta period [26]. However, another Spanish cohort study confirmed that a third dose of mRNA-

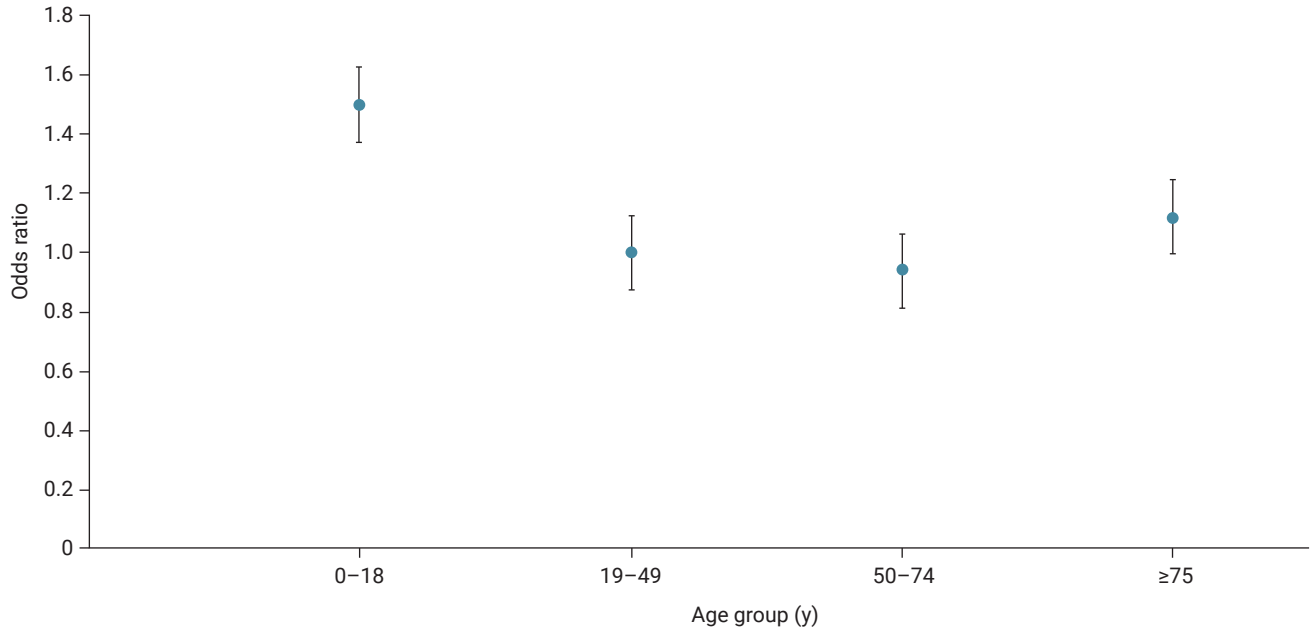


**Figure 3.** Adjusted odds ratios by age group of index cases, Republic of Korea, July 25, 2021 to January 15, 2022.

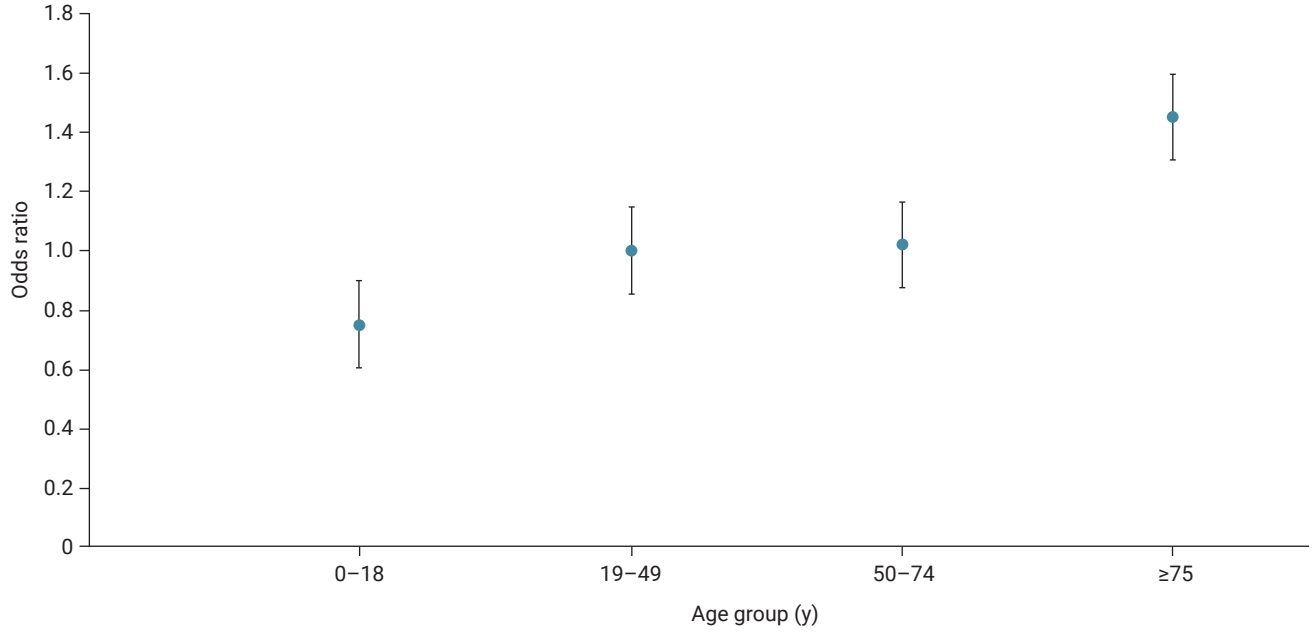


**Figure 4.** Adjusted odds ratios by age group of index cases, Republic of Korea, February 7 to September 3, 2022.

based COVID-19 vaccination was moderately effective in preventing infection by the Omicron variant for one month, with lower efficacy compared to the Delta period [27].

During both Delta and Omicron periods, the SARs for individuals experiencing their second and third infections were higher, with higher risks of infection, compared to those with initial COVID-19 infection. Animal experimental studies have demonstrated that reinfected animals did not shed the virus at sufficient levels to infect naïve animals, with no nasal and oral shedding of the virus [28,29], and evidence on transmissibility among reinfected patients after their initial infection with COVID-19 has been inconclusive. Therefore,


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**Table 4.** Adjusted odds ratios by sex, age, vaccination status, and reinfection status of index cases, Republic of Korea, February 7 to September 3, 2022

| Index | SAR (%) | cOR (95% CI) | aOR (95% CI) |
|---|---|---|---|
| Total | 43.1 | | |
| Sex | | | |
| Male | 44.4 | 1.00 | 1.00 |
| Female | 41.8 | 0.90 (0.90–0.90) | 0.93 (0.93–0.93) |
| Age (y) | | | |
| 0–18 | 50.1 | 1.48 (1.47–1.48) | 0.75 (0.75–0.75) |
| 19–49 | 38.8 | 1.00 | 1.00 |
| 50–74 | 38.3 | 0.96 (0.96–0.96) | 1.02 (1.01–1.02) |
| ≥75 | 47.0 | 1.36 (1.35–1.38) | 1.45 (1.44–1.47) |
| Vaccination status | | | |
| Unvaccinated | 55.7 | 1.00 | 1.00 |
| Dose 1 | 42.2 | 0.60 (0.59–0.60) | 0.83 (0.82–0.84) |
| Dose 2 | 38.8 | 0.52 (0.52–0.52) | 0.72 (0.72–0.73) |
| Dose 3 | 36.6 | 0.47 (0.47–0.47) | 0.55 (0.55–0.55) |
| Dose 4 | 32.6 | 0.40 (0.40–0.41) | 0.41 (0.40–0.41) |
| Infection status | | | |
| Initial infection | 43.7 | 1.00 | 1.00 |
| Second infection | 15.9 | 0.24 (0.24–0.24) | 0.19 (0.19–0.20) |
| Third infection | 13.5 | 0.18 (0.16–0.20) | 0.16 (0.15–0.18) |

SAR, secondary attack rate; cOR, crude odds ratio; CI, confidence interval; aOR, adjusted odds ratio.

additional investigation of transmission among reinfected COVID-19 patients may be required [30].

Although a previous study investigated SARs in Korea by COVID-19 vaccination status, the result predated the Omicron period and did not analyze risk factors such as reinfection and age group [9]. The current study used the large datasets reported to the CIMS during the Delta and Omicron periods, identifying risk factors such as age group, vaccination status, and reinfection. Children and adolescents, who are more susceptible to becoming infected with SARS-CoV-2, may have lower transmissibility without being vaccinated [25,31,32], and older individuals may be more likely to develop symptoms, since they have lower vaccine-induced immunity compared to young adults [25,32]. Furthermore, vaccinated individuals may be less likely to practice social distancing than unvaccinated people [33]. In this respect, other aspects should be considered in interpreting the effects of risk factors. Since the World Health Organization has recently lifted the Public Health Emergency of International Concern for COVID-19, a follow-up study on risk factors such as reinfection needs to be conducted to provide evidence-based guidelines [34]. We hope that the results of this study can help develop age-specific immunization plans and responses to reduce the SAR in preparing for emerging infectious diseases or potential new VOCs of SARS-CoV-2.

This study has some limitations. First, because COVID-19 rapid antigen tests became available to use for confirmation during the Omicron period, limiting to the identification of variant types, we were not able to include all confirmed COVID-19 cases in Korea during the Delta and Omicron periods. Therefore, the result might not be representative of the entire population. Second, our analysis included only the number of vaccine doses administered without accounting for their type or the time elapsed following vaccination. Third, isolation for close contacts was not required during the Omicron period; thus, those contacts might have had a risk of infection through community transmission.

## Notes

### Ethics Approval

Information about all study participants was obtained after obtaining consent in accordance with the Infectious Diseases Control and Prevention Act. The study was exempted from review by the Public Institutional Review Board designated by the Ministry of Health and Welfare (No. P01-202305-01-020).

### Conflicts of Interest

The authors have no conflicts of interest to declare.

### Funding

None.

### Availability of Data

The data used in this study are protected under the Personal Information Protection Act.

### Authors' Contributions

Conceptualization: JL, MK, DL; Data curation: JL, SK, DL; Formal analysis: JL, GP; Methodology: SEL, JL, DL; Project administration: JL; Writing–original draft: JL; Writing–review & editing: all authors. All authors read and approved the final manuscript.

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Original Article

# Increased viral load in patients infected with severe acute respiratory syndrome coronavirus 2 Omicron variant in the Republic of Korea

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## ABSTRACT

**Objectives:** Coronavirus disease 2019 (COVID-19) has been declared a global pandemic owing to the rapid spread of the causative agent, severe acute respiratory syndrome coronavirus 2. Its Delta and Omicron variants are more transmissible and pathogenic than other variants. Some debates have emerged on the mechanism of variants of concern. In the COVID-19 wave that began in December 2021, the Omicron variant, first reported in South Africa, became identifiable in most cases globally. The aim of this study was to provide data to inform effective responses to the transmission of the Omicron variant.
**Methods:** The Delta variant and the spike protein D614G mutant were compared with the Omicron variant. Viral loads from 5 days after symptom onset were compared using epidemiological data collected at the time of diagnosis.
**Results:** The Omicron variant exhibited a higher viral load than other variants, resulting in greater transmissibility within 5 days of symptom onset.
**Conclusion:** Future research should focus on vaccine efficacy against the Omicron variant and compare trends in disease severity associated with its high viral load.

**Keywords:** Omicron variant; SARS-CoV-2; Transmissibility

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## Introduction

The World Health Organization (WHO) tracks variants of concern, variants of interest, and variants under monitoring of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). These variants are classified according to their impact on public health. The Delta and Omicron

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variants have been classified as variants of concern, and each has distinct characteristics in terms of transmission, pathogenicity, and immune evasion mechanisms [1]. These differences are related primarily to amino acid substitutions in the receptor-binding domain, which facilitate the binding of the viral spike (S) protein to host cells [2]. The Omicron variant was first reported in South Africa on November 24, 2021, and was classified as a variant of concern by the WHO Technical Advisory Group on Virus Evolution [3,4]. The Omicron variant surged to global predominance, and the first confirmed case of infection in the Republic of Korea was reported on December 1, 2021. Currently, most coronavirus disease 2019 (COVID-19) cases globally are caused by sublineages of Omicron [5,6].

The Omicron variant is classified as including more than 113 sublineages, according to the Phylogenetic Assignment of Named Global Outbreak Lineages (PANGOLIN) website. Thirty-two mutations have been identified in the S protein, including 15 amino acid substitutions in the receptor-binding domain, leading to changes in its viral characteristics, such as increased transmissibility and immune evasion [7,8]. The mutational signature of the Omicron variant has resulted in high transmission levels, contributing significantly to global outbreaks [9,10]. Therefore, to prevent and control additional widespread public health crises, it is important to understand the properties of the Omicron variant, including its transmissibility, virulence, immune response, and disease severity.

The BA.2 sublineage of the Omicron variant spread rapidly in February 2022 [11]. BA.2 has a growth advantage over BA.1; it is also more transmissible than BA.1 and was the most widely reported Omicron sublineage internationally during the first half of 2022. Furthermore, a Japanese study has shown that BA.2 is associated with a severe disease in hamsters [12]. The study has also demonstrated strong protection against BA.2 reinfection following BA.1 infection [12].

During the recent COVID-19 wave in the Republic of Korea, the Omicron variant was detected in most patients with COVID-19. Furthermore, the characteristics of the Omicron variant were compared with those of the S protein D614G mutant (detected in the GH clade predominant during the second and third waves) and Delta variant (2020–2021) in the Republic of Korea, focusing on its increased transmissibility. Specifically, epidemiological data collected at the time of diagnosis were used to compare viral load from the day of infection to 5 days post-infection. We aimed to provide sufficient data to inform effective responses to the transmission of the Omicron variant.

***HIGHLIGHTS***

- The viral loads of Omicron variant from 5 days after symptom onset were compared with the Delta variant and the spike protein D614G mutant.
- The Omicron variant exhibited a higher viral load than other variants, resulting in greater transmissibility within 5 days of symptom onset.
- Future research should focus on vaccine efficacy against the Omicron variant and compare trends in disease severity associated with its high viral load.

## Materials and Methods

### Specimen Collection and Real-Time Reverse-Transcription Polymerase Chain Reaction Testing for SARS-CoV-2

In total, 19,996 COVID-19-positive specimens (nasopharyngeal and oropharyngeal swabs) were collected. Among them, 17,086 specimens were collected from infected patients in the second and third waves in 2020, 1,691 were from patients infected with the Delta variant in 2021, and 1,219 were from patients infected with the BA.1.1 (1,084 cases) and BA.2 (135 cases) sublineages of the Omicron variant. The specimens were subjected to RNA extraction, followed by real-time reverse-transcription polymerase chain reaction (RT-PCR) [13]. Briefly, RNA was extracted from 140 μL of each sample using a Viral RNA Mini Kit (Qiagen), according to the manufacturer's protocol. Subsequently, RT-PCR was performed and the cycle threshold (Ct) value of the SARS-CoV-2 target genes was determined. The primer and probe sequences used for RNA-dependent RNA polymerase gene detection were as follows: 5′-GTGARATGGTCATGTGTGGCGG-3′ (forward), 5′-CARATGTTAAASACACTATTAGCATA-3′ (reverse), and 5′-CAGGTGGAACCTCATCAGGAGATGC-3′ (probe in 5-FAM/3′-BHQ format). The primer and probe sequences used for E gene detection were as follows: 5′-ACAGGTACGTTAATAGTTAATAGCGT-3′ (forward), 5′-ATATTGCAGCAGTACGCACACA-3′ (reverse), and 5′-ACACTAGCCATCCTTACTGCGCTTCG-3′ (probe in 5-FAM/3′-BHQ format). All specimens were handled in a biosafety cabinet, according to the laboratory biosafety guidelines from the Korea Disease Control and Prevention Agency for COVID-19.

### Lineage Assignment of SARS-CoV-2 by Full-Genome and S Protein Sequencing

This study analyzed more than 1,600 cases (random

sampling) per week, with reference to European Centre for Disease Control recommendations to detect mutations that may exist at a rate of 1% in 100,000 confirmed COVID-19 cases per week.

For full-genome sequencing, cDNA was amplified from the total RNA using ARTIC primer pools (https://artic.network/ncov-2019), QIAseq SARS-CoV-2 Primer Panel, and QIAseq FX DNA Library UDI Kit (Qiagen). Libraries were prepared using the Nextera DNA Flex Library Prep Kit (Illumina). Sequencing was performed on a MiSeq instrument using MiSeq Reagent Kit v2 (Illumina) to obtain an average genome coverage of >1,000× for all the samples. The reads were trimmed and mapped to the Wuhan-Hu-1 reference genome (GenBank accession number: MN908947.3) using CLC Genomics Workbench version 20.0.3 (CLC Bio) [14]. The lineages and clades of the SARS-CoV-2 sequences were assigned using Nextclade v1.7. [15] and PANGOLIN [16].

The SARS-CoV-2 S protein-encoding gene was amplified using 1-step RT-PCR (Qiagen) with 6 primers selected from the ARTIC primer pools. Three overlapping fragments were amplified, purified, and sequenced at BIOFACT Co., Ltd.

### Calculation of Viral Copy Numbers

Plasmids carrying the SARS-CoV-2 E gene were used as a positive control. A standard curve was constructed based on the plasmid concentrations. The regression equation ($y = -3.5705x + 39.055$; y, Ct; x, copy) was obtained using the standard curve. The viral copy number in each sample was calculated using the above equation and expressed as a logarithm of base 10 [17].

### Statistical Analysis

Statistical analysis was performed using SAS ver. 9.4 (SAS Inc.). The frequency and percentage of categorical variables were obtained, and the median and interquartile range were calculated for the Ct values and age. One-way analysis of variance was used to examine differences in the Ct values for each variable. The threshold for statistical significance was set at less than 0.05 in all cases [16].

### Ethics Approval

All procedures involving human participants were performed in accordance with the ethical standards of the institutional and/or national research committees and the 1964 Declaration of Helsinki, including its later amendments, or with comparable ethical standards. The study was approved by the institutional review board of the Korea Disease Control and Prevention Agency (approval number: 2020-03-01-P-A) and was designated as a service to public health during the pandemic. Therefore, the review board waived the requirement for written informed consent from the participants, as outlined in the Title Laboratory Respondence to COVID-19.

## Results

### Characterization of the Confirmed Cases

After the first report of COVID-19 in mid-January 2020, the S, L, and V clades occurred predominantly among infections in the Republic of Korea until March 2020. Subsequently, the G, GH, and GR clades were reported and have been predominant globally since April 2020, with an increased mutation frequency in the S protein-encoding gene. These mutations affected virological features including viral transmission and disease severity. The S protein D614G mutant, identified in the GH clade, was predominant until December 2020; the Delta variant of the GK clade was detected between April and July 2021. The latest wave, caused by the highly transmissible Omicron variant, is ongoing (Table 1).

We analyzed 17,086 cases of D614G mutant infection reported in 2020, 1,691 cases of Delta variant infection, and 1,219 cases of infection with the BA.1.1 (1,084 cases) and BA.2 (135 cases) sublineages of the Omicron variant during the recent wave. Data was taken within 5 days of symptom onset. The clinical symptoms ranged from no symptoms to mild symptoms (fever, cough, and sore throat). The highest infection rate (32.1%) was observed in patients above the age of 60 and was caused by the D614G mutant. During the Delta wave, the highest infection rate (27.7%) was observed in patients aged 20–29 years. The infection rates of the BA.1.1 and BA.2 sublineages in the same age group were 22.5% and 24.4%, respectively. The overall incidence of COVID-19 was higher in women (51.6%) than in men (48.4%). However, the incidence of Delta variant infection was higher among men (52.6%). The Ct distribution of the SARS-CoV-2 strain isolated during the D614G wave showed the highest rate of infection (25.8%) in the 15–20-year age group; a similar Ct distribution

**Table 1.** Details of the severe acute respiratory syndrome coronavirus 2 variants analyzed in this study

| | D614G | Delta | Omicron (BA.1.1 and BA.2) |
|---|---|---|---|
| Time period | May 5, 2020 to December 31, 2020 | April 22, 2021 to July 21, 2021 | December 22, 2021 to February 26, 2022 |
| Characteristic | G, GH, and GR clades | GK clade | GRA clade |


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was observed for the Delta variant, which also showed the highest rate of infection (42.6%) in that age group. The Ct value of individuals with the highest infection rate from the BA.1.1 and BA.2 sublineages was relatively low in patients below 15 years of age (62.0% and 83.7%, respectively); however, the value was higher than that from the D614G mutant and Delta variant (Table 2). In addition, statistical significance ($p < 0.001$) was confirmed in the age and sex of infected individuals and the Ct of the D614G mutant, Delta, Omicron BA.1.1, and BA.2 variants.

### Daily Average Ct and Viral Load after Symptom Onset

The overall mean Ct value within 5 days of symptom onset was 21.41 for the D614G mutant (range, 7.06–38.65; 95% confidence interval [CI], 21.31–21.51), 16.43 for the Delta variant (range, 7.61–34.40; 95% CI, 16.22–16.64), 15.36 for the BA.1.1 sublineage (range, 9.55–31.78; 95% CI, 15.15–15.57), and 13.58 for the BA.2 sublineage (range, 10.90–24.54; 95% CI, 13.25–13.91). Notably, the Ct value for the Omicron sublineages was lower than those for the D614G mutant and Delta variant. For the latter 2 variants, the Ct value gradually decreased each day after symptom onset. Conversely, the Ct value of the BA.1.1 and BA.2 sublineages hardly changed (Table 3; Figure S1). In addition, statistical significance ($p < 0.0001$) was confirmed among each variant group and day. For the BA.2 sublineage, a high viral load was seen soon after symptom onset. All Ct values were measured using RT-PCR reagents and equipment, based on the same primers and probes. However, since the data were collected from different laboratories, variations may have occurred, as virus extraction protocols and RT-PCR performance may differ in different laboratory conditions, including operator and extraction methods. Therefore, a quality evaluation of the diagnostic laboratories was conducted to minimize the potential for detection bias.

The Ct value is inversely proportional to the amount of target nucleic acid in a sample. To compare the differences in viral load, the mean Ct value within 5 days of symptom onset was converted to viral load. Patients infected with the BA.2 sublineage had an approximately 155-fold higher viral load ($1.36\times10^{10}$ copies/mL) than those with the D614G mutant ($8.76\times10^{7}$ copies/mL), a 6-fold higher viral load than those with the Delta variant ($2.16\times10^{9}$ copies/mL), and a 3-fold higher viral load ($4.32\times10^{9}$ copies/mL) than those with the BA.1.1 sublineage. Furthermore, patients infected with BA.2 had a viral load of $1.22\times10^{10}$ copies/mL on the day of symptom onset (day 0); this was approximately 214-fold higher than that in patients with the D614G mutant ($5.69\times10^{7}$ copies/mL), 9-fold higher than that in patients with the Delta variant ($1.42\times10^{9}$ copies/mL), and 4-fold higher than that in patients with the BA.1.1 sublineage ($3.44\times10^{9}$ copies/mL). Similarly, the viral load on day 4 after symptom onset ($1.84\times10^{10}$ copies/mL) was approximately 131-fold higher than that in patients with the D614G mutant ($1.41\times10^{8}$ copies/mL), 30-fold higher

**Table 2.** Characteristics of COVID-19 cases reported in the Republic of Korea by variant

| Characteristic | Total | D614G | Delta | Omicron | | *p* |
|---|---|---|---|---|---|---|
| | | | | BA.1.1 | BA.2 | |
| Total | 19,996 | 17,086 | 1,691 | 1,084 | 135 | |
| Median age (y) | 48 (29–61) | 50 (31–63) | 35 (24–49) | 29 (18–46) | 34 (23–48) | |
| Age group (y) | | | | | | < 0.001 |
| 0–9 | 890 (4.5) | 702 (4.1) | 53 (3.1) | 125 (11.5) | 10 (7.4) | |
| 10–19 | 1,460 (7.3) | 1,097 (6.4) | 161 (9.5) | 187 (17.3) | 15 (11.1) | |
| 20–29 | 2,859 (14.3) | 2,114 (12.4) | 468 (27.7) | 244 (22.5) | 33 (24.4) | |
| 30–39 | 2,613 (13.1) | 2,121 (12.4) | 306 (18.1) | 165 (15.2) | 21 (15.6) | |
| 40–49 | 2,831 (14.1) | 2,371 (13.9) | 301 (17.8) | 132 (12.2) | 27 (20.0) | |
| 50–59 | 3,593 (18.0) | 3,197 (18.7) | 270 (16.0) | 116 (10.7) | 10 (7.4) | |
| ≥ 60 | 5,750 (28.8) | 5,484 (32.1) | 132 (7.8) | 115 (10.6) | 19 (14.1) | |
| Sex | | | | | | < 0.001 |
| Female | 10,319 (51.6) | 8,864 (51.9) | 801 (47.4) | 581 (53.6) | 73 (54.1) | |
| Male | 9,677 (48.4) | 8,222 (48.1) | 890 (52.6) | 503 (46.4) | 62 (45.9) | |
| Cycle threshold | | | | | | < 0.001 |
| < 15 | 4,892 (24.5) | 3,484 (20.4) | 623 (36.8) | 672 (62.0) | 113 (83.7) | |
| 15–20 | 5,443 (27.2) | 4,415 (25.8) | 720 (42.6) | 288 (26.6) | 20 (14.8) | |
| 20–25 | 4,007 (20.0) | 3,630 (21.2) | 274 (16.2) | 101 (9.3) | 2 (1.5) | |
| 25–30 | 3,494 (17.5) | 3,404 (19.9) | 68 (4.0) | 22 (2.0) | 0 (0) | |
| > 30 | 2,160 (10.8) | 2,153 (12.6) | 6 (0.4) | 1 (0.1) | 0 (0) | |

Data are presented as median (interquartile range) or *n* (%).

**Table 3.** Daily mean Ct values of patients with COVID-19 from the day of symptom onset

| Day of symptom onset | D614G | | Delta | | Omicron BA.1.1 | | Omicron BA.2 | | *p* |
|---|---|---|---|---|---|---|---|---|---|
| | Total cases | Mean Ct value (range) | Total cases | Mean Ct value (range) | Total cases | Mean Ct value (range) | Total cases | Mean Ct value (range) | |
| 0 | 11,654 | 22.08 (7.30–38.65) | 519 | 17.08 (8.25–34.40) | 651 | 15.72 (10.47–31.78) | 79 | 13.76 (10.90–24.54) | <0.001 |
| 1 | 2,199 | 20.24 (7.40–38.39) | 589 | 15.54 (7.61–30.14) | 218 | 14.80 (9.95–29.49) | 26 | 13.33 (11.31–17.42) | <0.001 |
| 2 | 1,334 | 19.08 (7.06–37.90) | 299 | 16.01 (8.27–34.00) | 123 | 15.12 (9.55–28.02) | 12 | 13.71 (12.78–16.08) | <0.001 |
| 3 | 872 | 19.63 (8.01–36.34) | 160 | 16.55 (9.57–29.38) | 60 | 14.71 (11.50–26.62) | 13 | 13.13 (11.19–15.21) | <0.001 |
| 4 | 591 | 20.67 (8.29–36.09) | 80 | 18.38 (10.69–27.17) | 22 | 14.09 (11.21–19.95) | 4 | 13.12 (11.14–15.00) | <0.001 |
| 5 | 436 | 21.11 (7.21–37.07) | 44 | 19.68 (9.82–33.36) | 10 | 14.22 (12.63–20.59) | 1 | 12.49 (12.49) | <0.001 |
| Total | 17,086 | 21.41 (7.06–38.65) | 1,691 | 16.43 (7.61–34.40) | 1,084 | 15.36 (9.55–31.78) | 135 | 13.58 (10.90–24.54) | <0.001 |

Ct, cycle threshold.

than that in patients with the Delta variant ($6.17\times10^8$ copies/mL), and 2-fold higher than that in patients with the BA.1.1 sublineage ($9.79\times10^9$ copies/mL). Notably, within 4 days of symptom onset, the viral load was considerably higher for the BA.2 sublineage of Omicron than for the D614G mutant (approximately 32–214-fold), Delta variant (approximately 4–30-fold), and BA.1.1 sublineage (approximately 2–4-fold). This suggests that the BA.2 sublineage is associated with a high viral load at disease onset (Figure 1).

## Discussion

In the Republic of Korea, SARS-CoV-2 viral load was investigated as a potential contributing factor to the rise in Omicron infections observed in early 2022 compared with those seen until the end of 2021. The initial viral load within 5 days of symptom onset was found to be approximately 32–214-fold higher from the BA.2 sublineage than that observed during the D614G wave (mainly caused by the GH clade). Furthermore, BA.2's viral load was approximately 4- to 30-fold and 2- to 4-fold higher than from the Delta variant and BA.1.1 sublineage, respectively. Additionally, previous studies have indicated that BA.2 is inherently more transmissible than BA.1 [12]. However, this difference in transmissibility is considerably smaller than that between BA.1 and Delta [11,18]. As of the time of writing for this manuscript, according to the Global Initiative on Sharing All Influenza Data, the incidence of BA.2 is proportionally increasing to other Omicron sublineages (BA.1 and BA.1.1) [7]. Thus, patients infected with the BA.1.1 and BA.2 sublineages of the Omicron variant may show an increased viral transmission. This may be an important factor contributing to the increased number of patients with COVID-19 during the Omicron wave (mean, >100,000 per day) compared with that observed during the D614G (mean, 186 per day) and Delta waves (mean, 713 per day). The current data suggest high viral replication and transmission; thus, epidemiological studies are required to determine the reproduction rate of this variant.

The SARS-CoV-2 S protein interacts with the host's angiotensin-converting enzyme 2 (ACE2) receptor through its receptor-binding domain [19,20]. However, a mutation in the receptor-binding domain can directly affect the interaction between the virus and ACE2. SARS-CoV-2, which harbors the D614G mutation, in which glutamic acid (D) at 614 is substituted with glycine (G) in the S protein, exhibits an improved ability to bind to ACE2, further enabling it to infect humans and cause widespread transmission [9,21]. The H69/V70 deletion is also associated with a 2-fold increase in infectivity, whereas the N501Y and K417N counterparts are associated with stronger binding to ACE2 [10]. Additionally, the P681H mutation in the furin cleavage domain at 681 to 687 prevents the proper formation of the S1/S2 unit, thereby altering the infectivity and pathogenicity of the virus [22,23]. The Omicron variant harbors a mutation at 614 in the S protein receptor-binding domain, as well as K417N, T478K, N501Y, and P681H mutations in the furin cleavage site of the S protein [13]. The increased transmission of the Omicron variant has been attributed to the D614G and H69/V70 deletions, as well as the K417N, T478K, and N501Y mutations. The P681H mutation is associated with altered viral infectivity and pathogenicity.

Our results suggest that the increased viral load of the Omicron variant may have influenced the scale of the recent wave. However, additional studies are required to determine the association between clinical disease severity and virological features. A previous study reported increased transmissibility compared with that of the S protein D614G mutant and the Alpha and Delta variants, which was related to conformational stability (i.e., binding free energy between the S protein and ACE2) [24]. Therefore, further research should be performed to compare the trend of disease severity caused by the high viral loads of the BA.1.1 and BA.2 sublineages of the Omicron variant with previous waves



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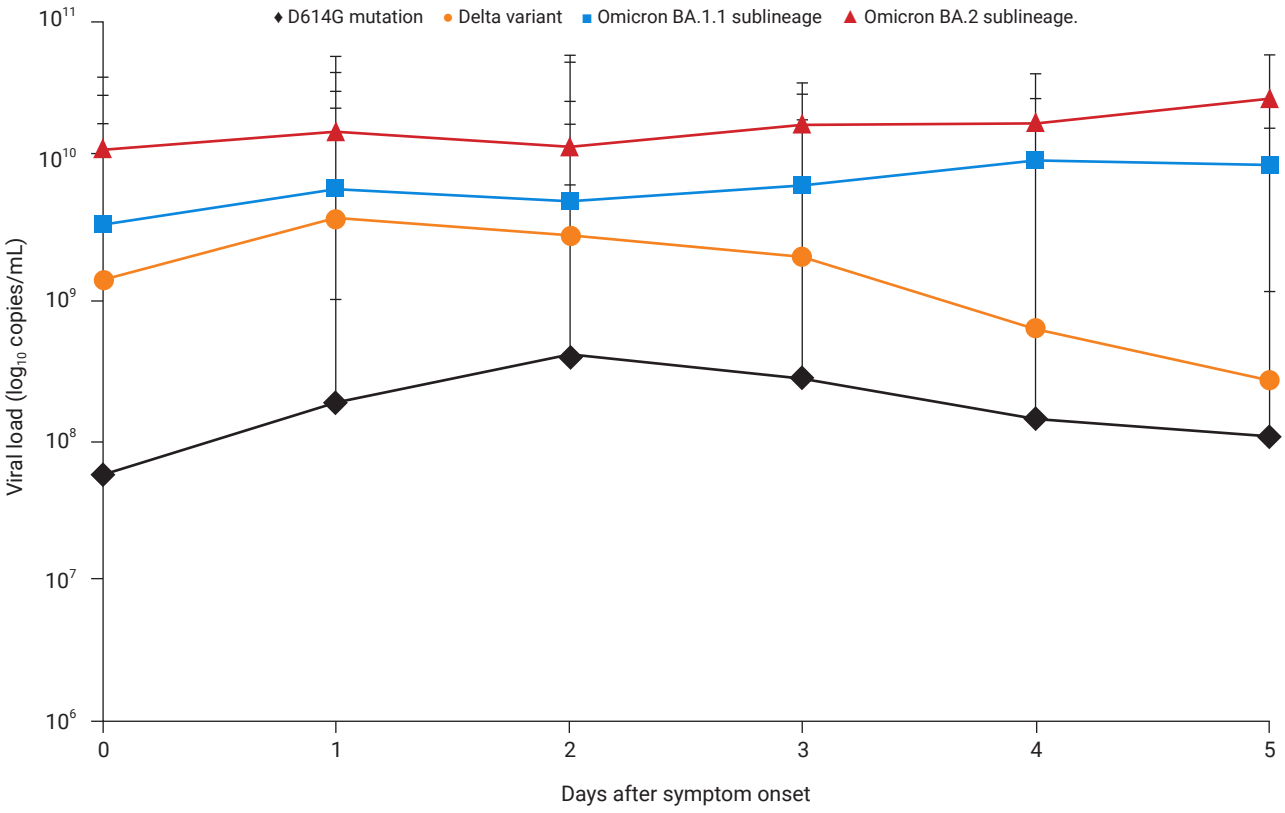


**Figure 1.** Viral load based on the average cycle threshold (Ct) values of severe acute respiratory syndrome coronavirus 2 variants from the day of symptom onset in the Republic of Korea.

and analyze vaccine efficacy in light of the current Omicron wave.

## Supplementary Material

**Figure S1.** Mean cycle threshold (Ct) values for each severe acute respiratory syndrome coronavirus 2 variant from 0 to 5 days after onset of symptoms. Supplementary data are available at Supplementary data are available at https://doi.org/10.24171/j.phrp.2023.0024.

## Notes

### Ethics Approval

All procedures involving human participants were performed in accordance with the ethical standards of the institutional and/or national research committees and the 1964 Declaration of Helsinki, including its later amendments, or with comparable ethical standards. The study was approved by the institutional review board of the Korea Disease Control and Prevention Agency (approval number: 2020-03-01-P-A) and was designated as a service to public health during the pandemic. Therefore, the review board waived the requirement for written informed consent from the participants, as outlined in the Title Laboratory Respondence to COVID-19.

### Conflicts of Interest

The authors have no conflicts of interest to declare.

### Funding

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### Availability of Data

The datasets generated and/or analyzed during the current study are available from the corresponding author upon reasonable request. The SARS-CoV-2 whole genome and Sanger sequences are available in the Global Initiative on Sharing All Influenza Data (http://www.gisaid.org/).

### Authors' Contributions

Conceptualization: JMK, EJK; Data curation: JMK; Formal analysis: JMK, DK; Funding acquisition: CKY, EJK; Investigation: JMK, NJL, SHW; Methodology: JMK, DK, EJK; Project administration: CKY, EJK; Software: JMK; Resources: NJL, SHW, JL, HL, AKP, JAK, CYL, IHK; Supervision: CKY, EJK; Validation: JMK, EJK; Visualization: JMK; Writing–original draft: all authors; Writing–review & editing: all authors. All authors read and approved the final manuscript.

### Additional Contributions

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transport of patient specimens, the staff at the Korea Disease Control and Prevention Agency and local government, and private testing agencies for their contributions to controlling COVID-19.

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Original Article

# Effects of an arteriovenous fistula stenosis prevention program in patients receiving hemodialysis

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## ABSTRACT

**Objectives:** To increase the efficiency of hemodialysis, an appropriate vascular pathway must be created, and its function must be maintained. This study aimed to identify the effects of an arteriovenous fistula (AVF) stenosis prevention program on upper muscular strength, blood flow, physiological indexes, and self-efficacy among patients receiving hemodialysis.
**Methods:** The participants were patients receiving hemodialysis at Keimyung University Dongsan Medical Center in Daegu, Republic of Korea. They were divided into experimental and control groups based on the day of the week they received hemodialysis at the outpatient department and included 25 participants each. The study was conducted for 8 weeks.
**Results:** The AVF stenosis prevention program was effective in improving upper extremity muscle strength ($F = 15.23$, $p < 0.001$) and blood flow rate ($F = 36.00$, $p < 0.001$). As a result of the program, the phosphorus index level, which is a physiological indicator in hemodialysis patients, decreased ($F = 8.64$, $p < 0.001$). Encouragement and support through text messages and practice lists also resulted in an increase in self-efficacy ($F = 18.62$, $p < 0.001$).
**Conclusion:** The AVF stenosis prevention program in this study resulted in an increase in upper extremity muscle strength through grip strength exercises and was effective in preventing AVF stenosis by increasing the blood flow rate.

**Keywords:** Arteriovenous fistula; Hemodialysis units, hospital; Patient care planning

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## Introduction

Chronic kidney disease (CKD) affects more than 10% of the global population [1,2]. The worldwide prevalence of CKD in 2017 was 9.1% and has increased by 29.3% since 1990 [3]. According to the Centers for Disease Control, 15% of adults in the United States have CKD [4], and approximately 80% receive hemodialysis [5], which removes uremic substances from the blood by adsorption using convection and diffusion dialysis membranes with a semipermeable membrane as a boundary [6]. Long-term hemodialysis requires an arteriovenous fistula (AVF)

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that can withstand repeated punctures and maintain a blood flow rate of 600 mL/min or more [2].

However, complications related to vascular access in patients receiving hemodialysis increase with the dialysis period. The incidence of AVF stenosis is 16% to 28% within 1 year and 26% to 36% within 2 years [7]. Approximately 30% of cases are caused by the failure of vascular maturation due to a lack of overall AVF management, interventions due to early loss of function, and reoperations [8]. Vascular access complications, including AVF, are responsible for numerous hospitalizations and substantial medical expenses in patients receiving hemodialysis [9]. Nonetheless, the rate of noncompliance concerning self-management in patients receiving hemodialysis may be as high as 50% [10,11].

To prevent AVF stenosis and occlusion, exercise therapy to improve upper extremity muscle strength and maintain the patency of blood vessels and a diet that helps prevent blood clots are crucial [12,13]. The upper extremity muscle strength of patients receiving hemodialysis is extremely weak, and patients' mean physical performance is significantly lower than that of healthy adults by an average of 50% [11,14]. Gradual strength exercise improves patients' upper extremity muscle strength [15], arteriosclerosis, blood pressure, and the blood flow rate, resulting in structural and functional changes in blood vessels [9,14]. Vascular calcification, which causes AVF stenosis, is common in these patients, with risk factors including sex, age, underlying disease, dialysis period, AVF type, and blood calcium and phosphorus levels [16]. Vascular calcification can be controlled by maintaining stable levels of calcium and phosphorus in the blood through dialysis while also incorporating exercise therapy and a healthy diet [17,18]. Education combined with exercise and diet increases the size and blood flow of AVFs and prevents hyperphosphatemia [11,15,17]. However, there are few studies on programs that combine exercise therapy and diet to prevent AVF stenosis.

In patients receiving hemodialysis, active self-management including strict water restriction, diet, medication, and vascular channel management is essential for minimizing discomfort and complications related to renal dysfunction [11,15]. Self-efficacy refers to an individual's belief in their ability to practice certain behaviors under certain situations, and its promotion induces behavioral changes by increasing trust in treatment and confidence in health promotion behaviors [19]. Therefore, patients should understand AVF management, treatment procedures, and their role in treatment procedures, and programs should be conducted to enhance their perceived self-efficacy [20].

In previous studies on exercise therapy for dialysis patients, simple repetitive motion exercises using rubber balls [15,21], rubber bands [22], and grippers [23] were predominant. However, muscle exercise using a gripper is more effective in increasing the venous size and blood flow of an AVF than simple repetitive training using a rubber ball with low elasticity [24]. Kim and Choi [18] also conducted a survey on a phosphorus-restricted diet and related patient knowledge and self-monitoring of one's eating habits using a journal; their intervention also involved diet education and counseling to demonstrate the effects of calcium and phosphorus levels.

Therefore, this study conducted a complex program combining the strengthening of upper extremity muscles through progressive exercise therapy using a gripper and a phosphorus-restricted diet to prevent vascular calcification, evaluated changes in physiological indicators of vascular calcification in patients receiving hemodialysis, and investigated the effect on blood flow velocity, which is a clinical indicator of stenosis. Additionally, patients receiving hemodialysis received health education using videos and informational magazines for vascular self-care, health counseling using AVF self-management practice checklists, and text messages to encourage active participation in various programs. This study investigated the effects of the program on AVF stenosis and self-efficacy.

### HIGHLIGHTS

- Patients undergoing hemodialysis for end-stage renal failure should receive knowledge about self-care through ongoing individual education and feedback rather than temporary education interventions.
- In this study, text messages and self-care practice helped patients lead a healthy lifestyle during dialysis by enhancing their self-efficacy.
- The program in this study effectively prevented arteriovenous fistula (AVF) stenosis in hemodialysis patients, and it is expected to be useful for continuous vascular management and as part of nursing interventions for the effective self-management of AVFs.

## Materials and Methods

### Study Design

This study used a non-equivalent control group pretest-posttest design to develop a nursing intervention program for AVF management and verify its effectiveness. The study design is illustrated in Table 1.


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**Table 1.** Study design

| Subject | Preliminary investigation | Intervention | Post-investigation 1 | Post-investigation 2 |
|---|---|---|---|---|
| Experimental group | Ye1 | Xe | Ye2 | Ye3 |
| Control group | Yc1 | | Yc2 | Yc3 |

AVF, arteriovenous fistula; Xe, AVF stenosis prevention program (AVF upper extremity strength exercise, health education on phosphorus-restricted diet and AVF management, health counseling, and text messages); Ye1, Yc1, investigation of general and disease-related characteristics, upper extremity muscle strength measurement, blood flow velocity measurement, serum calcium and phosphorus measurement, and self-efficacy measurement; Ye2, Ye3, Yc2, and Yc3, measurement of upper extremity muscle strength, blood flow rate, serum calcium and phosphorus levels, and self-efficacy.

## Participants

The participants included 50 outpatients receiving hemodialysis at Keimyung University Dongsan Medical Center in Daegu, Republic of Korea, from December 15, 2016, to February 5, 2017. Convenience sampling was used. To prevent the spread and contamination of the experimental effect, 25 dialysis patients on Mondays, Wednesdays, and Fridays were selected as the experimental group, and 25 dialysis patients on Tuesdays, Thursdays, and Saturdays were selected as the control group. The specific selection criteria were as follows: (1) those aged from 20 to 75 years who had undergone hemodialysis through an AVF 3 times a week for more than 6 months; (2) those with no history of mental illness; (3) those who understand the content of the AVF stenosis prevention program and could verbally communicate; and (4) those with a blood flow rate of 600 mL/min or more [25].

The sample size for this study was calculated using G*Power 3.1 (Heinrich-Heine-Universität Düsseldorf), and the number of participants was based on a previous study involving an intervention program for patients receiving hemodialysis [25,26]. Based on a significance level of 0.05, median effect size of 0.35, and power of 0.80 for 2 groups with 3 measurements, the required sample size was at least 46. Considering a possible dropout rate of 10%, 50 participants were recruited, with 25 each in the experimental and control groups. No participants dropped out during the study [27].

## Measurements

### Participants' general and disease-related characteristics

The participants' general characteristics comprised 7 items: sex, age, marital status, family type, education, occupation, and economic status. Eleven disease-related characteristics were collected: dialysis period, causative disease, current body weight, weight gain after dialysis, heparin usage during dialysis, maturation period after AVF surgery, vascular occlusion experience, current location of AVF, current AVF use period, smoking status, and current medications.

### Upper extremity strength

Upper extremity muscle strength was measured using a digital dynamometer (KH-100; Gyeongin Industrial Co.), which was held such that the second joint of the finger formed a right angle. The participant then lowered the arm naturally to ensure that the dynamometer did not touch the torso or lower body. A higher grip strength score indicated better upper extremity muscle strength.

### Blood flow rate

After exchanging the position of the arterial and venous conduits with the value measured using the ultrasound dilution method, the speed of the dialyzer was maintained at 200 to 250 mL/min, and temporary recirculation was induced. After injecting 10 mL of normal saline, the measured value was recorded using an ultrasound machine. The normal blood flow rate range is more than 600 mL/min, and rates below that threshold indicate the progression of AVF stenosis [25].

### Physiological indicators

Blood tests for calcium and phosphorus, which are risk factors for vascular calcification, were performed at the Department of Diagnostic Laboratory Medicine after collecting 5 mL of blood from a plain tube after 12 hours of fasting immediately before starting hemodialysis. Blood calcium and phosphorus levels were measured using the results of routine monthly testing performed in a hemodialysis room. In patients receiving hemodialysis, the normal range for serum calcium is 8.5 to 10.2 mg/dL, and it is 3.5 to 5.5 mg/dL for serum phosphorus [18].

### Self-efficacy

The self-efficacy tool developed by Kim and Kim [28] for patients receiving hemodialysis was modified and supplemented by Choi and Lee [29] to create the 10-item measurement tool used in this study. Each item is scored on a 4-point scale with 4 points for "strongly agree," 3 points for "somewhat agree," 2 points for "not very much," and 1 point for "hardly ever." Higher scores indicate higher self-efficacy. At the time of the tool's development, the tool had a

Cronbach's α of 0.81 [28], and it was 0.73 in the study by Choi and Lee [29] and 0.71 in this study.

## Data Collection

The data were collected from outpatients receiving hemodialysis in the artificial kidney room of Keimyung University Dongsan Medical Center. The purpose and methods of this study were explained to the professor of nephrology and the head nurse in the artificial kidney room, and consent was obtained before proceeding with the study. Gift certificates were given to the study subjects as a gesture of appreciation.

## Procedure

### Preliminary investigation

The general and disease-related characteristics, self-efficacy, and upper grip strength of the experimental and control groups were measured using a pre-experiment questionnaire, and blood calcium and blood phosphorus tests were performed before starting hemodialysis. After starting dialysis, the blood flow rate was measured using the ultrasound dilution method.

### Content of the AVF stenosis prevention program

The program featured upper extremity strength exercises, a phosphorus-restricted diet, health education and health counseling on AVF management methods, and text messages. Its validity was verified by 5 experts: 1 professor of nephrology, 1 kidney center nurse, and 3 nursing professors. The content validity index (CVI) was determined. The composition and content of the AVF program were evaluated using a content validity evaluation table. Possible answers included "very appropriate" (4 points), "suitable" (3 points), "inappropriate" (2 points), and "very inappropriate" (1 point). Based on the number of expert-assigned scores of 3 or more points, the CVI was calculated to be ≥ 0.8 points.

### Health education

Weekly training on AVF muscle strength exercises, diet, and AVF management was provided for patients receiving hemodialysis via health information magazines, direct demonstrations, and videos.

(1) AVF upper extremity strength exercise: Based on a previous study, the upper extremity of the AVF was exercised using a hand gripper, and the gripper strength was gradually increased. The intensity of the gripper (GD Grip) was set based on 8 step-by-step exercises, and the intensity and frequency were adjusted. During weekly counseling, we monitored patients' performance of the exercise and provided direct demonstrations. Step 1 started by adjusting the strength of the gripper to 8 kg and with 30 repetitions. Two sets of 30 repetitions were performed per day. The second, third, and fourth steps required 40, 50, and 60 repetitions, respectively. In step 5, the strength of the gripper was adjusted to 16 kg, and 2 sets of 30 repetitions were performed per day. Similarly, steps 6, 7, and 8 required 2 sets each of 40, 50, and 60 repetitions, respectively.

(2) Diet: Diets lasted for 8 weeks based on previous research and covered the following areas: phosphorus and the role it plays in the body, problems that occur when the blood phosphate level is high, how to prevent complications, foods with high phosphorus content, and the relationship between calcification and vascular ducts. Health information magazines were used to educate patients receiving hemodialysis on healthy eating regimens and complications.

(3) AVF management: To educate patients about AVF vascular management, video education was provided on AVF complications, self-management, lifestyle, proper hemostasis methods, and vascular compression methods.

### Health counseling

Health counseling involved a checklist of AVF upper extremity strength exercises, explaining the results of physiological indicators, confirming the correct upper extremity strength exercise methods, determining whether exercises were performed, and confirming the implementation of AVF self-management and a phosphorus-restricted diet.

### Text messages

Weekly text messages were sent to encourage the participants to practice the AVF exercises, the phosphorus-restricted diet, and vascular self-management.

### Program application

The experimental group received a nursing intervention focused on AVF prevention, while the control group received general nursing interventions. Before the intervention, the experimental group was educated about the purpose of the study and the process of the program. A list of actions was prepared to confirm whether each participant performed the upper extremity exercises according to the plan, which was checked weekly. AVF management and phosphorus-restricted diet education were conducted using health information magazines and videos. The program was implemented in 8 sessions, and health education was conducted for 20 minutes during dialysis, including 10 minutes of education using videos and a health information magazine. After completing dialysis every Friday, individual counseling was conducted for 20 minutes in the counseling room, and a text message was sent.


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In the first week of the experiment, the first stage of the AVF upper extremity exercise was introduced, and a demonstration was performed using an actual gripper. The strength of the gripper was adjusted to 8 kg, and the participants were taught to practice the grasping and unfolding exercise in 1 set of 30 repetitions, with 2 sets each day.

The patients were taught about the significance of a phosphorus-restricted diet and vascular calcification, and AVF management was taught through a video. Counseling was conducted to ensure that the participants practiced the exercises and diet and to encourage them to practice. A text message was sent after the video training on AVF management. In weeks 2, 3, and 4 of the experiment, upper extremity grip exercises were introduced at each stage. After training was provided using a health information magazine, the practice list was checked, and text messages were sent. In week 5, the results of the risk index after the first post-survey were interpreted, and the researchers explained the action plan, gave feedback, and sent a text message to those in the high-risk group, which performed poorly. In weeks 6, 7, and 8, step-by-step upper extremity grip exercises were introduced, and dietary education and AVF management methods were retaught using health information magazines. The patient's practice list was checked, and text messages were sent.

#### Follow-up surveys

Follow-up surveys were completed 4 and 8 weeks after individual education and counseling. Upper grip strength, blood flow rate, physiological indicators, and self-efficacy were measured in both groups. The AVF stenosis prevention program structure is depicted in Table 2.

### Data Analysis

The collected data were analyzed using IBM SPSS ver. 23.0 (IBM Corp.). The general and disease-related characteristics of the participants were analyzed using frequencies, percentages, means, and standard deviations. Pre-intervention homogeneity tests for general characteristics, disease-related characteristics, upper extremity muscle strength, self-efficacy, physiological indicators, and blood flow velocity were conducted using the chi-square test, Fisher exact test, and the t-test. For dependent variables, a normality test was performed using the Shapiro-Wilk test, and differences between the experimental and control groups were analyzed using repeated measures analysis of variance (ANOVA).

### Ethical Considerations

Data were collected after receiving approval (IRB No: 40525-201610-HR-114-01) through research deliberation by the Institutional Review Board of Keimyung University.

## Results

### Tests for Homogeneity between Groups

#### Homogeneity of general characteristics and disease-related characteristics

Between-group baseline homogeneity was confirmed for all general and disease-related characteristics.

In total, 56% of participants in the experimental group were male, and 60% of those in the control group were female. Additionally, 52% of the experimental group and 56% of the control group were aged 54 years or older. The duration of dialysis was fewer than 5 years for 56% of the experimental group and more than 5 years for 60% of the control group. Hypertension was the most common causative disease in each group, at 40% in the experimental group and 48% in the control group. There was no AVF occlusion in 60% and 48% of those in the experimental and control groups, respectively, and the most common AVF location was the left forearm in both groups (experimental group, 44%; control group, 40%). The duration of AVF was fewer than 4 years in 56% of the experimental group and more than 4 years in 64% of the control group. Information on other demographic and disease-related characteristics is presented in Table 3.

#### Baseline homogeneity tests for dependent variables

No statistically significant differences were observed in the baseline homogeneity test for the dependent variables; therefore, the homogeneity of the 2 groups was confirmed ($t = 0.85–1.30$, $p = 0.201–0.968$). Prior to the experiment, the average upper hand grip strength was 22.68 points in the experimental group and 22.77 points in the control group, and the average blood flow rate was 1,221.20 mL/min in the experimental group and 1,319.20 mL/min in the control group. The average serum calcium was 9.25 mg/dL in the experimental group and 9.37 mg/dL in the control group, and the average serum phosphorus was 6.36 mg/dL in the experimental group and 5.87 mg/dL in the control group. Additionally, the average self-efficacy was 2.66 points in the experimental group and 2.61 points in the control group (Table 4).

### Hypothesis Validation

#### Validation of hypothesis 1

Hypothesis 1: There will be differences in the upper extremity muscle strength of the experimental and control groups participating in the AVF stenosis prevention program over time.

The mean grip strength score of the experimental group

**Table 2.** Arteriovenous fistula stenosis prevention program

| Periods | Components | Contents | Methods | Duration (min) |
|---|---|---|---|---|
| Week 1 | Health education | Step 1 workout: 30 reps at 8 kg intensity | Demonstration and practice | 5 |
| | | Importance of a phosphorus-restricted diet and vascular calcification | Health information magazine | 5 |
| | | Definition of AVF and postoperative management | Video | 10 |
| | Health counseling | Check target exercise, diet, AVF management, write exercise practice list data | Face-to-face counseling | 20 |
| | Sending text messages | Encourage target exercise and dietary transition | Text message | |
| Week 2 | Health education | Step 2 workout: 40 reps at 8 kg intensity | Demonstration and practice | 5 |
| | | Phosphorus-related food information | Health information magazine | 5 |
| | | AVF complications and self-management | Video | 10 |
| | Health counseling | Encourage and confirm exercise, diet, and AVF management practice | Practice checklist | 20 |
| | Sending text messages | Encourage participants to exercise and change their diet | Text message | |
| Week 3 | Health education | Step 3 workout: 50 reps at 8 kg | Demonstration and practice | 5 |
| | | The relationship between phosphorus-related foods and blood vessels | Health information magazine | 5 |
| | | AVF management and poultice after hemodialysis | Video | 10 |
| | Health counseling | Encourage and confirm exercise, diet, and AVF management practice | Practice checklist | 20 |
| | Sending text messages | Encourage participants to exercise and change their diet | Text message | NA |
| Week 4 | Health education | Step 4 workout: 60 reps at 8 kg intensity | Demonstration and practice | 5 |
| | | Phosphorus-restricted dietary education | Health information magazine | 5 |
| | | AVF management | Video | 10 |
| | Health counseling | Encourage and confirm exercise, diet, and AVF management practice | Practice checklist | 20 |
| | Sending text messages | Encourage participants to exercise and change their diet | Text message | NA |
| Week 5 | Health education | Step 5 workout: 30 reps at 16 kg intensity | Demonstration and practice | 5 |
| | | Phosphorus-restricted diet retraining | Health information magazine | 5 |
| | | Re-education on the need for AVF management | Video | 10 |
| | Health counseling | - Encourage and confirm exercise, diet, and AVF management practice<br>- Interpretation of biometric indicators, reinforcement of risk groups, and explanation of action plans | Practice checklist | 20 |
| Week 6 | Health education | Step 6 workout: 40 reps at 16 kg intensity | Demonstration and practice | 5 |
| | | Introduction to dietary best practices | Health information magazine | 5 |
| | | Introduction of best practices for AVF management | Health information magazine | 10 |
| | Health counseling | - Encourage and confirm exercise, diet, and AVF management practice<br>- Feedback according to physiological indicator results | Practice checklist | 20 |
| | Sending text messages | Encourage participants to exercise and change their diet | Text message | NA |
| Week 7 | Health education | Step 7 workout: 50 reps at 16 kg intensity | Demonstration and practice | 5 |
| | | Introduction to dietary best practices | Health information magazine | 5 |
| | | Introduction of best practices for AVF management | Health information magazine | 10 |
| | Health counseling | Encourage and confirm exercise, diet, and AVF management practice | Practice checklist | 20 |
| | Sending text messages | Encourage participants to exercise and change their diet | Text message | NA |
| Week 8 | Health education | Step 8 workout: 60 reps at 16 kg intensity | Demonstration and practice | 5 |
| | | Phosphorus-restricted diet retraining | Health information magazine | 5 |
| | | Re-education of AVF management method | Video | 10 |
| | Health counseling | Encourage and confirm exercise, diet, and AVF management practice | Practice checklist | 20 |
| | Sending text messages | Encourage participants to exercise and change their diet | Text message | NA |

Reps, repetitions; AVF, arteriovenous fistula; NA, not available.


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**Table 3.** Comparison of homogeneity of participants' general characteristics and disease-related characteristics ($n = 50$)

| Characteristic | Experimental group ($n = 25$) | Control group ($n = 25$) | $\chi^2$/Fisher[a] | $p$ |
|---|---|---|---|---|
| Sex | | | | |
| Male | 14 (56.0) | 10 (40.0) | 1.28 | 0.258 |
| Female | 11 (44.0) | 15 (60.0) | | |
| Age (y) | | | | |
| < 54 | 12 (48.0) | 11 (44.0) | 0.08 | 0.777 |
| ≥ 54 | 13 (52.0) | 14 (56.0) | | |
| Marital status | | | | |
| Married | 18 (72.0) | 14 (56.0) | 1.61[a] | 0.517 |
| Not married | 4 (16.0) | 5 (20.0) | | |
| Other[b] | 3 (12.0) | 6 (24.0) | | |
| Family | | | | |
| Yes | 22 (88.0) | 21 (84.0) | 0.17[a] | 0.500 |
| No | 3 (12.0) | 4 (16.0) | | |
| Education | | | | |
| Less than middle school | 6 (24.0) | 7 (28.0) | 0.14 | 0.931 |
| High school | 11 (44.0) | 11 (44.0) | | |
| College or higher | 8 (32.0) | 7 (28.0) | | |
| Job status | | | | |
| Employed | 10 (40.0) | 6 (24.0) | 1.47 | 0.225 |
| Not employed | 15 (60.0) | 19 (76.0) | | |
| Economic status | | | | |
| Medium or higher | 15 (60.0) | 12 (48.0) | 0.73 | 0.395 |
| Low | 10 (40.0) | 13 (52.0) | | |
| Dialysis period (y) | | | | |
| < 5 | 14 (56.0) | 10 (40.0) | 1.28 | 0.258 |
| ≥ 5 | 11 (44.0) | 15 (60.0) | | |
| Causative disease | | | | |
| Diabetes | 6 (24.0) | 3 (12.0) | 1.37[a] | 0.821 |
| Hypertension | 10 (40.0) | 12 (48.0) | | |
| Chronic glomerulonephritis | 7 (28.0) | 8 (32.0) | | |
| Other[c] | 2 (8.0) | 2 (8.0) | | |
| Body weight (kg) | | | | |
| < 60 | 12 (48.0) | 12 (48.0) | 0.00 | 1.000 |
| 60–69 | 8 (32.0) | 8 (32.0) | | |
| ≥ 70 | 5 (20.0) | 5 (20.0) | | |
| Weight gain after dialysis (kg) | | | | |
| 1–2 | 7 (28.0) | 7 (28.0) | 1.80 | 0.407 |
| 2–3 | 8 (32.0) | 12 (48.0) | | |
| > 3 | 10 (40.0) | 6 (24.0) | | |
| Heparin usage (U) | | | | |
| ≤ 600 | 23 (92.0) | 19 (76.0) | 2.38[a] | 0.123 |
| ≥ 800 | 2 (8.0) | 6 (24.0) | | |
| Maturity period (wk) | | | | |
| ≤ 5 | 7 (28.0) | 7 (28.0) | 0.00 | 1.000 |
| ≥ 6 | 18 (72.0) | 18 (72.0) | | |
| Occlusion experience | | | | |
| None | 15 (60.0) | 12 (48.0) | 5.33[a] | 0.083 |
| 1 or 2 | 9 (36.0) | 6 (24.0) | | |
| ≥ 3 | 1 (4.0) | 7 (28.0) | | |

(Continued to the next page)

**Table 3.** Continued

| Characteristic | Experimental group (*n* = 25) | Control group (*n* = 25) | $\chi^2$/Fisher[a] | *p* |
|---|---|---|---|---|
| Location of AVF | | | | |
| Left wrist | 5 (20.0) | 3 (12.0) | 5.34[a] | 0.394 |
| Left forearm | 11 (44.0) | 10 (40.0) | | |
| Left upper arm | 6 (24.0) | 3 (12.0) | | |
| Right wrist | 0 (0) | 3 (12.0) | | |
| Right forearm | 1 (4.0) | 3 (12.0) | | |
| Right upper arm | 2 (8.0) | 3 (12.0) | | |
| Duration of AVF use (y) | | | | |
| < 4 | 14 (56.0) | 9 (36.0) | 2.01 | 0.156 |
| ≥ 4 | 11 (44.0) | 16 (64.0) | | |
| Smoking status | | | | |
| Non-smoker | 23 (92.0) | 21 (84.0) | 0.76[a] | 0.334 |
| Smoker | 2 (8.0) | 4 (16.0) | | |
| No. of medications | | | | |
| < 7 | 13 (52.0) | 12 (48.0) | 0.08 | 0.777 |
| ≥ 8 | 12 (48.0) | 13 (52.0) | | |

Data are presented as *n* (%).
AVF, arteriovenous fistula.
[a]Fisher exact test. [b]Divorced, cohabitation, widowed. [c]Polycystic kidney disease, urinary tract disease.

**Table 4.** Baseline homogeneity test of dependent variables (*n* = 50)

| Variable | Experimental group (*n* = 25) | Control group (*n* = 25) | t | *p* |
|---|---|---|---|---|
| Upper arm strength | 22.68 ± 10.11 | 22.77 ± 6.49 | −0.04 | 0.968 |
| Blood flow rate (mL/min) | 1,221.20 ± 374.61 | 1,319.20 ± 669.69 | −0.64 | 0.527 |
| Calcium (mg/dL) | 9.25 ± 0.43 | 9.37 ± 0.56 | −0.85 | 0.401 |
| Phosphorus (mg/dL) | 6.36 ± 0.29 | 5.87 ± 0.46 | 1.30 | 0.201 |
| Self-efficacy | 2.66 ± 0.42 | 2.61 ± 0.36 | 0.51 | 0.616 |

Data are presented as mean ± standard deviation.

was 22.68 points at baseline, 26.04 points after 4 weeks, and 32.21 points after 8 weeks; for the control group, the mean score was 22.77 points at baseline, 22.12 points after 4 weeks, and 20.98 points after 8 weeks. Repeated measures ANOVA for changes in upper extremity muscle strength between the groups showed a statistically significant interaction between the group and time point (F = 15.23, $p < 0.001$). A significant difference was observed between the groups (F = 4.32, $p = 0.043$) as well as between the measurement time points (F = 7.09, $p = 0.002$) (Table 5). Therefore, the first hypothesis was confirmed.

### Validation of hypothesis 2

Hypothesis 2: There will be a difference in the blood flow velocity between the experimental and control groups participating in the AVF stenosis prevention program over time.

The mean blood flow velocity of the experimental group was 1,221.20 mL/min at baseline, 1,252 mL/min after 4 weeks, and 1,499.20 mL/min after 8 weeks. For the control group, it was 1,319.20 mL/min at baseline, 1,296.80 mL/min after 4 weeks, and 1,212.80 mL/min after 8 weeks. The results of repeated measures ANOVA for changes in blood flow velocity in the groups showed a significant interaction between the group and time point (F = 36.00, $p < 0.001$) and between the groups. (F = 300.89, $p < 0.001$). A significant difference was also observed between the time points (F = 7.17, $p = 0.010$) (Table 5). Therefore, the second hypothesis was confirmed.

### Validation of hypothesis 3

Hypothesis 3: The experimental and control groups participating in the AVF stenosis prevention program will experience changes in physiological indicators over time.

Additional hypothesis 3–1: The serum calcium index will differ between the experimental and control groups participating in the AVF stenosis prevention program over time.

The average serum calcium of the experimental group was 9.25 mg/dL at baseline, 9.01 mL/min after 4 weeks of the intervention, and 9.29 mg/dL after 8 weeks. For the


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**Table 5.** Effects of the arteriovenous fistula stenosis prevention program ($n$ = 50)

| Variable | Group | Before the experiment | 4 wk after the experiment | 8 wk after the experiment | F | | $p$ | |
|---|---|---|---|---|---|---|---|---|
| | | | | | Group | Time | Group | Time |
| Upper arm strength | Exp. | 22.68 ± 10.11 | 26.04 ± 11.98 | 32.21 ± 12.55 | 4.32 | 7.09 | 0.043 | 0.002 |
| | Cont. | 22.77 ± 6.49 | 22.12 ± 6.40 | 20.98 ± 6.36 | 15.23 | | < 0.001 | |
| Blood flow rate (mL/min) | Exp. | 1,221.20 ± 374.61 | 1,252.00 ± 356.42 | 1,499.20 ± 422.72 | 300.89 | 7.17 | < 0.001 | 0.010 |
| | Cont. | 1,319.20 ± 669.69 | 1,296.80 ± 682.95 | 1,212.80 ± 643.99 | 36.00 | | < 0.001 | |
| Calcium (mg/dL) | Exp. | 9.25 ± 0.43 | 9.01 ± 0.53 | 9.29 ± 0.62 | 0.33 | 2.20 | 0.570 | 0.277 |
| | Cont. | 9.37 ± 0.56 | 9.26 ± 0.67 | 9.14 ± 0.62 | 2.23 | | 0.142 | |
| Phosphorus (mg/dL) | Exp. | 6.36 ± 0.29 | 5.48 ± 0.92 | 5.01 ± 0.63 | 3.72 | 0.09 | < 0.001 | < 0.001 |
| | Cont. | 5.87 ± 0.46 | 5.52 ± 0.95 | 5.47 ± 1.01 | 8.64 | | < 0.001 | |
| Self-efficacy | Exp. | 2.66 ± 0.42 | 2.76 ± 0.33 | 3.00 ± 0.27 | 4.26 | 19.59 | 0.045 | < 0.001 |
| | Cont. | 2.60 ± 0.35 | 2.60 ± 0.35 | 2.61 ± 0.35 | 18.62 | | < 0.001 | |

Data are presented as mean ± standard deviation.
Exp, experimental group ($n$ = 25); Cont, control group ($n$ = 25).

control group, it was 9.37 mg/dL at baseline and 9.26 mg/dL after 4 weeks. After 8 weeks, it was 9.14 mg/dL. The results of repeated measures ANOVA on the change in the calcium index between the groups showed no interaction between the groups and the time point (F = 2.23, $p$ = 0.142), no significant difference between the groups (F = 0.33, $p$ = 0.570), and no significant difference between time points (F = 2.20, $p$ = 0.277) (Table 5). Additional hypothesis 3–1 was rejected.

Additional hypothesis 3–2: The experimental and control groups participating in the AVF stenosis prevention program will show differences in the serum phosphorus index over time.

The average serum phosphorus of the experimental group was 6.36 mg/dL at baseline, 5.48 mg/dL after 4 weeks, and 5.01 mg/dL after 8 weeks. For the control group, it was 5.87 mg/dL at baseline, 5.52 mg/dL after 4 weeks, and 5.47 mg/dL after 8 weeks. As a result of repeated measures ANOVA for the changes in the phosphorus index of the groups, a significant difference was found in the interaction between the groups and the time point (F = 8.64, $p$ < 0.001) and between the groups (F = 3.72, $p$ < 0.001). A significant difference was also observed between the time points (F = 0.09, $p$ < 0.001) (Table 5). Additional hypothesis 3–2 was confirmed.

### Validation of hypothesis 4

Hypothesis 4: There will be a difference in self-efficacy between the experimental and control groups participating in the AVF stenosis prevention program over time.

The mean self-efficacy of the experimental group was 2.66 points at baseline, 2.76 points after 4 weeks, and 3.00 points after 8 weeks. For the control group, it was 2.60 points at baseline, 2.60 points after 4 weeks, and 2.61 points after 8 weeks. Repeated measures ANOVA for the change in self-efficacy between the groups showed a statistically significant interaction between the groups and the time point (F = 18.62, $p$ < 0.001). Significant differences between the measurement time points (F = 19.59, $p$ < 0.001) and between the groups (F = 4.26, $p$ = 0.045) were also observed (Table 5). Therefore, hypothesis 4 was confirmed.

## Discussion

This study investigated the effects of an AVF stenosis prevention program for patients receiving hemodialysis on upper extremity muscle strength, blood flow rate, physiological indicators, and self-efficacy and to examine the clinical implementation of an AVF nursing intervention program.

The AVF stenosis prevention program featured exercise therapy, a phosphorus-restricted diet, and AVF self-care; these have been used in previous studies [12,13,20,30] to prevent vascular maturation failure and vascular calcification, which are factors that correspond to AVF stenosis. Exercise therapy aims to increase the blood vessel size and blood flow of AVF blood vessels [31]. The phosphorus-restricted diet was intended to prevent hyperphosphatemia, a factor in vascular calcification [12]. Previous studies utilized single therapies despite the pathophysiological complexity of vascular calcification; therefore, the therapy regimen in this study that combined exercise, dietary restriction, and vascular self-management was designed to comprehensively mediate factors related to vascular calcification in patients receiving hemodialysis. Additionally, given the low rate of self-management of patients receiving hemodialysis [18], self-monitoring was strengthened to enhance self-efficacy using a practice list to foster self-actualization, and text message support and feedback counseling were included to increase patients' self-management practice. Therefore, in this study,

upper extremity muscle strength and blood flow velocity (as clinical indicators of AVF stenosis), serum calcium and phosphorus (as risk indicators of vascular calcification), and self-efficacy were utilized as variables to understand the effects of the AVF program.

Consequently, the AVF stenosis prevention program for patients receiving hemodialysis applied in this study was found to be effective in enhancing upper extremity muscle strength through gripping exercises and preventing AVF stenosis by reducing blood phosphorus levels and improving the blood flow rate.

Upper extremity strength exercises are recommended to promote the arterialization of veins after AVF surgery in patients receiving hemodialysis and to increase blood vessel patency through increased blood flow and vasodilation. In patients receiving hemodialysis who participated in the AVF stenosis prevention program, upper extremity muscle strength showed a synergistic effect with time, with scores increasing by 3.36 points after 4 weeks and 6.18 points after 8 weeks. These results were higher than the 0.9-point increase in the study by Lee [32], in which muscle-strengthening exercises were used to increase the patency of blood vessels in the same participants, resulting in a 1.79-point decrease in the control group. Additionally, Heo [24] reported that, as grip strength improved, the hand, elbow, and shoulder joints also showed higher muscle strength. Kim [33] reported that patients using a gripper could prevent muscle atrophy or loss without applying 100% force, suggesting that gripper exercises are effective in improving upper extremity muscle strength. Exercises with grippers are considered extremely effective in increasing muscle strength in the weakened AVF-containing upper extremities of patients receiving hemodialysis due to the proven effect of gradual muscle exercise in improving upper extremity muscle strength. In particular, the grip strength scores at 4 and 8 weeks were 26.04 points and 32.21 points, respectively, indicating a greater strength increase in the final 4 weeks than in the first 4 weeks. Thus, 2 months of steady exercise was shown to be more effective than 1 month of exercise. Although more women participated in this study than men and a higher proportion of patients received dialysis for 5 or more years in the control group than in the experimental group, the upper extremity muscle strength results were significant. This could be the result of steady and systematic upper grip strength exercise and management, and it was found that more active interventions by nurses are crucial in clinical practice.

Blood flow velocity, a clinical indicator of AVF stenosis, showed increases of 31 mL/min after 4 weeks and 278 mL/min after 8 weeks compared to before the program. The blood flow rate significantly increased after 8 weeks rather than 4 weeks, showing similar results to those of the increases in upper extremity exercise after 8 weeks and 4 weeks, which is likely attributable to increased blood flow velocity as blood flow increases. This finding is the same as that in a study by Henedy [21], in which the blood flow rate of the AVF increased as a result of increased blood flow due to an increase in the thickness of the arteries and veins from AVF exercise. These results are likely due to the encouragement and support given to patients receiving hemodialysis via text messages and the assistance given to them regarding the proper implementation of the exercise method through repeated and systematic health education and weekly demonstrations. Although it was not possible to measure the increase in vein thickness after routine upper extremity grip exercises, the participants shared that they visually observed the thickening of the AVF blood vessels during counseling. As a result of training to directly assess the thrill in the AVF during AVF self-management, the participants shared that the thrill increased after the start of exercise. However, the measured blood flow rate never fell below 600 mL/min, and in the control group, which did not practice the exercises, the blood flow rate decreased by 106.4 mL/min compared to before the program.

In this study, a phosphorus-restricted diet program was implemented to control calcium and phosphorus levels, which are risk indicators for the vascular calcification of AVFs in patients receiving hemodialysis. Consequently, among those who participated in this study's AVF stenosis prevention program, normal calcium levels were maintained, while phosphorus levels decreased over time. The blood calcium level was 9.25 mg/dL before the program, 9.00 mg/dL after 4 weeks, and 9.28 mg/dL after 8 weeks, with no significant difference between time points and the interaction between the groups and time points. This indicates that the patients maintained a normal level. Contrary to the results regarding the multiplication of calcium and phosphorus levels as a physiological index in a study by Lee et al. [34], who conducted a phosphorus-related nursing intervention, calcium levels did not change in the present study. Among the risk indicators of vascular calcification, the average phosphorus value was 6.36 mg/dL before the program; it decreased by 0.88 to 5.48 mg/dL after 4 weeks and further decreased to 5.01 mg/dL after 8 weeks. Therefore, reducing serum phosphorus levels through periodic and repeated education and counseling is considered effective in terms of the development and application of the program.

In this study, the average self-efficacy score of patients receiving hemodialysis was 2.66 out of 4 points; in the study by Kim and Choi [18], who used the same tool for patients


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receiving hemodialysis, the average self-efficacy score was 3.24, indicating low self-efficacy. In terms of the self-efficacy measurement, water and dietary management scores were high, but the exercise and blood vessel management scores were relatively low. However, after the program, the self-efficacy scores for exercise and vascular management increased. This was likely due to the effect of weekly individual counseling and education on upper grip strength exercises and AVF management. In this study, direct health counseling was provided to identify difficulties and problems in self-care, devise more suitable methods, and encourage motivation and confidence through text messages. The majority of patients (60%–76%) did not have jobs due to their frequent hospitalization and prolonged illness. Participation in this research program increased social contact, which invigorated patients and improved their quality of life, which is thought to have led to increased social activity. Therefore, patients receiving hemodialysis with chronic diseases should receive assistance to maintain a healthy lifestyle through self-care, including dieting and blood vessel management, and routine, rather than one-off, nursing interventions.

To summarize, the program in this study was confirmed to be effective in preventing AVF stenosis in patients receiving hemodialysis, and it is expected to be useful for continuous vascular management. Additionally, it will be useful in nursing intervention programs to increase the effectiveness of AVF self-management, as it has shown promising results in patients receiving hemodialysis for ensuring homogeneity in the improvement of upper extremity muscle strength, self-efficacy, the phosphorus index, and the blood flow rate to prevent AVF stenosis. However, future studies should be conducted to supplement our findings since this study included patients receiving hemodialysis in an artificial kidney room at a single hospital only, and the exogenous variables related to the participants' meal intake and nutritional status were insufficient.

## Conclusion

This study aimed to prevent AVF stenosis in patients undergoing hemodialysis by conducting an AVF stenosis prevention program over 8 weeks for 50 outpatient dialysis patients at Keimyung University Dongsan Medical Center in Daegu, Republic of Korea. The AVF stenosis prevention program resulted in an increase in upper extremity muscle strength through grip strength exercises and was effective in preventing AVF stenosis by increasing the blood flow rate. A phosphorus-restricted diet and AVF management methods ensured normal calcium index values and led to a decrease in phosphorus index levels. Additionally, given that encouragement and support through text messages and practice lists improved self-efficacy, a program should be implemented that provides ongoing education.

Our suggestions for future studies are as follows. First, for the treatment and self-management of patients receiving hemodialysis, routine individual education programs and materials that consider patients' dietary intake and nutritional status should be designed. Second, the program in this study should be expanded and repeated as an effective nursing intervention for the prevention and management of AVF stenosis in patients receiving hemodialysis. Third, a follow-up study is needed to determine whether the preventive effect on AVF stenosis continues after the end of the program.

## Notes

### Ethics Approval

This study was approved by the Institutional Review Board of Keimyung University (IRB No: 40525-201610-HR-114-01) and performed in accordance with the principles of the Declaration of Helsinki. Written informed consent was obtained for the publication of this study and accompanying images.

### 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: all authors; Data curation: all authors; Formal analysis: all authors; Funding acquisition: all authors; Investigation: HL; Methodology: GB, EL; Project administration: all authors; Resources: all authors; Software: all authors; Supervision: all authors; Validation: all authors; Visualization: all authors; Writing–original draft: all authors; Writing–review & editing: all authors. All authors read and approved the final manuscript.

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**Original Article**

# Prevalence and patterns of adverse events following childhood immunization and the responses of mothers in Ile-Ife, South West Nigeria: a facility-based cross-sectional survey

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## ABSTRACT

**Objectives:** This study aimed to examine the prevalence and pattern of adverse events following childhood immunization and the responses of mothers in Ile-Ife, South West Nigeria.
**Methods:** This descriptive cross-sectional study was conducted among 422 mothers of children aged 0 to 24 months attending any of the 3 leading immunization clinics in Ile-Ife, Nigeria. The respondents were selected using the multi-stage sampling technique. Data were collected using a pretested structured interviewer-administered questionnaire and analyzed using IBM SPSS ver. 26.0. The chi-square test was used to test associations, while binary logistic regression was used to determine the predictors of mothers' responses to adverse events following immunization (AEFIs). A $p$-value of $< 0.05$ was considered statistically significant.
**Results:** The mean age of the respondents was 29.99 ± 5.74 years. About 38% of the children had experienced an AEFI. Most mothers believed that the pentavalent vaccine was the most common cause of AEFIs (67.5%). Fever (88.0%) and pain and swelling (76.0%) were the most common AEFIs. More than half of the mothers (53.7%) administered home treatment following an AEFI. Younger mothers (odds ratio [OR], 2.43; 95% confidence interval [CI], 1.20–5.01), mothers who delivered their children at a healthcare facility (OR, 3.24; 95% CI, 1.08–9.69), and mothers who were knowledgeable about reporting AEFIs (OR, 2.53; 95% CI, 1.04–7.70) were most likely to respond appropriately to AEFIs.
**Conclusion:** The proportion of mothers who responded poorly to AEFIs experienced by their children was significant. Therefore, strategies should be implemented to improve mothers' knowledge about AEFIs to improve their responses.

**Keywords:** Adverse events; Child; Immunization; Nigeria; Prevalence; Vaccines

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## Introduction

Immunization is one of the greatest success stories recorded in modern medicine and one of the most impactful and cost-effective public health strategies ever adopted to protect individuals, families, and the public from infectious diseases and, more recently, from cancers and other chronic diseases [1]. Immunization prevents deaths in all age groups and currently protects 2 to 3 million children yearly from life-threatening childhood diseases [2]. Although childhood immunization has been proven to be objectively beneficial, occasional associated adverse events, which could lead to debilitating conditions that may require hospital admission, are a major source of concern as they may arouse public suspicion and could potentially lead to a loss of immunization gains and heighten vaccine hesitancy. The World Health Organization (WHO) defines adverse events following immunization (AEFIs) as any untoward medical occurrence that follows immunization and that does not necessarily have a causal relationship with vaccine use. The adverse event may be any unfavorable or unintended sign, abnormal laboratory finding, symptom, or disease [3]. AEFIs can be categorized as vaccine product-related reactions, vaccine quality defect-related reactions, immunization error-related reactions (formerly "program errors"), immunization anxiety-related reactions, and coincidental events [3]. In addition, vaccine reactions could be classified as serious or non-serious, with local or systemic manifestations. They could range from fever, irritability, pain at the injection site, skin rash, sores, and difficulty breathing to weakness of the limbs, convulsions, aseptic meningitis, encephalitis, and even death. AEFIs can lead to death or a life-threatening condition that requires hospitalization with or without permanent sequelae [3,4]. AEFIs have been observed globally and have been suggested to be a significant factor contributing to the low vaccination coverage in Nigeria [5].

The country's current immunization program offers the Bacillus Calmette–Guérin (BCG), polio 3, PENTA3/DPT3, measles, and yellow fever vaccines. The coverage rates are currently suboptimal, with rates of 51.3% for the BCG vaccine, 34% for the polio vaccine, 34.4% for the pentavalent vaccine, 48.1% for the measles vaccine, and 39% for the yellow fever vaccine according to 2021 Multiple Indicator Cluster Survey (MICS) reports [6]. With new vaccines likely to be added to national programs and an increase in the frequency at which vaccines are administered (through, for example, mass immunization campaigns) based on national targets, the immunization schedule will contain more vaccine antigens, possibly resulting in more AEFIs. The MICS report also indicated that 64% of children aged 12 to 23 months did not receive all routine immunizations and that 11% of women refused to vaccinate their children due to their fear of side effects, while 26% did not vaccinate their children due to mistrust and fear [6]. The reported rates of AEFIs in studies vary widely across states in Nigeria, ranging from 19.3% to 57% [7]. Thus, investigation and reporting on AEFIs are critical, given inconsistent rates of AEFIs and reporting about AEFIs across states. However, the Nigerian government, supported by the WHO, has made efforts to strengthen the country's AEFI surveillance system by forming the National Expert Committee, which is responsible for ensuring that Nigerian health workers can monitor and prevent AEFIs [8]. Regardless of the actual cause, an AEFI may lead to public suspicion about vaccines, resulting in vaccine hesitancy among parents who may refuse further vaccination for their children. This leaves children vulnerable to vaccine-preventable diseases. In addition, it may result in poor vaccination coverage due to mothers who are cautious about vaccination for their children due to their personal experience, the experiences of members of their community, rumors, or distrust about vaccines [9]. AEFIs affect vaccination uptake due to parental concerns about the health of children, as it did in the early 21st century in northern Nigeria when there was widespread parental polio vaccine refusal due to widespread rumors and distrust about the vaccine [9].

Previous and recent surveys have found wide disparities in the reported rates of AEFIs [7] in different parts of the country, possibly due to contextual differences, socioeconomic inequality, and vaccine-related issues in different geopolitical zones of the country. Therefore, this study aimed to determine the prevalence and prevailing patterns of AEFIs and the responses of mothers in Ile-Ife, South West Nigeria, to fill the contextual gap for evidence-based programming and planning related to AEFIs at the regional and national levels.

### *HIGHLIGHTS*

- A high prevalence of adverse events following immunization (AEFI) among respondents was found.
- The appropriateness of mothers' responses to AEFIs was also found to be poor.
- Mothers' awareness about reporting AEFIs and delivery at a healthcare facility predicted an appropriate response to AEFIs.



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## Materials and Methods

### Study Area

This study was conducted in Ile-Ife, Osun, South West Nigeria, between May and July 2022. Ile-Ife consists of 2 local government areas (LGAs; Ife Central and Ife East) and is considered the most populous city in Osun, with a population of 355,281 people, of whom 131,965 are children younger than 5 years old [10]. The LGAs each have major healthcare facilities for administering immunizations. Ife Central, the study site, has 11 wards with 23 public healthcare facilities with a population of 82,240 children under 5 years old as of the time of this study.

### Study Design and Participants

This was a healthcare facility-based descriptive cross-sectional study conducted with mothers of children aged 0 to 24 months who attended any of the 3 leading immunization clinics in Ile-Ife, Osun, Nigeria. The minimum sample size was estimated using the formula for single proportion [11] and was calculated to be 422 based on an AEFI prevalence of 46.5% [12], an error margin of 5%, and a 95% confidence interval (CI) given a possible 10% non-response rate. The study enrolled mothers with at least 1 eligible child aged 0 to 24 months who had previously completed a full vaccination regimen and mothers who brought their children to 1 of the 3 immunization clinics for the child's ninth month of vaccinations and who consented to participate in the study. Completion of a full vaccination regimen was confirmed by checking the immunization cards presented by mothers whose children had completed immunization before enrollment in the study. In addition, the ninth month of immunization was used as a reference for enrollment so mothers could easily recall necessary information about previous AEFI experiences following any of the administered vaccines [11]. By the time a child reaches 9 months of age in Nigeria, they are expected to have received all basic immunizations, including BCG, polio 3, PENTA3/DPT3, the measles vaccine, and the yellow fever vaccine, as outlined in the standard vaccination schedule. These immunizations are considered to be an indicator of full coverage, meaning the child would have been exposed to all necessary antigens by this point.

The index child' refers to the child chosen for the study about whom the mother provided information for the study. If the mother had more than 1 eligible child, the child whose birthday was nearest to the interview period was selected as the index child.

### Sampling Technique

As described below, a multi-stage sampling technique was used to select the 422 participants for the study. (1) First stage: Ife Central was randomly chosen from the 2 LGAs in Ile-Ife using simple random sampling by balloting. (2) Second stage: Three major healthcare facilities were purposively chosen among the healthcare facilities in Ife Central since they are major delivery points for immunization services in and around Ile-Ife. These healthcare facilities included the Urban Comprehensive Health Centre (UCHC) at Obafemi Awolowo University Teaching Hospital Complex, Eleyele; the Comprehensive Health Centre (CHC), Enuwa; and the Central Immunization Office (CIO), Aderemi, Ile-Ife. (3) Third stage: A list of mothers with index children who attended the clinic was generated daily in each healthcare facility to form the sampling frame. The participants were then selected from the list using a simple random sampling method by balloting. The number of children registered at UCHC Eleyele averaged 120 per week, while at CHC Enuwa and CIO Aderemi the average was 80 children per week each. Therefore, the sample size proportions allotted to each clinic were 182 from UCHC Eleyele and 120 each from CHC Enuwa and CIO Aderemi. This sampling technique was preferred to give all mothers who met the inclusion criteria an equal chance to be selected. The immunization days at the clinics were Monday through Friday, and the participants were recruited on any of the immunization days. We repeated the process until the targeted number of interviewees was reached.

### Data Collection Instruments

Data collection was performed using a structured interviewer-administered questionnaire. The questionnaire was designed to meet the study's objective with multiple questions adapted from the WHO Global Manual on Surveillance of Adverse Events Following Immunization [3] and went through several drafts and reviews. The final draft was pretested with 20 mothers of children aged 0 to 24 months at the immunization clinic of another healthcare facility, and the findings and experiences from the pretest were utilized to modify the instrument. The final tool had 4 sections. The first section covered the participants' sociodemographic characteristics such as age, sex, education level, occupation, marital status, religion, and others. The second section assessed the participants' knowledge of childhood vaccines with other related questions. The third section assessed the participants' knowledge of and awareness about reporting AEFIs using yes or no questions, the occurrence of AEFIs, and the responses of mothers to AEFIs. AEFIs were defined as any untoward

medical occurrence that followed immunization and that did not necessarily have a causal relationship with vaccine use that occurred within 28 days after vaccination [3]. The fourth section examined the participants' perceptions of AEFI.

### Data Analysis

Data entry and analysis were performed using IBM SPSS ver. 26.0 (IBM Corp.). The descriptive analysis used frequencies and percentage distributions to represent the sociodemographic characteristics of respondents with AEFI patterns presented as bar graphs. In addition, associations between sociodemographic variables, awareness about reporting AEFIs, and the responses of mothers following AEFIs were examined using the Pearson chi-square test with the Fisher exact correction applied where applicable. The outcome variable for the bivariate and multivariate analyses was the response of mothers following an AEFI, which was dichotomized as an "appropriate response" or an "inappropriate response." An appropriate response in this study was defined as when mothers took the affected child to a healthcare facility within 24 hours of the onset of an AEFI, regardless of initial management at home. In addition, the independent variables, such as awareness about reporting AEFIs, and sociodemographic variables, such as age, marital status, occupation, and others, were recategorized into dichotomous variables for bivariate analyses. Lastly, we conducted binary logistic regression to determine odds ratios (ORs) and 95% CIs to assess the independent effect of selected explanatory variables on the response of mothers following an AEFI. The level of significance was set at $p < 0.05$.

**Table 1.** Sociodemographic characteristics of the study respondents ($n = 422$)

| Characteristic | Frequency (%) |
|---|---|
| Mothers' age (y) | |
| ≤20 | 6 (1.4) |
| 20–29 | 192 (45.5) |
| 30–39 | 198 (46.9) |
| ≥40 | 26 (6.2) |
| Education level | |
| No education | 11 (2.6) |
| Primary education | 8 (1.9) |
| Secondary education | 182 (43.1) |
| Tertiary education | 221 (52.4) |
| Marital status | |
| Not married | 25 (5.9) |
| Married | 416 (98.6) |
| Occupation | |
| Employed | 383 (90.8) |
| Unemployed | 39 (9.2) |
| Sex of the index child | |
| Male | 222 (52.6) |
| Female | 200 (47.4) |
| Birth order | |
| 1–2 | 288 (68.2) |
| 3–4 | 116 (27.5) |
| ≥5 | 18 (4.3) |
| Antenatal clinic attendance | |
| Yes | 394 (93.4) |
| No | 28 (6.6) |
| Place of delivery | |
| Healthcare facility | 378 (89.6) |
| Home | 44 (10.4) |
| Ethnicity | |
| Yoruba | 360 (85.3) |
| Igbo | 37 (8.8) |
| Hausa | 5 (1.2) |
| Others | 20 (4.7) |

## Results

A total of 422 mothers participated in the study, as indicated in Table 1. The number of participants in their 20s (45.5%) was comparable to the number of participants in their 30s (46.9%). The mean age was 29.99 ± 5.74 years. Nearly all of the participants were married (98.6%), and 52.4% had a tertiary education. The majority of the participants were of Yoruba descent from South West Nigeria (85.3%). A large proportion (93.4%) attended antenatal clinics and delivered their children at healthcare facilities (89.6%). Over two-thirds (68.2%) had 1 to 2 children, and most of the index children were boys (52.6%). A high proportion of the study respondents (90.8%) were employed.

Overall, 37.9% of the index children had experienced an AEFI (Table 2). The majority of the AEFIs reported by mothers in the study were generalized/systemic in presentation (58.6%) and mainly occurred within 6 hours of vaccination (63.8%). In addition, according to the mothers, the pentavalent vaccine was believed to be the most prevalent cause of AEFIs (67.5%), followed by the pneumococcal conjugate vaccine (65.6%) and the BCG vaccine (26.2%). Fever (88.0%) and pain and swelling (76.0%) were the most common AEFIs experienced (Figure 1). Irritability and excessive crying comprised 20.5% of AEFIs, while rare and more serious vaccine reactions such as seizures were less frequent (1.3%) among the AEFIs reported by mothers. The responses of mothers following the development of AEFIs in their children varied, with most mothers (53.7%) treating the child at home using paracetamol, tepid sponging, or other methods, while 26.3% reported that they went to a hospital within 24 hours of the onset of symptoms and 20.0% that they went to a hospital



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more than 24 hours after symptom onset (Figure 2).

As a result of bivariate analysis, factors such as the sex of the child, birth order, and ethnicity had *p*-values of ≥0.20 [11] and were not included in the logistic regression. However, as a result of binary logistic regression, maternal age, place of delivery, and awareness about reporting AEFIs remained significant determinants of the response of mothers following an AEFI. Younger mothers were twice as likely to respond appropriately following an AEFI than older mothers (OR, 2.43; 95% CI, 1.20–5.01). In addition, mothers who delivered in healthcare facilities were 3 times more likely to respond appropriately to AEFIs than those who delivered at home (OR, 3.24; 95% CI, 1.08–9.69). Awareness about reporting AEFIs was also significantly associated with responding appropriately following an AEFI. The odds of responding appropriately to an AEFI were 2.5 times higher (OR, 2.53; 95% CI, 1.04–7.70) among mothers who were aware of reporting AEFIs (Table 3).

**Table 2.** Prevalence of AEFI among children under 5 years old in Ile-Ife, Nigeria

| Variable | Frequency (%) |
|---|---|
| Child's experience of an AEFI (*n* = 422) | |
| Experienced | 160 (37.9) |
| Not experienced | 262 (62.1) |
| AEFI by site reported (*n* = 160)[a] | |
| Local | 123 (41.4) |
| Systemic/generalized | 174 (58.6) |
| Time until the onset of AEFIs (h) | |
| <6 | 102 (63.8) |
| 6–12 | 40 (25.0) |
| 13–23 | 11 (6.9) |
| ≥24 | 7 (4.4) |
| Vaccines linked to AEFIs[a] | |
| Bacillus Calmette–Guérin | 42 (26.2) |
| Pentavalent vaccine | 108 (67.5) |
| Pneumococcal conjugate vaccine | 105 (65.6) |
| Oral polio vaccine | 36 (22.5) |
| Inactivated polio vaccine | 39 (24.3) |
| Measles vaccine | 8 (5.0) |
| Yellow fever vaccine | 1 (0.6) |

AEFI, adverse event following immunization.
[a]Multiple responses.

## Discussion

This study examined the prevalence and pattern of AEFIs and the response of mothers in Ile-Ife, South West Nigeria. With the introduction of new vaccines to the national immunization schedule, more frequent vaccinations to meet national targets, and exposure to more vaccine antigens, there is an increased likelihood of AEFIs. Therefore, the availability of information on background rates and patterns of reported AEFIs will help address AEFI-related concerns.

In this study, about 37.9% of children were reported by mothers to have experienced an AEFI in some form. This rate was consistently lower than the rates reported in North Central [12], North West [13], and South South [14] Nigeria, although it was slightly higher than the rate reported in an earlier study in North West Nigeria in 2016 [15]. The consistently different rates across regions, including the rate reported in this study, may be a result of contextual differences in study settings, differences in the education levels of mothers between regions as documented in past studies [12–15], coincidental events that may have been reported as AEFIs by mothers in some of the studies due to a close temporal association with the timing of immunization, different vaccine handling and storage techniques, differences in the manufacturers of vaccines across zones, and, notably, ethnic and genetic differences between children, given that many studies from different zones of the country employed a similar cross-sectional research design. There may also be differences among

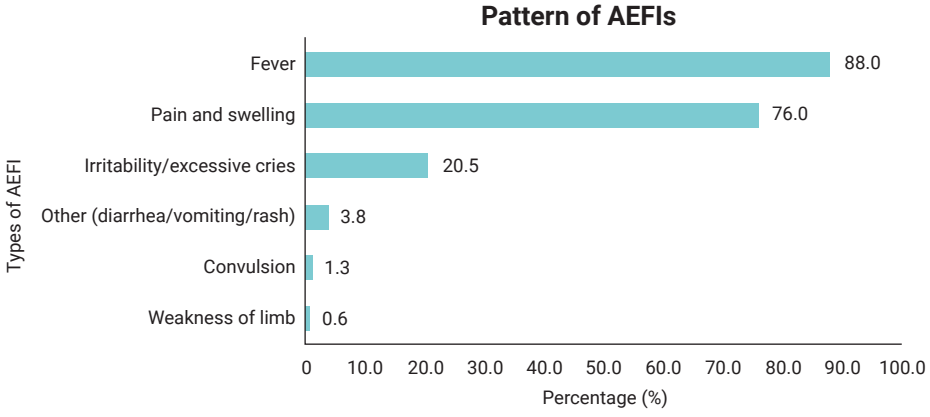


**Figure 1.** Pattern of adverse events following immunization (AEFI) among children under 5 years old in Ile-Ife, Nigeria. Multiple responses.

mothers in their level of awareness about reporting AEFIs across zones, which is also closely linked to the education level of mothers.

This study found a generalized/systemic presentation to be the most common site of AEFIs reported by mothers and the pentavalent vaccine to be the vaccine most often believed to be the cause of AEFIs. The finding regarding generalized presentation is consistent with earlier studies [13,15–17]. The finding that the pentavalent vaccine was the most frequently cited cause of an AEFI is also not unexpected since it is a combination of 5 vaccines in a single dose and has been reported to be associated with increased incidence of AEFIs and due to the diphtheria, pertussis, and tetanus (DPT) components of the pentavalent vaccine [13,18,19]. We found fever to be the most common AEFI observed by mothers following the vaccination of their children. This finding is similar to the results of many previous Nigerian [12–15] and international [20,21] studies that found fever to be the most common AEFI. However, the rate reported in our study was slightly higher than that in other studies, with 8 in 10 vaccinated children experiencing fever. This finding is not surprising since most of the respondents involved in this study received the pentavalent vaccine. Moreover, previous studies that compared the DPT vaccine and the pentavalent vaccine found fever to be the most common complication of the DPT vaccine, which is a component of the pentavalent vaccine [22]. Likewise, considering the antigenic nature of vaccines introduced into the body, the normal physiologic reaction of the body can cause fever due to the production of cytokines.

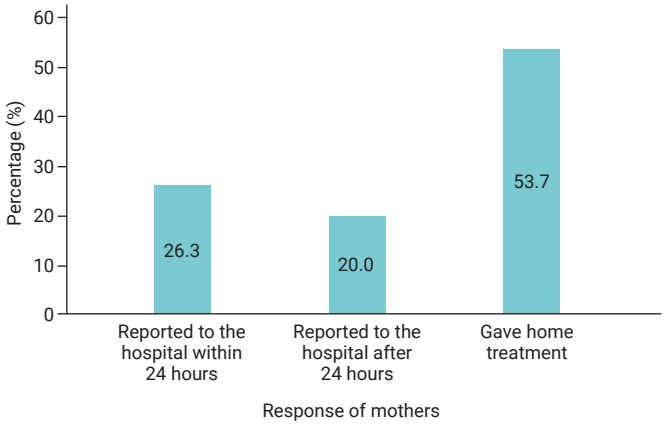


**Figure 2.** Responses of mothers regarding adverse events following immunization in Ile-Ife, Nigeria.

Regarding the responses of mothers to AEFIs, approximately 5 in 10 mothers managed the AEFI at home using simple treatments such as paracetamol and tepid sponging. However, in addition to initial treatment at home, it would

**Table 3.** Factors associated with the responses of mothers following an AEFI in Ile-Ife, Nigeria

| Variable | Appropriate response | Inappropriate response | OR (95% CI) | *p* |
|---|---|---|---|---|
| Mother's age (y) | | | | |
| ≤29 | 23 (37.1) | 39 (62.9) | 2.43 (1.20–5.01) | 0.013 |
| ≥30 | 19 (19.4) | 79 (80.6) | 1 | |
| Occupation | | | | |
| Employed | 35 (24.5) | 108 (75.5) | 0.46 (0.17–1.27) | 0.152 |
| Unemployed | 7 (41.2) | 10 (58.8) | 1 | |
| Marital status | | | | |
| Not married | 6 (42.9) | 8 (57.1) | 1 | |
| Married | 36 (24.7) | 110 (75.3) | 2.29 (0.07–6.79) | 0.139 |
| Education level | | | | |
| Primary education or lower | 1 (20.0) | 4 (80.0) | 1 | |
| Secondary education or above | 41 (26.5) | 114 (73.5) | 0.70 (0.09–5.10) | 0.206[a)] |
| Antenatal clinic attendance | | | | |
| Yes | 37 (25.0) | 111 (75.0) | 0.47 (0.15–1.49) | 0.303 |
| No | 5 (41.7) | 7 (58.3) | 1 | |
| Place of delivery | | | | |
| Healthcare facility | 38 (30.2) | 88 (69.8) | 3.24 (1.08–9.69) | 0.030[a)] |
| Home | 4 (11.8) | 30 (88.2) | 1 | |
| Awareness about reporting an AEFI | | | | |
| Yes | 35 (31.3) | 77 (68.8) | 2.53 (1.04–7.70) | 0.032 |
| No | 7 (14.6) | 41 (85.4) | 1 | |

Data are presented as *n* (%) unless otherwise specified.
OR, odds ratio; CI, confidence interval; AEFI, adverse effect following immunization.
[a)]Fischer exact test.



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have been appropriate for the mothers to report the AEFI to a healthcare facility within 24 hours to receive a health worker's assessment and reassurance, which only about a quarter of the mothers in this study did. Reporting at healthcare facilities is important not only to the child but also for the health system to record AEFIs following all childhood immunizations in order to respond appropriately due to vaccine safety concerns and issues with handling and monitoring vaccines. The findings regarding the appropriateness of the mothers' responses align with those of a study of mothers in Jos, North Central Nigeria [12], although we found a higher level than was reported in the previous study. This finding contrasts with the results of a study of mothers from Benin City, South South Nigeria [14], where almost all (99%) of the respondents reported AEFIs to a healthcare facility; however, the study did not measure the time since the onset of symptoms when classifying the responses of mothers unlike in our study. The timing of mothers' responses is, however, essential for effectively managing the response to AEFIs among both mothers and children since it offers an opportunity to calm the anxiety of mothers and provide care for the child. The contrasting findings of this study provide further evidence for contextual differences in AEFI-related issues across the country's regions.

In our study, the mothers' ages, place of delivery, and awareness about reporting AEFIs were significantly associated with the appropriateness of mothers' responses to AEFIs. The finding that younger mothers were more likely to report AEFIs than older mothers in this study could be due to past experiences with AEFIs among older mothers, who may have been less anxious about AEFIs due to a previous positive or negative experience, unlike younger mothers who may not have had any experience with AEFIs and thus responded to their child's symptoms with more urgency. This finding suggests that experience with childcare impacts mothers' childcare practices related to care-seeking and their reaction to their child's illness. We also found that mothers who delivered at healthcare facilities were more likely to report AEFIs, possibly because they were previously informed about immunization by health workers and may have had the opportunity to be educated before or during the child's first vaccination, which is often administered before discharge after delivery. Antenatal clinic attendance did not show any significant association with the appropriateness of mothers' responses to AEFIs, possibly because information about AEFIs are not sufficiently covered in antenatal health education. In addition, some women who attend antenatal clinics end up not delivering in healthcare facilities and miss the opportunity to receive information on AEFIs when their children are vaccinated. Lastly, awareness about AEFIs was significantly associated with the appropriateness of mothers' responses when reporting AEFIs in this study. This may not be surprising since knowledge improves children's health practices and care-seeking behaviors, as established in previous studies [14,23], and other studies that reported that education impacts vaccination completion [24,25] give support to the finding in this study that awareness improves AEFI reporting, as similarly suggested in an earlier study [14]. Based on the findings presented above, there is a need to strengthen the country's AEFI surveillance system further by devising and implementing AEFI educational programs targeting pregnant women at antenatal clinics for mothers during postnatal visits and at immunization clinics. This is essential since it would enable health workers to better gather data directly from mothers. In addition, delivery at healthcare institutions should be encouraged since it provides mothers with an opportunity to receive vital information about childcare. It is worth noting that a significantly higher percentage of mothers in our study were employed compared to the national average of women in the workforce [26]. However, we found no significant association between occupation and the appropriateness of the mothers' responses to AEFIs. This result may be due to the purposive sampling used to determine our study location. This finding has implications for future research, which may yield different findings from this study.

The study's strength is that it provides insight into the prevalence of AEFIs in the South West region of Nigeria, given the wide disparities in the rates of AEFIs reported in other regions, and suggest the need for a national survey to determine the prevalence of AEFIs and identify the various factors associated with reporting AEFIs among mothers for effective planning and programming related to AEFIs at both the national and regional levels.

Although this study provides valuable insights, it also has multiple important limitations. First, we were unable to determine the incidence of AEFIs in response to specific vaccines since the number of children who received each vaccine was not recorded. Second, data on the occurrence of AEFIs in the index children were self-reported by mothers, which may have resulted in the over- or under-reporting of AEFIs in the study due to possible recall bias and the inability to verify the data due to the nature of the study design. A cohort study design is suggested in the future to determine the incidence of AEFIs rather than the cross-sectional design used in the current study. Third, the experiences of mothers often vary widely based on the ages of their children, although this was minimized by including

children at the ninth month of vaccinations to ensure similarity. Lastly, the cross-sectional nature of the data restricted the ability to infer causal relationships.

## Conclusion

Our study indicates that a significant proportion of mothers (approximately one-third) reported AEFIs among their children. However, our findings also highlighted a general lack of appropriate responses from mothers in such situations. Awareness of AEFIs and the place of delivery, among other factors, were strongly related to the appropriateness of the mothers' responses. To improve mothers' awareness of AEFIs and strengthen their responses to AEFIs, we recommend the implementation of targeted educational programs for mothers about AEFI-related issues.

## Notes

### Ethics Approval

The study protocol was approved by the Ethical Committee of the Institute of Public Health, Obafemi Awolowo University, Ile-Ife (No: IPH/OAU/12/1991). Informed consent was obtained from the respondents before the interview, and the data were anonymized. The confidentiality of the respondents was assured and maintained during and after the 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: OAO, FOF; Data curation: OAO, FOF; Formal analysis: OAO; Investigation: MS, RU, MAA; Methodology: all authors; Project administration: FOF; Resources: FOF, MS, RU, MAA; Software: OAO; Supervision: OAO, FOF; Validation: OAO, FOF, MS, RU, MAA; Writing–original draft: OAO; Writing–review & editing: all authors. All authors read and approved the final manuscript.

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**Original Article**

# Mental health and its determinants among adolescents living in families with separated or divorced parents in an urban area of Vietnam

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## ABSTRACT

**Objectives:** We assessed the prevalence of stress, anxiety, and depression among adolescents living in families with separated or divorced parents in Hue City, Vietnam and identified factors associated with these conditions.

**Methods:** This cross-sectional study enrolled 309 adolescents, aged 12 to 17 years, living in families with separated or divorced parents in Hue City, Vietnam. The depression anxiety stress scale-21 (DASS-21) was used to measure stress, anxiety, and depression. Predictors of overall and individual mental health problems were identified using ordered and binary logistic regression, respectively.

**Results:** The DASS-21 scale revealed a 49.2% prevalence of stress, while anxiety and depression had s prevalence rates of 61.5%. Among participants, 42.4% experienced all 3 mental health issues. Several factors were identified as significant predictors of mental health problems, including poor to average economic status (adjusted odds ratio [aOR], 2.00; 95% confidence interval [CI], 1.21–3.31; $p = 0.007$); being in high school (aOR, 5.02; 95% CI, 2.93–8.60; $p < 0.001$); maternal occupation of teacher, healthcare professional, or official (aOR, 2.39; 95% CI, 1.13–5.03; $p = 0.022$); longer duration of family separation or divorce (aOR, 1.24; 95% CI, 1.05–1.45; $p = 0.009$); living with one's mother (aOR, 1.69; 95% CI, 1.03–2.76; $p = 0.04$); alcohol consumption (aOR, 1.70; 95% CI, 0.99–2.92; $p = 0.050$); and being bullied (aOR, 5.33; 95% CI, 1.10–25.69; $p = 0.037$). Most of these factors were associated with stress, anxiety, and depression. Additionally, smoking was associated with stress.

**Conclusion:** Adolescents with separated or divorced parents were at increased risk of stress, anxiety, and depression. The findings of this study provide important implications for prevention programs.

**Keywords:** Adolescent; Anxiety; Depression; Divorce; Emotional stress; Separated

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## Introduction

Adolescence is a crucial period of physical, emotional, and social change that has a major impact on the health and well-being of young individuals. With 1.2 billion adolescents worldwide, adults and families must provide support and guidance as they navigate through life. Amidst numerous economic, cultural, and social shifts, adolescents encounter various health challenges, including mental health issues. The World Health Organization has reported that approximately 15% of children and adolescents experience mental health problems, making it the primary cause of disability for this age group [1].

Vietnam contains approximately 14 million adolescents aged 10 to 19 years, with two-thirds residing in rural areas. Recent data from a United Nations Children's Fund national survey revealed that approximately 8% to 29% of children and young people are at risk of mental health problems, with rates varying by province, gender, and respondent population and depending on the study measurement approach [2]. A 2022 study conducted in Hanoi, the largest urban area in northern Vietnam, found that 38% of middle school students experienced anxiety, 33% reported stress, and 26.1% exhibited depression [3]. Similarly, another recent study among high school students reported prevalence rates of stress, anxiety, and depression at 41.7%, 49.0%, and 43.6%, respectively, primarily at mild and moderate levels [4]. Consequently, mental health among students is a public health concern that necessitates attention and effective intervention from both family and school perspectives. The family and school environment play a significant role in adolescent development, and parental separation negatively impacts academic performance and mental health [5]. Stress, anxiety, and depression are common mental health disorders faced by children living with divorced parents, with girls being more vulnerable than boys [6]. The prevalence of mental health problems in this population can also be attributed to factors such as family structure, socioeconomic conditions, cultural background, and parents' lack of knowledge about children's health issues [6].

Numerous studies have identified factors that contribute to an increased likelihood of stress, anxiety, and depression. A cross-sectional survey conducted among junior high school students in Malaysia and Greece revealed that parental marital status significantly increased the risk of depression, with participants from separated or divorced families facing 2 to 3 times higher risk than those with biological parents living together [7,8]. Similarly, a study conducted in Lebanon indicated a link between parental separation and adolescent anxiety [9]. Recent research conducted in Vietnam has also demonstrated that the quality of the parent-child relationship, grade level, and female gender are factors associated with depression, anxiety, and stress disorders among middle school students [3]. According to a previous study, children with divorced parents experience depression, anxiety, and thoughts of suicide at rates 1.29, 1.12, and 1.48 times higher, respectively, than children without divorced parents. They also have an increased likelihood of engaging in risky behaviors such as drinking alcohol (1.43 times) and smoking (1.64 times) [10].

Vietnam, like other low-middle-income countries, has experienced rapid economic growth and urbanization in recent years. Such changes may also promote a shift in societal and family structures, particularly in people's perceptions of parenting and marriage roles [11]. According to data from the 2019 Viet Nam General Statistics Office, the divorce rate has risen over the last decade, increasing from 1.11% in 2007 to 2.92% in 2017 among the population aged 15 years and older [12,13]. The divorce rate was found to be higher among women and those living in urban areas [11]. Several factors have been identified in the Vietnamese context to explain the high divorce rate, including lifestyle differences, adultery, domestic violence, social issues, and economic problems [12]. Additionally, as the age at first marriage increases, so does the divorce rate. This trend results in a greater number of adolescents living in divorced families [11].

Numerous studies have recently investigated the prevalence of mental health issues; however, the findings in the general adolescent population may not accurately represent the situation for those living in families affected by separation

### HIGHLIGHTS

- This is the first comprehensive survey examining the mental health of adolescents living in families with separated or divorced parents in urban Vietnam.
- Nearly half of the surveyed adolescents reported experiencing negative emotional states, such as stress, anxiety, and depression, as measured by the depression anxiety stress scale-21.
- The duration of family separation or divorce, low socioeconomic status, experience of bullying, and engagement in risky health behaviors were identified as significant predictors of poor mental health among the surveyed population.

or divorce. To our knowledge, this is the first study to be conducted on this subject. In terms of practical implications, the present research is anticipated to provide evidence for more effective interventions to address mental health issues in this population.

### Aims

The aims of this study were to ascertain the prevalence of stress, anxiety, and depression among middle and high school adolescents with separated or divorced parents, utilizing the depression anxiety stress scale-21 (DASS-21) tool, and to pinpoint the factors influencing mental health among the study participants.

## Materials and Methods

### Participants and Study Design

In October 2022, a cross-sectional study was conducted at 2 middle schools and 2 high schools in Hue City, Vietnam. A total of 342 students were invited to participate; however, 33 were excluded due to non-response or refusal by their guardians. Consequently, 309 eligible participants met the inclusion criteria, which included adolescent age, parental divorce/ separation, and approval from both students and guardians.

### Minimal Sample Size Calculation

In this study, we used the single proportion formula with a 95% confidence interval (CI) to calculate the sample size. This calculation was based on the previous prevalence rates of each DASS-21 subscale item among high school students in Hue City: 46.1% for stress, 68.2% for anxiety, and 49.6% for depression [14]. We aimed for a precision level of 6%, which resulted in a calculated sample size of 267. Considering a maximum non-response rate of 15%, the final calculated sample size was adjusted to 314 participants. Ultimately, we collected data from 309 of the 342 invited high school students who chose to participate in this study.

### Data Collection Process

All students from separated or divorced families were invited to participate. We used convenience sampling to select 4 schools from a total of 26 public middle and high schools for inclusion in the study.

The data collection for this study was carried out in several stages. Initially, a pilot survey was conducted among 20 high school students to assess the content and flow of the questionnaire. Subsequently, middle and high school teachers were enlisted to help identify potential participants. Data collectors were then trained in data collection techniques and addressing questions regarding the questionnaire. Students were provided with an information sheet and a consent form, which required the signature of their parents or guardians before participating in the survey. Once consent was obtained, students completed the survey using a self-administered questionnaire enclosed in an envelope. Upon completion, each student sealed the responses in the envelope and returned it to the collaborating teacher. The research supervisor then reviewed all questionnaires before submitting them to the principal investigator. In cases where students exhibited mild to severe symptoms, their teachers, parents, or guardians were notified, and the students were referred to free psychological counseling services.

### Variables and Measurement

#### Dependent variables

Three mental health problems—stress, anxiety, and depression—were measured using the DASS, specifically the DASS-21 scale, a well-known self-report form. This measurement tool has been well-validated and widely used in various populations in Vietnam, including adolescents [15]. The aim of the DASS-21 is to detect stress, anxiety, and depression in both clinical and non-clinical settings. The scale consists of 21 items, divided into 3 subscales of 7 items each: depression, anxiety, and stress. Respondents rated each item on a 4-point Likert scale, ranging from 0 (indicating that the item did not apply to them at all) to 3 (indicating that the item applied most of the time). The total score for each subscale was calculated by summing the scores of the 7 items, with a range of 0 to 21; higher scores indicated greater severity. For classification purposes, the suggested thresholds for each subscale were as follows [16]. For stress, scores of 0 to 14 were interpreted as normal, 15 to 18 as mild, 19 to 25 as moderate, and ≥26 as severe; participants with scores greater than 17 were considered to have stress. For anxiety, scores of 0 to 7 were considered normal, 8 to 9 mild, 10 to 14 moderate, and ≥15 severe; a score greater than 7 was interpreted as indicating anxiety. For depression, scores of 0–9 were interpreted as normal, 10 to 13 as mild, 14 to 20 as moderate, and ≥21 as severe; a score greater than 9 was considered to indicate having depression.

In our analysis, we calculated the sum of all 3 DASS-21 subscales—stress, anxiety, and depression—to represent a spectrum of mental health issues and provide an overall measure of the mental health burden among respondents.

#### Independent variables

Demographic information, including age, gender, birth



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order, and academic performance in the previous semester (average, good, or very good to excellent), as well as current living arrangements (living with mother or living with father), and school level (middle school [grades 6 to 9] or high school [grades 10 to 12]) was provided.

Information on parental and family structure encompassed the education level (illiteracy/primary school, middle school, high school, or higher) and occupation (teacher/healthcare professional/official, housewife/worker/farmer, or business) of both mother and father, the household economic status (poor to average or normal), and the number of years since separation or divorce.

Data on health-risk behaviors were also collected, including smoking (current smoking status), drinking (current drinking status), physical inactivity (measured by frequency and duration of activity per week, in accordance with World Health Organization recommendations), and engagement in fighting (frequency and involvement in physical altercations). Participants were also surveyed about their experiences of being bullied or physically assaulted. This questionnaire was recently used in the 2019 national survey among teenagers aged 13 to 17 years from the Global School-based Student Health Survey Vietnam [17].

### Data Analysis

The primary data were entered and analyzed using Stata ver. 16.0 (StataCorp LP), with *p*-values less than 0.05 considered to indicate statistical significance. Descriptive statistics, including frequencies, percentages, means, and standard deviations, were computed for all data. Due to significant differences in mental health problems between middle school and high school students, we stratified the results by school level when describing the prevalence of stress, anxiety, and depression. We combined all 3 DASS-21 subscales and classified them as ordinal categorical variables, with students grouped as follows: no mental health issues, only 1 issue, 2 of the 3 issues, and all 3 issues. Based on this outcome, we conducted a cumulative odds ordinal logistic regression with proportional odds to determine the relationship between factors and overall mental health problems. A multivariate binary logistic model was also employed to analyze the association between factors and individual subscales of the DASS-21. The Hosmer-Lemeshow test was utilized to evaluate the goodness of fit of the logistic regression model, enabling assessment regardless of the number and nature (quantitative or qualitative) of the independent variables.

### Ethical Consideration

The study received ethical approval from the Institutional Ethics Committee for Biomedical Research at Hue University of Medicine and Pharmacy in Hue City, Vietnam (code: H2021/424, dated 26/8/2021). The principals of each school granted permission to conduct the study. Before completion of the questionnaires, parents/guardians were given information about the study and asked to provide written informed consent. Participants were informed of their right to voluntarily participate in the study.

## Results

Table 1 displays the general characteristics of the study participants. Among the 309 schoolchildren, 56.6% were male, with an equal distribution of students across the school levels. Two-thirds of the total sample size originated from households classified as poor to average in economic status. A large proportion of participants were either the eldest or the youngest child in their family, and two-thirds resided with their mothers. Furthermore, the majority of students' parents had attained a high school education. The average duration of family separation or divorce was 3.02 years.

Regarding health-risk behaviors, 11.0% of students reported smoking, 42.7% reported alcohol consumption, and 68.0% reported physical inactivity. A high prevalence of alcohol use was noted among high school students.

Additionally, 8.7% of students reported involvement in fights, 8.1% indicated experiencing physical assault, and 5.5% reported being bullied. These rates were higher among middle school students.

As shown in Table 2, the DASS-21 scale indicated a prevalence of 49.2% for stress, while both anxiety and depression had similar prevalence rates of 61.5%. Among those experiencing anxiety and depression, 29.1% and 19.7% reported severe to extremely severe levels, respectively. Additionally, high school students exhibited a higher prevalence of mental health issues compared to middle school students. Notably, the proportion of high school students classified as having very severe anxiety was quite high, at 24.4%. A detailed distribution of all items can be found in Table 3.

Figure 1 depicts the prevalence of various mental health issues among the students. The survey revealed that 42.4% of the participating students experienced all 3 mental health problems, while 17.8% reported having 2 issues. Only 9.4% reported having a single mental health problem. Consequently, the overall percentage of students with mental health problems was 69.6%.

Table 4 presents the results of an ordered logistic regression analysis examining factors associated with an increased risk of mental health problems in the study population. The

**Table 1.** General demographics and health-risk behaviors among all study participants and by school ($n = 309$)

| Characteristic | Category | All | Middle school | High school | *p* |
|---|---|---|---|---|---|
| Sex | Male | 175 (56.6) | 100 (57.5) | 74 (42.5) | 0.74 |
| | Female | 134 (43.4) | 75 (55.6) | 60 (44.4) | |
| Age (y) | 12–15 | 184 (59.5) | 172 (98.9) | 2 (1.1) | |
| | 16–17 | 125 (40.5) | 12 (8.9) | 123 (91.1) | |
| | Mean ± SD | 14.83 ± 1.89 | | | |
| Household economic status | Good | 127 (41.1) | 84 (48.3) | 90 (51.7) | 0.004 |
| | Poor to average | 182 (58.9) | 43 (31.9) | 92 (68.1) | |
| Education | Middle school (grade 6–9) | 174 (56.3) | | | |
| | High school (grade 10–12) | 135 (43.7) | | | |
| Academic performance | Average | 61 (19.7) | 44 (25.3) | 17 (12.6) | 0.001 |
| | Good | 169 (54.7) | 80 (46.0) | 89 (65.9) | |
| | Very good to excellent | 79 (25.6) | 50 (28.7) | 29 (21.5) | |
| Mother's education | Primary school or not completed | 46 (14.9) | 18 (10.3) | 28 (20.7) | 0.005 |
| | Middle school | 50 (16.2) | 28 (16.1) | 22 (16.3) | |
| | High school | 76 (24.6) | 37 (21.3) | 39 (28.9) | |
| | Higher education | 137 (44.3) | 91 (52.3) | 46 (34.1) | |
| Mother's occupation | Teacher/healthcare professional/official | 98 (31.7) | 59 (33.9) | 39 (28.9) | 0.31 |
| | Housewife/worker/famer | 118 (38.2) | 60 (34.5) | 58 (43.0) | |
| | Business | 93 (30.1) | 55 (31.6) | 38 (28.1) | |
| Father's education | Primary school or not completed | 39 (12.6) | 19 (10.9) | 20 (14.8) | 0.089 |
| | Middle school | 59 (19.1) | 30 (17.2) | 29 (21.5) | |
| | High school | 83 (26.9) | 42 (24.1) | 41 (30.4) | |
| | Higher education | 128 (41.4) | 83 (47.7) | 45 (33.3) | |
| Father's occupation | Teacher/healthcare professional/official | 77 (24.9) | 48 (27.6) | 29 (21.5) | 0.010 |
| | Housewife/worker/famer | 170 (55.0) | 83 (47.7) | 87 (64.4) | |
| | Business | 62 (20.1) | 43 (24.7) | 19 (14.1) | |
| Order of child in the family | Only child | 64 (20.7) | 42 (24.1) | 22 (16.3) | 0.31 |
| | Oldest | 104 (33.7) | 59 (33.9) | 45 (33.3) | |
| | Middle | 48 (15.5) | 26 (14.9) | 22 (16.3) | |
| | Youngest | 93 (30.1) | 47 (27.0) | 46 (34.1) | |
| Year of divorce | Mean ± SD (range) | 3.02 ± 1.52 (1–6) | 3.029 ± 1.66 (1–6) | 2.94 ± 1.31 (1–6) | 0.422 |
| Parent lived with | Mother | 208 (67.3) | 113 (64.9) | 95 (70.4) | 0.31 |
| | Father | 101 (32.7) | 61 (35.1) | 40 (29.6) | |
| Smoking | No | 275 (89.0) | 158 (90.8) | 117 (86.7) | 0.25 |
| | Yes | 34 (11.0) | 16 (9.2) | 18 (13.3) | |
| Drinking | No | 177 (57.3) | 119 (68.4) | 58 (43.0) | < 0.001 |
| | Yes | 132 (42.7) | 55 (31.6) | 77 (57.0) | |
| Fighting | No | 282 (91.3) | 152 (87.4) | 130 (96.3) | 0.006 |
| | Yes | 27 (8.7) | 22 (12.6) | 5 (3.7) | |
| Being beaten | No | 284 (91.9) | 155 (89.1) | 129 (95.6) | 0.038 |
| | Yes | 25 (8.1) | 19 (10.9) | 6 (4.4) | |
| Being bullied | No | 292 (94.5) | 160 (92.0) | 132 (97.8) | 0.026 |
| | Yes | 17 (5.5) | 14 (8.0) | 3 (2.2) | |
| Physical inactivity | No | 99 (32.0) | 53 (30.5) | 46 (34.1) | 0.50 |
| | Yes | 210 (68.0) | 121 (69.5) | 89 (65.9) | |

Data are presented as *n* (%) unless otherwise specified.
SD, standard deviation.



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**Table 2.** Prevalence of stress, anxiety, and depression using DASS-21 scale and subscale by school level

| Symptom classification | No | Yes | Mild | Moderate | Severe | Very severe |
|---|---|---|---|---|---|---|
| All (*n* = 309) | | | | | | |
| Stress | 157 (50.8) | 152 (49.2) | 44 (14.2) | 63 (20.4) | 45 (14.6) | |
| Anxiety | 119 (38.5) | 190 (61.5) | 48 (15.5) | 52 (16.8) | 29 (9.4) | 61 (19.7) |
| Depression | 119 (38.5) | 190 (61.5) | 24 (7.8) | 105 (34.0) | 48 (15.5) | 13 (4.2) |
| Stress | | | | | | |
| Middle school | 117 (67.2) | 57 (32.8) | 21 (12.1) | 22 (12.6) | 14 (8.0) | |
| High school | 40 (29.6) | 95 (70.4) | 23 (17.0) | 41 (30.4) | 31 (23.0) | |
| Anxiety | | | | | | |
| Middle school | 91 (52.3) | 83 (47.7) | 20 (11.5) | 22 (12.6) | 13 (7.5) | 28 (16.1) |
| High school | 28 (20.7) | 107 (79.3) | 28 (20.7) | 30 (22.2) | 16 (11.9) | 33 (24.4) |
| Depression | | | | | | |
| Middle school | 96 (55.2) | 78 (44.8) | 11 (6.3) | 38 (21.8) | 22 (12.6) | 7 (4.0) |
| High school | 23 (17.0) | 112 (83.0) | 13 (9.6) | 67 (49.6) | 26 (19.3) | 6 (4.4) |

Data are presented as *n* (%).
DASS-21, depression anxiety stress scale-21.

analysis revealed several statistically significant predictors of various mental health problems, including poor to average economic status (adjusted odds ratio [aOR], 2.00; 95% CI, 1.21–3.31; $p = 0.007$); being in high school (aOR, 5.02; 95% CI, 2.93–8.60; $p < 0.001$); maternal occupation of teacher, healthcare professional, or official (aOR, 2.39; 95% CI, 1.13–5.03; $p = 0.022$); longer duration of family separation or divorce (aOR, 1.24; 95% CI, 1.05–1.45; $p = 0.009$); living with one's mother (aOR, 1.69; 95% CI, 1.03–2.76; $p = 0.04$); consuming alcohol (aOR, 1.70; 95% CI, 0.99–2.92; $p = 0.050$); and being bullied (aOR, 5.33; 95% CI, 1.10–25.69; $p = 0.037$).

The results of multivariate binary logistic regression for each subscale revealed that predictors of stress included poor to average economic status (aOR, 1.97; 95% CI, 1.07–3.62; $p = 0.029$); being in high school (aOR, 5.02; 95% CI, 2.74–9.18; $p < 0.001$); maternal occupation of teacher, healthcare professional, or official (aOR, 4.06; 95% CI, 1.59–10.39; $p = 0.003$); and current smoking (aOR, 3.15; 95% CI, 1.05–9.41; $p = 0.040$). A marginal association was observed between being bullied (aOR, 6.21; 95% CI, 0.99–38.94; $p = 0.051$) and experiencing stress.

The results of multivariate binary logistic regression regarding the predictors of anxiety revealed several significantly associated factors: poor to average economic status (aOR, 2.05; 95% CI, 1.13–3.72; $p = 0.018$); being in high school (aOR, 4.29; 95% CI, 2.31–7.97; $p < 0.01$); maternal middle school education level (aOR, 3.09; 95% CI, 1.04–9.20; $p = 0.043$); longer duration of family separation or divorce (aOR, 1.27; 95% CI, 1.06–1.53; $p = 0.011$); and current alcohol consumption (aOR, 2.00; 95% CI, 1.04–3.84; $p = 0.037$).

Several factors were found to be significantly associated with depression, including poor to average economic status (aOR, 2.75; 95% CI, 1.47–5.17; $p = 0.002$), being in high school (aOR, 6.28; 95% CI, 3.27–12.07; $p < 0.001$); longer duration of family separation or divorce (aOR, 1.22; 95% CI, 1.01–1.48; $p = 0.041$); living with one's mother (aOR, 2.40; 95% CI, 1.20–4.42; $p = 0.005$); current alcohol consumption (aOR, 2.73; 95% CI, 1.35–5.52; $p = 0.005$); and being bullied (aOR, 20.12; 95% CI, 1.49– 271.27; $p = 0.024$).

All 4 regression models underwent goodness-of-fit testing using the Hosmer-Lemeshow chi-square test. The *p*-values for all tests were determined to be greater than 0.05, indicating good fit for the models.

## Discussion

### Summary of Findings

This study was the first to investigate the prevalence of stress, anxiety, and depression among adolescents from separated or divorced families in Hue City, Vietnam and to identify associated factors. The results showed that 49.2%, 61.5%, and 61.5% of respondents reported experiencing stress, anxiety, and depression, respectively. Nearly half of the respondents reported negative emotional states across all 3 subscales (42.4%), while 7 in 10 reported encountering at least 1 of the 3 states. A high proportion of anxiety and depression cases were classified as severe or very severe. Several factors were found to be positively associated with an increased occurrence of mental health problems, including lower economic status; being a high school student; maternal occupation of teacher, healthcare professional, or official; longer duration of family separation or divorce; living with one's mother; drinking alcohol; and being bullied. Lower economic status and being a high school student were found to have significant independent associations with all 3 DASS-21 subscales. Additionally, being subjected to bullying was independently associated with increased levels of both

**Table 3.** Distribution of responses to all items in the DASS-21 scale

| Code | DASS-21 item | Did not apply to me at all | Applied to me to some degree or some of the time | Applied to me to a considerable degree or a good part of time | Applied to me very much or most of the time |
|---|---|---|---|---|---|
| Stress | | | | | |
| DA1 | I found it hard to wind down | 118 (38.2) | 88 (28.5) | 84 (27.2) | 19 (6.1) |
| DA6 | I tended to over-react to situations | 121 (39.2) | 112 (36.2) | 60 (19.4) | 16 (5.2) |
| DA8 | I felt that I was using a lot of nervous energy | 96 (31.1) | 109 (35.3) | 78 (25.2) | 26 (8.4) |
| DA11 | I found myself getting agitated | 145 (46.9) | 109 (35.3) | 46 (14.9) | 9 (2.9) |
| DA12 | I found it difficult to relax | 129 (41.7) | 85 (27.5) | 75 (24.3) | 20 (6.5) |
| DA14 | I was intolerant of anything that kept me from getting on with what I was doing | 86 (27.8) | 120 (38.8) | 78 (25.2) | 25 (8.1) |
| DA18 | I felt that I was rather touchy | 84 (27.2) | 90 (29.1) | 94 (30.4) | 41 (13.3) |
| | Total score | 7.15±4.5 | | | |
| Anxiety | | | | | |
| DA2 | I was aware of dryness of my mouth | 118 (38.2) | 121 (39.2) | 53 (17.2) | 17 (5.5) |
| DA4 | I experienced breathing difficulty (e.g., excessively rapid breathing, breathlessness in the absence of physical exertion) | 161 (52.1) | 93 (30.1) | 38 (12.3) | 17 (5.5) |
| DA7 | I experienced trembling (e.g., in the hands) | 150 (48.5) | 101 (32.7) | 32 (10.4) | 26 (8.4) |
| DA9 | I was worried about situations in which I might panic and make a fool of myself | 100 (32.4) | 104 (33.7) | 82 (26.5) | 23 (7.4) |
| DA15 | I felt I was close to panic | 163 (52.8) | 94 (30.4) | 33 (10.7) | 19 (6.1) |
| DA19 | I was aware of the action of my heart in the absence of physical exertion (e.g., sense of heart rate increase, heart missing a beat) | 176 (57.0) | 82 (26.5) | 39 (12.6) | 12 (3.9) |
| DA20 | I felt scared without any good reason | 169 (54.7) | 91 (29.4) | 41 (13.3) | 8 (2.6) |
| | Total score | 5.46±4.38 | | | |
| Depression | | | | | |
| DA3 | I couldn't seem to experience any positive feeling at all | 109 (35.3) | 101 (32.7) | 81 (26.2) | 18 (5.8) |
| DA5 | I found it difficult to work up the initiative to do things | 70 (22.7) | 103 (33.3) | 106 (34.3) | 30 (9.7) |
| DA10 | I felt that I had nothing to look forward to | 139 (45.0) | 74 (23.9) | 73 (23.6) | 23 (7.4) |
| DA13 | I felt downhearted and blue | 129 (41.7) | 101 (32.7) | 68 (22.0) | 11 (3.6) |
| DA16 | I was unable to become enthusiastic about anything | 103 (33.3) | 102 (33.0) | 90 (29.1) | 14 (4.5) |
| DA17 | I felt that I wasn't worth much as a person | 178 (57.6) | 85 (27.5) | 34 (11.0) | 12 (3.9) |
| DA21 | I felt that life was meaningless | 174 (56.3) | 82 (26.5) | 39 (12.6) | 14 (4.5) |
| | Total score | 6.46±4.23 | | | |

Data are presented as *n* (%) or mean±standard deviation.
DASS-21, depression anxiety stress scale-21.

stress and depression. Furthermore, residing in a separated or divorced family for an extended period and current alcohol consumption were associated with a higher risk of experiencing depression and anxiety. Finally, having a mother employed as a teacher, healthcare professional, or official and current smoking were independently linked to elevated stress levels.

## Previous Findings Globally and in Vietnam

Research on the effects of parental divorce/separation on adolescents has been relatively scarce in the public health literature. The authors endeavored to collect all relevant documents pertaining to this subject within the context of Vietnam, but we discovered only a small number of studies. In one past study, Son et al. [18] investigated prevalent

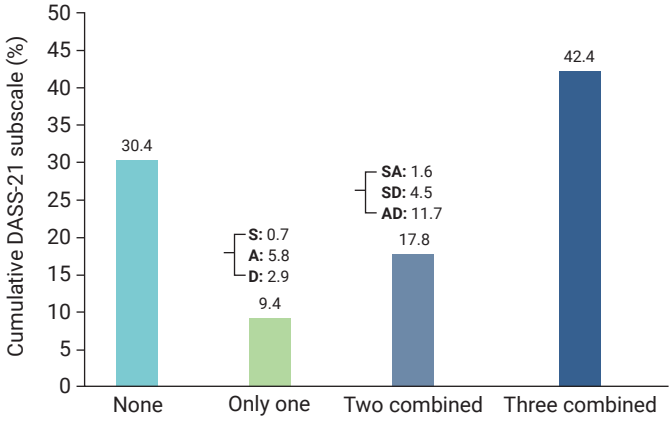


**Figure 1.** Prevalence (%) of mental health issues among middle and high school students (*n*=309).
DASS-21, depression anxiety stress scale-21; S, stress; A, anxiety; D, depression.



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**Table 4.** Factors associated with mental health problems: multivariate ordered logistic and binary logistic regression

| Factor | Combination[a] | | Stress[b] | | Anxiety[b] | | Depression[b] | |
|---|---|---|---|---|---|---|---|---|
| | aOR (95% CI) | *p* | OR (95% CI) | *p* | OR (95% CI) | *p* | OR (95% CI) | *p* |
| Sex (ref: male) | | | | | | | | |
| Female | 1.27 (0.78–2.07) | 0.332 | 1.59 (0.89–2.86) | 0.118 | 1.02 (0.58–1.80) | 0.935 | 1.25 (0.69–2.28) | 0.465 |
| Household economic status (ref: good) | | | | | | | | |
| Poor to average | 2.00 (1.21–3.31)[c] | 0.007[c] | 1.97 (1.07–3.62)[c] | 0.029[c] | 2.05 (1.13–3.72)[c] | 0.018[c] | 2.75 (1.47–5.17)[c] | 0.002[c] |
| Academic school (ref: middle) | | | | | | | | |
| High school | 5.02 (2.93–8.60)[c] | < 0.001[c] | 5.02 (2.74–9.18)[c] | < 0.001[c] | 4.29 (2.31–7.97)[c] | < 0.001[c] | 6.28 (3.27–12.07)[c] | < 0.001[c] |
| Academic performance (ref: good) | | | | | | | | |
| Average | 1.10 (0.59–2.07) | 0.758 | 0.74 (0.34–1.59) | 0.439 | 0.98 (0.46–2.06) | 0.954 | 1.63 (0.74–3.57) | 0.222 |
| Very good to excellent | 0.73 (0.42–1.29) | 0.284 | 0.70 (0.36–1.36) | 0.297 | 0.76 (0.39–1.46) | 0.412 | 0.76 (0.38–1.53) | 0.446 |
| Mother's education (ref: primary school or less) | | | | | | | | |
| Middle school | 1.67 (0.70–4.01) | 0.251 | 1.11 (0.39–3.19) | 0.845 | 3.09 (1.04–9.20)[c] | 0.043[c] | 1.48 (0.49–4.48) | 0.491 |
| High school | 1.80 (0.78–4.16) | 0.168 | 1.49 (0.54–4.08) | 0.439 | 1.89 (0.70–5.12) | 0.212 | 1.63 (0.57–4.72) | 0.364 |
| Higher education | 0.80 (0.32–2.00) | 0.630 | 0.53 (0.17–1.65) | 0.275 | 1.28 (0.43–3.85) | 0.657 | 0.83 (0.26–2.70) | 0.763 |
| Mother's occupation (ref: business) | | | | | | | | |
| Housewife/worker/famer | 0.84 (0.48–1.47) | 0.540 | 0.94 (0.46–1.91) | 0.866 | 0.82 (0.42–1.61) | 0.560 | 0.81 (0.40–1.63) | 0.555 |
| Teacher/healthcare professional/official | 2.39 (1.13–5.03)[c] | 0.022[c] | 4.06 (1.59–10.39)[c] | 0.003[c] | 1.62 (0.69–3.81) | 0.266 | 1.96 (0.80–4.82) | 0.142 |
| Father's education (ref: primary school or less) | | | | | | | | |
| Middle school | 0.68 (0.28–1.62) | 0.382 | 0.79 (0.28–2.22) | 0.659 | 0.68 (0.24–1.91) | 0.467 | 0.64 (0.22–1.91) | 0.424 |
| High school | 0.46 (0.20–1.09) | 0.079 | 0.46 (0.17–1.30) | 0.144 | 0.60 (0.22–1.64) | 0.318 | 0.52 (0.18–1.52) | 0.232 |
| Higher education | 0.61 (0.24–1.55) | 0.299 | 0.58 (0.19–1.74) | 0.330 | 0.78 (0.26–2.29) | 0.650 | 0.73 (0.23–2.32) | 0.597 |
| Father's occupation (ref: business) | | | | | | | | |
| Housewife/worker/famer | 0.83 (0.45–1.53) | 0.544 | 0.85 (0.40–1.79) | 0.664 | 0.83 (0.40–1.73) | 0.620 | 0.80 (0.38–1.71) | 0.567 |
| Teacher/healthcare professional/official | 0.66 (0.29–1.48) | 0.312 | 0.51 (0.19–1.4) | 0.192 | 0.98 (0.38–2.56) | 0.974 | 0.71 (0.26–1.94) | 0.504 |
| Order of child in the family (ref: only child) | | | | | | | | |
| Oldest | 1.32 (0.67–2.57) | 0.423 | 1.65 (0.75–3.62) | 0.216 | 1.38 (0.63–2.99) | 0.419 | 0.75 (0.33–1.72) | 0.503 |
| Middle | 1.33 (0.62–2.87) | 0.465 | 0.75 (0.30–1.91) | 0.548 | 2.38 (0.92–6.20) | 0.075 | 1.08 (0.41–2.88) | 0.876 |
| Youngest | 1.58 (0.81–3.08) | 0.178 | 1.54 (0.70–3.38) | 0.284 | 1.53 (0.71–3.30) | 0.277 | 0.93 (0.41–2.10) | 0.859 |
| Year of divorce | 1.24 (1.05–1.45)[c] | 0.009[c] | 1.1 (0.91–1.32) | 0.332 | 1.27 (1.06–1.53)[c] | 0.011[c] | 1.22 (1.01–1.48)[c] | 0.041[c] |
| Parent lived with (ref: father) | | | | | | | | |
| Mother | 1.69 (1.03–2.76)[c] | 0.04[c] | 1.29 (0.72–2.32) | 0.394 | 1.35 (0.76–2.40) | 0.302 | 2.40 (1.20–4.42)[c] | 0.005[c] |
| Current smoking (ref: no) | | | | | | | | |
| Yes | 2.03 (0.81–5.07) | 0.130 | 3.15 (1.05–9.41)[c] | 0.040[c] | 1.15 (0.40–3.26) | 0.796 | 1.27 (0.41–3.91) | 0.679 |
| Current drinking (ref: no) | | | | | | | | |
| Yes | 1.70 (0.99–2.94)[c] | 0.050[c] | 1.48 (0.79–2.79) | 0.223 | 2.00 (1.04–3.84)[c] | 0.037[c] | 2.73 (1.35–5.52)[c] | 0.005[c] |

(Continued to the next page)

**Table 4.** Continued

| Factor | Combination[a] | | Stress[b] | | Anxiety[b] | | Depression[b] | |
|---|---|---|---|---|---|---|---|---|
| | aOR (95% CI) | *p* | OR (95% CI) | *p* | OR (95% CI) | *p* | OR (95% CI) | *p* |
| Being beaten (ref: no) | | | | | | | | |
| Yes | 0.93 (0.27–3.21) | 0.908 | 0.72 (0.17–3.12) | 0.660 | 1.92 (0.41–9.06) | 0.410 | 0.91 (0.18–4.57) | 0.908 |
| Being bullied (ref: no) | | | | | | | | |
| Yes | 5.33 (1.10–25.69)[c] | 0.037[c] | 6.21 (0.99–38.94)[c] | 0.051[c] | 5.24 (0.67–40.78) | 0.114 | 20.12 (1.49–271.27)[c] | 0.024[c] |
| Fighting (ref: no) | | | | | | | | |
| Yes | 1.63 (0.54–4.91) | 0.387 | 2.94 (0.82–10.55) | 0.098 | 0.73 (0.21–2.55) | 0.624 | 1.09 (0.28–4.19) | 0.900 |
| Physical inactivity (ref: no) | | | | | | | | |
| Yes | 0.68 (0.39–1.16) | 0.154 | 0.56 (0.29–1.08) | 0.081 | 0.57 (0.30–1.10) | 0.094 | 0.66 (0.33–1.32) | 0.240 |
| /cut1 | 1.34 (−0.07 to 2.75) | | | | | | | |
| /cut2 | 1.91 (0.49–3.32) | | | | | | | |
| /cut3 | 2.89 (1.45–4.33) | | | | | | | |
| Hosmer-Lemeshow $\chi^2$ | $\chi^2$ = 26.43, $p$ = 0.439, $pR^2$ = 24.2% | | $\chi^2$ = 6.41, $p$ = 0.600, $pR^2$ = 24.3% | | $\chi^2$ = 5.04, $p$ = 0.754, $pR^2$ = 19.5% | | $\chi^2$ = 4.91, $p$ = 0.767, $pR^2$ = 26.0% | |

aOR, adjusted odds ratio; OR, odds ratio; CI, confidence interval; ref, reference.
[a]Ordered logistic regression model. [b]Binary logistic regression model. [c]Statistical significance.

psychological challenges and determined that children from non-intact families undergo psychological trauma. This trauma is evident in their emotions and attitudes towards both their family and their social lives.

Our study is unique in that it is the first to examine mental health issues among this specific group. We compared the rates of depression, anxiety, and stress to those of the general population to identify any differences. A survey conducted among students aged 11 to 18 years (grades 6 to 11) found that approximately 26% reported a moderate to high risk of experiencing mental health issues [19]. Another study with a sample of 403 participants aged 12 to 17 years reported an overall rate of mental health problems of 33.1% [2]. When compared to similar instruments used to identify depression, anxiety, and stress among the general adolescent and high school populations, the DASS-21 subscale item rates were higher in our study (generally above 70% in high school and greater than 32% to 45% in middle school). For example, Huong et al. [14] reported rates of depression, anxiety, and stress (measured using the DASS-21) at 46.1%, 68.2%, and 49.6%, respectively, among high school students. Moreover, 32.7% of the students reported experiencing all 3 conditions (depression, anxiety, and stress). In 2 other studies in Hanoi among middle school students, the prevalence of depression (identified using DASS-21) was 27% [20], anxiety 38%, and stress 33% [3]. Studies conducted globally have demonstrated that divorce can significantly impact the mental health of adolescents, increasing their risk of developing symptoms of anxiety, depression, and stress. For instance, a study conducted in Lebanon found that 57.1% and 45.8% of adolescents from divorced families reported experiencing depression and social anxiety, respectively [21].

The findings of this study are of utmost importance, as the high self-report rate serves as an alarming indicator of an underlying issue that demands urgent attention. Considering the high prevalence of mental health problems among adolescents with separated or divorced parents, early screening, diagnosis, and treatment should be integrated into routine health check-up programs. Furthermore, providing counseling support at school is an essential initial step, particularly since the understanding of students' mental health, especially for those with separated or divorced parents, remains incomplete. Previous studies have identified adolescents as a particularly susceptible group to experiencing stressful events, such as parental divorce [22,23]. This vulnerability is attributed to the numerous physical, mental, emotional, and social changes that transpire during this developmental stage, which can influence future health patterns [24,25]. Our findings align with these previous studies.



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### Factors Associated with Mental Health Problems

The study findings revealed significant associations between multiple factors and both the cumulative scale and individual subscales of the DASS-21. These findings align with prior research that has identified similar risk factors for mental health issues among adolescents. However, the study results also emphasize the distinct characteristics of individuals whose parents are separated or divorced.

In this study, we discovered that a longer duration of separation or divorce was associated with a 24% increased risk of mental health issues. This finding aligns with numerous longitudinal studies that have demonstrated significant increases in emotional and behavioral problems among adolescents following parental divorce, which persist over time [26,27]. These effects can be enduring and underscore the necessity of providing improved care for children of divorced parents [28].

Several studies have indicated that children who experience parental divorce at an older age generally exhibit less severe issues relative to those who experience it at a younger age [29]. However, our research did not uncover any statistically significant relationship between child age and the prevalence of mental health problems. Furthermore, we observed a significant difference between middle school and high school students. This observation aligns with a study carried out by Ho et al. [30] in the same city, which suggests that life satisfaction significantly contributes to moderating the indirect impact of academic stress on depressive disorders, particularly among high school students.

Our findings specifically indicate that children living with their mothers had a 1.69 times higher likelihood of experiencing mental health problems compared to those living with their fathers, a relationship that was particularly strong for depression (2.4 times higher). Although parental concern is often considered to reduce the risk of poor well-being in adolescents, excessive and overprotective maternal concerns due to increased risks, such as assault, suicidal ideation, and loneliness, have been strongly associated with mental health difficulties [31–33]. A longitudinal follow-up study in Norway discovered that the absence of a father figure in the family increased the risk of depression and anxiety, especially in boys [34]. However, our study did not investigate the level of attention provided by parents, which is a limitation.

Moreover, this study revealed that students whose mothers possessed high stability and knowledge of labor occupations also experienced an increased risk of stress. This can be attributed to the Asian social context, in which high academic and societal expectations exist for children. This leads to heightened pressure in school and life, ultimately contributing to increased stress [19,35].

The study results indicate that household economic status is a significant family factor associated with an increased risk of mental health issues, as indicated by both cumulative scores and each of the 3 individual subscales. This finding aligns with previous studies that emphasize family income as an important factor in this relationship [2,19,36]. It is widely acknowledged that low socioeconomic status during childhood negatively impacts psychological development and well-being [37]. Furthermore, economic issues within families may lead to separation or divorce, resulting in higher rates of these occurrences [11]. Providing social services to educate and support positive parenting practices in families facing economic challenges could be a valuable resilience strategy [38].

The study identified early alcohol consumption as a major consequence of parental divorce, which contributes to an increased risk of mental health issues in children, particularly anxiety and depression [39,40]. Furthermore, bullying was strongly associated with a higher risk of depression, as demonstrated by studies in Vietnam [41–43]. Another study by Obeid et al. [21] discovered that adolescents with divorced parents were relatively likely to experience social fear and avoidance, depression, and suicidal ideation. These findings underscore the importance of school and community mental health intervention programs devoting greater attention to this vulnerable population and incorporating risk reduction strategies into their plans.

The results of this study offer numerous suggestions for intervention and future research. Considering the high prevalence of stress, anxiety, and depression among adolescents from separated or divorced families, it is essential to provide mental health services to these young individuals.

Future research can build upon the findings of the current study by examining the specific mechanisms through which family factors affect adolescent mental health outcomes. Longitudinal studies can aid in establishing causal relationships between these factors and mental health outcomes, while qualitative studies can offer a deeper understanding of the experiences of adolescents from separated or divorced families. Furthermore, future research can explore the influence of cultural factors on adolescent mental health outcomes in divorced families, as cultural norms and values may significantly impact the experiences of adolescents in this context.

The current study had several limitations that should be considered when interpreting the results. First, the cross-sectional design of the study and the combined mental health outcome limited our ability to establish causal relationships

between the variables of interest. Second, selection bias may have been present due to the exclusion of private schools from this study. Furthermore, the class teacher's sample list was used to confirm the separation and divorce status of the minor's parents, which somewhat restricted the definition, as it did not require specific certification. Finally, the use of a questionnaire may have introduced information bias due to potential difficulties in understanding the questions and overestimation or underestimation of symptoms, which could result in inaccuracies. Despite these limitations, the study had a notable strength in that it is the first to be conducted among this vulnerable group, providing a more detailed understanding that will support the future development of prevention and intervention strategies. Additionally, we received enthusiastic support from the class teachers, school principals, and even a student council president during the study.

## Conclusion

The results of our study suggest that adolescents whose parents are separated or divorced have an increased risk of encountering mental health issues. This highlights the importance of implementing suitable prevention programs to assist them during this emotionally difficult period, particularly for those living with their mothers, experiencing low socioeconomic status, and participating in risky behaviors.

## Notes

### Ethics Approval

The study received ethical approval from the Institutional Ethics Committee for Biomedical Research at Hue University of Medicine and Pharmacy in Hue City, Vietnam (code: H2021/424, dated 26/8/2021). The principals of each school granted permission to conduct the study. Before completing the questionnaires, parents/guardians were given information about the study and asked to provide written informed consent. Participants were informed of their right to voluntarily participate in the study.

### Conflicts of Interest

The authors have no conflicts of interest to declare.

### Funding

The research was supported by funding from Hue University (DHH 2021-04-155).

### Availability of Data

The datasets are not publicly available; however, they can be obtained from the corresponding author upon reasonable request.

### Authors' Contributions

Conceptualization: BTT, MTuN, MTaN; Data curation: MTuN, VNHD, TTMT, TGN; Formal analysis: BTT, MTuN, TGN; Funding acquisition: all authors; Methodology: BTT, MTaN; Project administration: VNHD, TTMT; Visualization: VNHD, TTMT, TGN; Writing–original draft: BTT, MTuN, MTaN; Writing–review & editing: all authors. All authors read and approved the final manuscript.

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Short Communication

# Epidemiological characteristics of carbapenemase-producing *Enterobacteriaceae* outbreaks in the Republic of Korea between 2017 and 2022

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## ABSTRACT

**Objectives:** We aimed to describe the epidemiological characteristics of carbapenemase-producing *Enterobacteriaceae* (CPE) outbreaks in healthcare settings in the Republic of Korea between 2017 and 2022.

**Methods:** Under the national notifiable disease surveillance system, we obtained annual descriptive statistics regarding the isolated species, carbapenemase genotype, healthcare facility type, outbreak location and duration, and number of patients affected and recommended interventions. We used epidemiological investigation reports on CPE outbreaks reported to Korea Disease Control and Prevention Agency from June 2017 to September 2022.

**Results:** Among the 168 reports analyzed, *Klebsiella pneumoniae* (85.1%) was the most frequently reported species, while *K. pneumoniae* carbapenemase (KPC, 82.7%) was the most common carbapenemase genotype. Both categories increased from 2017 to 2022 ($p < 0.01$). General hospitals had the highest proportion (54.8%), while tertiary general hospitals demonstrated a decreasing trend ($p < 0.01$). The largest proportion of outbreaks occurred exclusively in intensive care units (ICUs, 44.0%), and the frequency of concurrent outbreaks in ICUs and general wards increased over time ($p < 0.01$). The median outbreak duration rose from 43.5 days before the coronavirus disease 2019 (COVID-19) pandemic (2017–2019) to 79.5 days during the pandemic (2020–2022) ($p = 0.01$), and the median number of patients associated with each outbreak increased from 5.0 to 6.0 ($p = 0.03$). Frequently recommended interventions included employee education (38.1%), and 3 or more measures were proposed for 45.2% of outbreaks.

**Conclusion:** In the Republic of Korea, CPE outbreaks have been consistently dominated by *K. pneumoniae* and KPC. The size of these outbreaks increased during the COVID-19 pandemic. Our findings highlight the need for continuing efforts to control CPE outbreaks using a multimodal approach, while considering their epidemiology.

**Keywords:** Carbapenem-resistant *Enterobacteriaceae*; Disease outbreaks; Drug resistance; *Klebsiella pneumoniae*; Public health surveillance; Republic of Korea

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## Introduction

Carbapenem-resistant *Enterobacteriaceae* (CRE) frequently exhibit a wide spectrum of antibiotic resistance, which restricts treatment options and leads to various infections, including urinary tract infections, pneumonia, and sepsis [1,2]. Among CRE strains, carbapenemase-producing *Enterobacteriaceae* (CPE) can transfer resistance genes to other Gram-negative bacilli through plasmids or other mechanisms, resulting in more rapid dissemination than non-CPE isolates [3].

A CPE strain was first identified in a healthcare facility in the Republic of Korea on December 3, 2010 [4], underscoring specific public health and clinical priorities. Consequently, all CRE cases have been classified as notifiable diseases across all healthcare facilities since June 3, 2017 [5,6]. According to data from the mandatory surveillance system of the Korea Disease Control and Prevention Agency (KDCA), the number of patients with CRE in healthcare facilities has steadily risen over time, increasing from 15,369 in 2019 to 23,311 in 2021. The percentage of CPE among patients with CRE has also demonstrated an annual upward trend, growing from 57.8% in 2019 to 63.4% in 2021 [7]. This increase aligned with a rising trend in ertapenem resistance among *Klebsiella pneumoniae* isolated from blood; this rate grew from 1.1% in 2019 to 6.8% in 2021, according to data from the Korean Global Antimicrobial Surveillance System [8].

To manage CPE, which is known to significantly impact the spread of CRE [3], the KDCA collects data on all epidemiological investigations conducted by local governments (17 cities and provinces) related to CPE outbreaks [6]. Our study was designed to describe the epidemiological characteristics of CPE outbreaks in healthcare settings by analyzing the epidemiological investigation data reported to the KDCA between June 2017 and September 2022, following the transition to a mandatory surveillance system.

**HIGHLIGHTS**

- In the Republic of Korea, carbapenemase-producing *Enterobacteriaceae* outbreaks in healthcare settings were dominated consistently by *Klebsiella pneumoniae and K. pneumoniae* carbapenemase from 2017–2022.
- Duration and number of patients related to each outbreak significantly increased during the coronavirus disease 2019 pandemic (2020–2022) compared with that in the pre-pandemic period (2017–2019).
- Multimodal approaches were simultaneously recommended for interventions following a number of epidemiological investigations of carbapenemase-producing *Enterobacteriacea*e outbreaks.

## Materials and Methods

### National Surveillance of CPE Outbreaks

In the Korean Notifiable Disease Surveillance System, CRE is defined as *Enterobacteriaceae* resistant to at least 1 carbapenem-based antibiotic (including imipenem, meropenem, ertapenem, and doripenem), as identified in clinical samples from healthcare settings, regardless of patient symptoms. All CRE-positive samples must be tested for carbapenemase, as CPE is strictly defined as carbapenemase-producing CRE. When 2 or more patients with CPE and epidemiological links are reported at a healthcare facility, epidemiologists of the city or province are required to conduct an investigation in accordance with the Guidelines for Healthcare-Associated Infectious Diseases [6].

### Database

We obtained data on CPE outbreaks from the KDCA mandatory surveillance system database. Epidemiological investigators from cities or provinces are required to report outbreaks at healthcare facilities to this system. Patient identification and sensitive information are not collected.

### Case Definitions

A CPE outbreak was defined as the presence of at least 2 patients with CPE and epidemiological associations within a healthcare facility, as investigated by local epidemiologists between June 2017 and September 2022. As of October 1, 2022, the KDCA had received reports of 192 cases. From these, we excluded cases with incorrect records of outbreak duration ($n$=10) and number of patients ($n$=7), cases determined not to be part of an outbreak following epidemiological investigation ($n$=5), and duplicate cases ($n$=2). As a result, a total of 168 reports were included in the analysis (Figure 1).

### Classification of Variables

Healthcare facilities were categorized according to the Medical Service Act as follows: tertiary general hospitals, general hospitals, hospitals, and intermediate care hospitals. General hospitals included healthcare facilities with 100 or more beds, with those possessing a high level of expertise in treating severe diseases designated as tertiary general hospitals. Hospitals comprised healthcare facilities with 30 or more beds; among these, institutions that

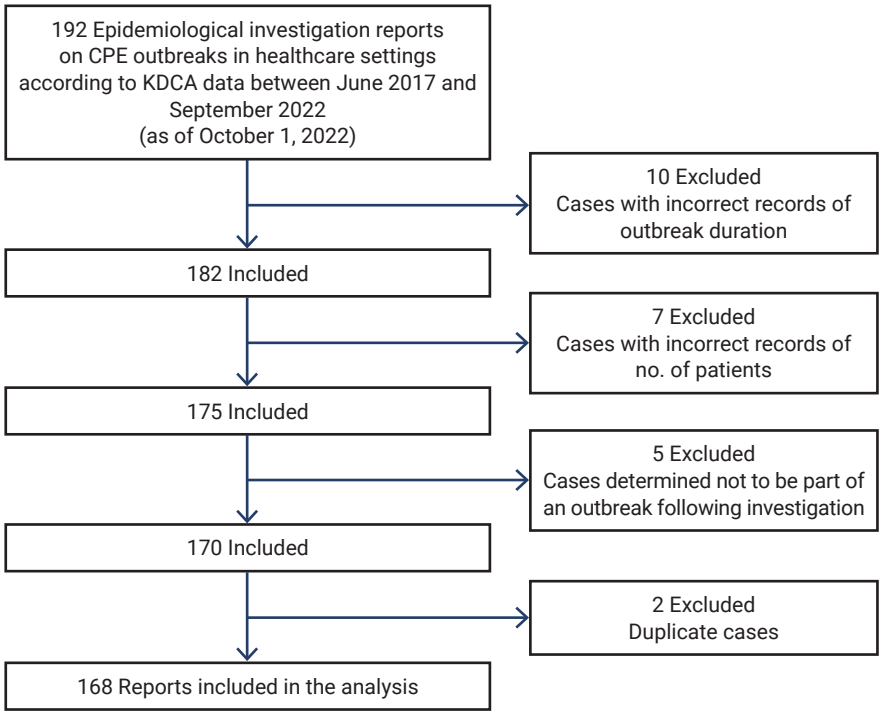


**Figure 1.** Flow diagram of study selection.
CPE, carbapenemase-producing *Enterobacteriaceae*; KDCA, Korea Disease Control and Prevention Agency.

provided care for patients with geriatric or chronic diseases, as well as patients recovering from surgery or injury, were classified as intermediate care hospitals.

Local epidemiologists recommended intervention measures following epidemiological investigations of CPE outbreaks. In our study, these measures were categorized based on the type of infection prevention and control (IPC), consistent with the descriptive content of each report. After accounting for the IPC strategies for CPE at the facility level [3,9–11] and the current state of Korean healthcare facilities, we selected the following categories: education of employees, including caregivers; active surveillance of high-risk groups; contact precautions; environmental cleaning; screening of patients with CRE contacts; patient isolation or cohorting; support for staff and infrastructure; surveillance of environmental cultures; on-site monitoring; improvement of bed density; timely notification of patients with CRE to the KDCA; and antibiotic stewardship. Two independent researchers participated in the categorization process, and when disagreements occurred, a final decision was made through discussion.

### Statistical Analysis

We present annual descriptive statistics on the isolated species, carbapenemase genotype, healthcare facility type, outbreak location and duration, and number of patients associated with CPE outbreaks. Additionally, we display the frequency of each recommended intervention following the epidemiological investigation, according to the type of healthcare facility. Variables are presented as either the number and percentage of outbreaks or the median and interquartile range (IQR). The Cochran-Armitage test (a yearly trend analysis adjusted for the number of outbreaks on a 12-month scale) or the Fisher exact test was utilized to compare categorical variables. For continuous variables that did not meet the normality assumption, the Mann-Whitney U-test was performed. The significance level was set at $p < 0.05$, and R statistical software ver. 4.2.0 (The R Foundation) was employed for the statistical analysis.

### Ethics Approval

This study received approval from the Institutional Review Board (IRB) of the KDCA (IRB No: 2023-01-02-PE-A) and was conducted in accordance with the principles of the Declaration of Helsinki.

## Results

A total of 168 epidemiological investigations of CPE outbreaks in healthcare settings were reported to the KDCA between June 2017 and September 2022 (Table 1).

### Clinical Characteristics of CPE Outbreaks

The most frequently isolated species was *K. pneumoniae* (143


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**Table 1.** Epidemiological characteristics of CPE outbreaks in healthcare settings as reported to the KDCA from June 2017–September 2022

| Characteristic | Total (*n* = 168) | 2017 (Jun.–Dec.) (*n* = 3) | 2018 (*n* = 35) | 2019 (*n* = 28) | 2020 (*n* = 15) | 2021 (*n* = 37) | 2022 (Jan.–Sep.) (*n* = 50) |
|---|---|---|---|---|---|---|---|
| Isolated species | | | | | | | |
| *Klebsiella pneumoniae* | 143 (85.1) | 1 (33.3) | 28 (80.0) | 21 (75.0) | 13 (86.7) | 35 (94.6) | 45 (90.0) |
| *Escherichia coli* | 51 (30.4) | 2 (66.7) | 7 (20.0) | 10 (35.7) | 2 (13.3) | 16 (43.2) | 14 (28.0) |
| *Enterobacter* spp. | 14 (8.3) | 0 (0) | 2 (5.7) | 2 (7.1) | 1 (6.7) | 4 (10.8) | 5 (10.0) |
| *Citrobacter* spp. | 14 (8.3) | 0 (0) | 1 (2.9) | 2 (7.1) | 2 (13.3) | 4 (10.8) | 5 (10.0) |
| *Klebsiella oxytoca* | 6 (3.6) | 0 (0) | 0 (0) | 1 (3.6) | 1 (6.7) | 1 (2.7) | 3 (6.0) |
| Other *Enterobacteriaceae* spp. | 7 (4.2) | 0 (0) | 2 (5.7) | 0 (0) | 0 (0) | 2 (5.4) | 3 (6.0) |
| Carbapenemase genotype | | | | | | | |
| KPC | 139 (82.7) | 1 (33.3) | 27 (77.1) | 19 (67.9) | 11 (73.3) | 35 (94.6) | 46 (92.0) |
| NDM | 47 (28.0) | 1 (33.3) | 7 (20.0) | 8 (28.6) | 4 (26.7) | 10 (27.0) | 17 (34.0) |
| OXA | 17 (10.1) | 2 (66.7) | 3 (8.6) | 4 (14.3) | 1 (6.7) | 1 (2.7) | 6 (12.0) |
| GES | 2 (1.2) | 0 (0) | 2 (5.7) | 0 (0) | 0 (0) | 0 (0) | 0 (0) |
| Healthcare facility type | | | | | | | |
| Tertiary general hospital | 27 (16.1) | 1 (33.3) | 11 (31.4) | 6 (21.4) | 2 (13.3) | 5 (13.5) | 2 (4.0) |
| General hospital | 92 (54.8) | 1 (33.3) | 19 (54.3) | 13 (46.4) | 6 (40.0) | 20 (54.1) | 33 (66.0) |
| Hospital | 19 (11.3) | 1 (33.3) | 1 (2.9) | 1 (3.6) | 4 (26.7) | 4 (10.8) | 8 (16.0) |
| Intermediate care hospital | 30 (17.9) | 0 (0) | 4 (11.4) | 8 (28.6) | 3 (20.0) | 8 (21.6) | 7 (14.0) |
| Outbreak location | | | | | | | |
| ICU | 74 (44.0) | 1 (33.3) | 20 (57.1) | 12 (42.9) | 9 (60.0) | 15 (40.5) | 17 (34.0) |
| General ward | 58 (34.5) | 1 (33.3) | 11 (31.4) | 13 (46.4) | 6 (40.0) | 14 (37.8) | 13 (26.0) |
| Both[a)] | 36 (21.4) | 1 (33.3) | 4 (11.4) | 3 (10.7) | 0 (0) | 8 (21.6) | 20 (40.0) |
| Outbreak duration (d) | 61.0 (26.8–121.0) | 62.0 (52.5–62.5) | 49.0 (22.0–77.5) | 35.0 (19.5–80.0) | 84.0 (23.0–154.0) | 60.0 (34.0–121.0) | 83.0 (29.5–162.2) |
| Patients related to each outbreak (*n*) | 6.0 (3.0–11.0) | 7.0 (4.5–13.5) | 6.0 (4.0–8.0) | 4.0 (2.8–6.0) | 5.0 (3.5–10.5) | 6.0 (3.0–11.0) | 7.0 (4.3–18.0) |

Data are presented as the no. of outbreaks (%) (multiple selection available) or median (interquartile range).

CPE, carbapenemase-producing *Enterobacteriaceae*; KDCA, Korea Disease Control and Prevention Agency; KPC, *Klebsiella pneumoniae* carbapenemase; NDM, New Delhi metallo-β-lactamase; OXA, oxacillinase; GES, Guiana extended-spectrum β-lactamase; ICU, intensive care unit.

[a)]Outbreaks occurred simultaneously in ICUs and general wards.

cases, 85.1%), followed by *Escherichia coli* (51 cases, 30.4%), and *Enterobacter* spp. and *Citrobacter* spp. (14 cases, 8.3% each) (Table 1). Outbreaks of *K. pneumoniae* significantly increased over time ($p < 0.01$) (Figure 2). The most commonly detected carbapenemase genotype was *K. pneumoniae* carbapenemase (KPC), affecting 139 cases (82.7%), followed by New Delhi metallo-β-lactamase (47 cases, 28.0%) and oxacillinase (17 cases, 10.1%). The proportion of outbreaks in which KPC was detected showed an increasing trend ($p < 0.01$).

## Epidemiological Characteristics of CPE Outbreaks

Among the types of healthcare facilities, epidemiological investigations were implemented most frequently in general hospitals (92 cases, 54.8%) (Table 1). A declining

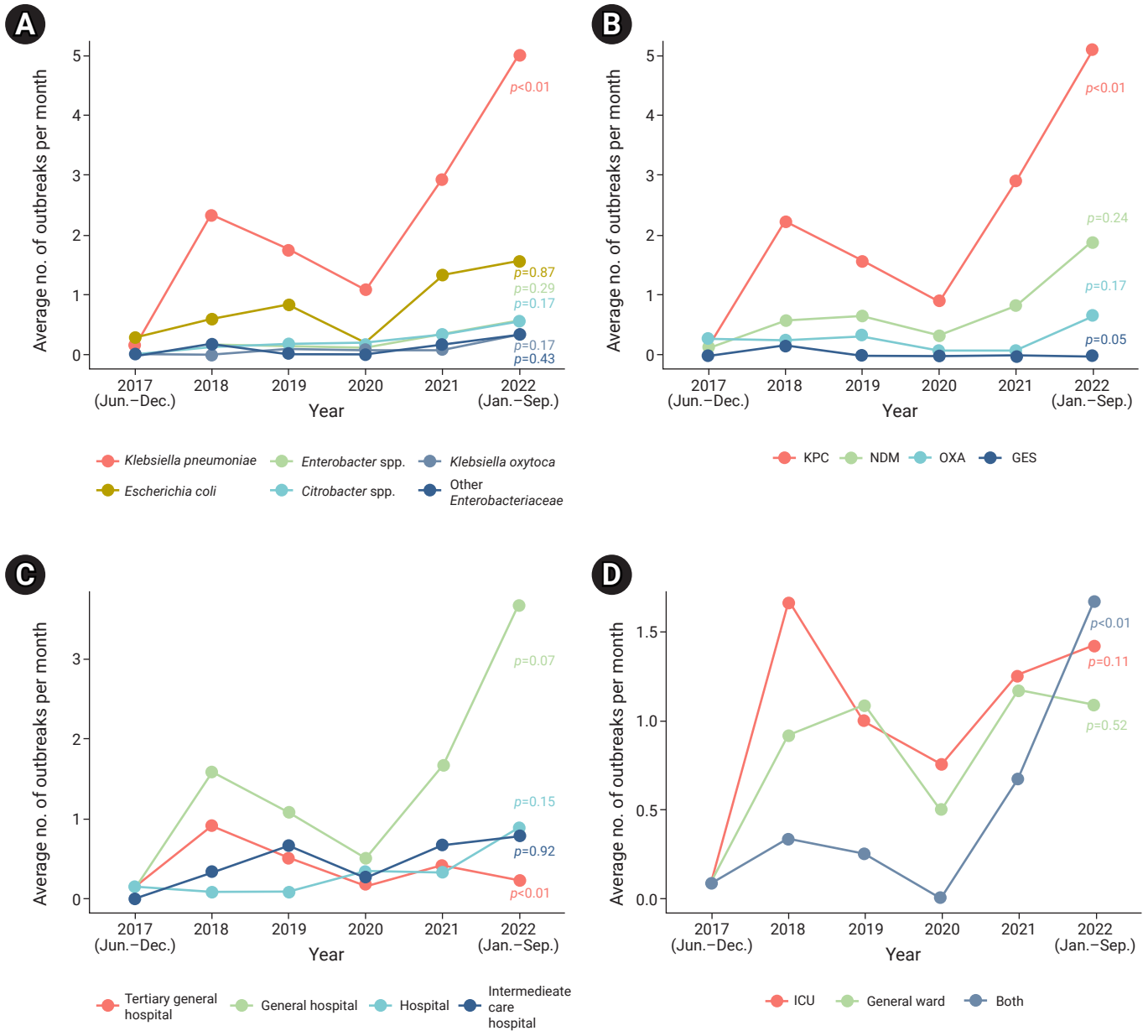


**Figure 2.** Trends of carbapenemase-producing *Enterobacteriaceae* (CPE) outbreaks in healthcare settings according to the Korea Disease Control and Prevention Agency (KDCA) data from June 2017–September 2022. *p*-values presented as labels were generated using the Cochran-Armitage test adjusted for the no. of outbreaks on a 12-month scale. (A) Isolated species. (B) Carbapenemase genotype. (C) Healthcare facility type. (D) Outbreak location.
KPC, *Klebsiella pneumoniae* carbapenemase; NDM, New Delhi metallo-β-lactamase; OXA, oxacillinase; GES, Guiana extended-spectrum β-lactamase; ICU, intensive care unit.



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trend was observed in tertiary general hospitals ($p < 0.01$) (Figure 2). Within facilities, intensive care units (ICUs) were the most common location of outbreaks (74 cases, 44.0%). The frequency of outbreaks occurring simultaneously in ICUs and general wards increased significantly over time ($p < 0.01$).

No statistically significant variations in the duration or number of patients associated with each outbreak were observed by year. However, a significant difference emerged when we compared the periods before and during the coronavirus disease 2019 (COVID-19) pandemic (2017–2019 and 2020–2022, respectively) (Figure 3). The median outbreak duration overall was 61.0 days (IQR, 26.8–121.0), with an increase from 43.5 days (IQR, 22.0–76.0) prior to the pandemic to 79.5 days (IQR, 29.5– 139.8) during the pandemic ($p = 0.01$). The median number of patients overall was 6.0 (IQR, 3.0–11.0), with an increase from 5.0 (IQR, 3.0–7.0) before the pandemic to 6.0 (IQR, 4.0–13.0) during the pandemic ($p = 0.03$).

### Recommended Interventions for Controlling CPE Outbreaks

In 146 cases (86.1%), additional intervention measures were advised, while no measures were recommended in 22 cases (13.1%) (Table 2). Notably, simultaneous implementation of 3 or more interventions was suggested for 76 cases (45.2%). The most frequently recommended intervention measure was employee education (64 cases, 38.1%), followed by active surveillance of high-risk groups (32.7%), contact precautions (31.5%), and environmental cleaning (30.4%). Recommendations for environmental cleaning ($p < 0.01$), patient isolation or cohorting ($p = 0.04$), surveillance of environmental cultures ($p = 0.03$), and timely notification of CRE to the KDCA ($p = 0.02$) differed significantly depending on the type of healthcare facility.

## Discussion

During the early stages of the COVID-19 pandemic in 2020, the number of CPE-related epidemiological investigation reports was lower than in previous years, but it gradually increased over time. A report from the European Centre for Disease Prevention and Control also indicated a reduced number of *E. coli* cases reported in 2020, which may be attributed to a decrease in healthcare activities, such as the reporting of antibiotic resistance rates, due to the COVID-19 pandemic [12].

Among the CPE outbreaks analyzed in the present study, *K. pneumoniae* and KPC showed increasing trends over time and were the most commonly detected species and carbapenemase genotype, respectively (with both found in ≥80% of outbreaks). This is consistent with other Korean studies [7,13]. The United States Centers for Disease Control

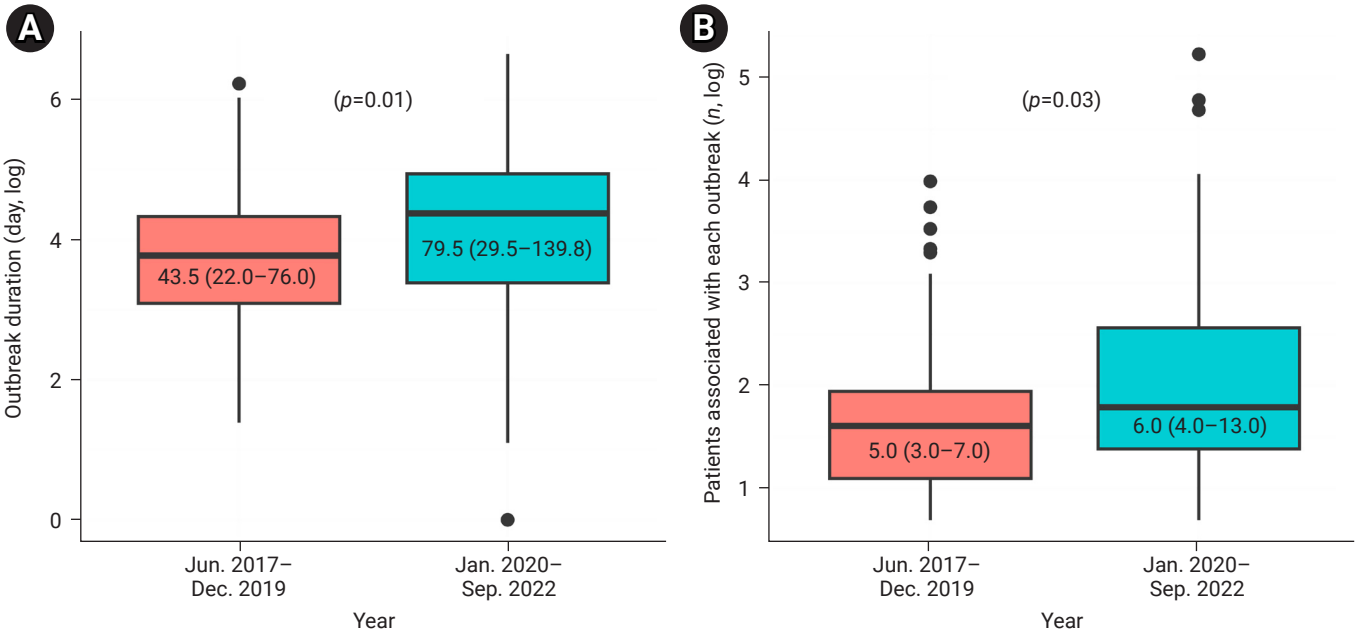


**Figure 3.** Size of carbapenemase-producing *Enterobacteriaceae* outbreaks in healthcare settings according to Korea Disease Control and Prevention Agency data from June 2017–September 2022. Labels are presented as median (interquartile range) before log transformation and *p*-values generated using the Mann-Whitney U-test. (A) Outbreak duration. (B) Patients associated with each outbreak.

**Table 2.** Frequency of interventions recommended to control CPE outbreaks in healthcare settings based on epidemiological investigations, as reported to the KDCA from June 2017–September 2022

| Characteristic | Total (*n* = 168) | Tertiary general hospital (*n* = 27) | General hospital (*n* = 92) | Hospital (*n* = 19) | Intermediate care hospital (*n* = 30) | *p*[a] |
|---|---|---|---|---|---|---|
| Type of recommended interventions | | | | | | |
| Education of employees, including caregivers | 64 (38.1) | 12 (44.4) | 34 (37.0) | 10 (52.6) | 8 (26.7) | 0.28 |
| Active surveillance of high-risk groups | 55 (32.7) | 11 (40.7) | 34 (37.0) | 3 (15.8) | 7 (23.3) | 0.17 |
| Contact precautions | 53 (31.5) | 11 (40.7) | 27 (29.3) | 7 (36.8) | 8 (26.7) | 0.60 |
| Environmental cleaning | 51 (30.4) | 5 (18.5) | 23 (25.0) | 13 (68.4) | 10 (33.3) | < 0.01 |
| Screening contacts of patients with CRE | 49 (29.2) | 5 (18.5) | 30 (32.6) | 7 (36.8) | 7 (23.3) | 0.40 |
| Patient isolation or cohorting | 40 (23.8) | 9 (33.3) | 16 (17.4) | 3 (15.8) | 12 (40.0) | 0.04 |
| Support for staff and infrastructure | 22 (13.1) | 2 (7.4) | 12 (13.0) | 4 (21.1) | 4 (13.3) | 0.60 |
| Surveillance of environmental cultures | 20 (11.9) | 2 (7.4) | 10 (10.9) | 0 (0) | 8 (26.7) | 0.03 |
| On-site monitoring | 15 (8.9) | 3 (11.1) | 6 (6.5) | 4 (21.1) | 2 (6.7) | 0.21 |
| Improvement of bed density | 13 (7.7) | 2 (7.4) | 7 (7.6) | 3 (15.8) | 1 (3.3) | 0.48 |
| Timely notification of CRE to KDCA | 6 (3.6) | 1 (3.7) | 1 (1.1) | 0 (0) | 4 (13.3) | 0.02 |
| Antibiotic stewardship | 4 (2.4) | 0 (0) | 4 (4.3) | 0 (0) | 0 (0) | 0.67 |
| No. of intervention types recommended for each outbreak | | | | | | |
| 0 (None of the above) | 22 (13.1) | 3 (11.1) | 15 (16.3) | 1 (5.3) | 3 (10.0) | 0.63 |
| 1–2 | 70 (41.7) | 12 (44.4) | 39 (42.4) | 8 (42.1) | 11 (36.7) | 0.94 |
| 3–7 | 76 (45.2) | 12 (44.4) | 38 (41.3) | 10 (52.6) | 16 (53.3) | 0.61 |

Data are presented as the no. of outbreaks (%) (multiple selections available).
CPE, carbapenemase-producing *Enterobacteriaceae*; KDCA, Korea Disease Control and Prevention Agency; CRE, carbapenem-resistant *Enterobacteriaceae*.
[a]Generated using the Fisher exact test.

and Prevention recommended strengthening contact tracing and surveillance in healthcare facilities to detect relatively rare carbapenemases, such as New Delhi metallo-β-lactamase [14]. Considering the rising trend of *K. pneumoniae* and KPC dominance within outbreaks, it may be necessary to enhance epidemiological investigations and IPC measures to control outbreaks associated with relatively rare species or carbapenemase types.

In the present study, more than 50% of epidemiological investigations were conducted in general hospitals; additionally, outbreaks in tertiary general hospitals investigated by local epidemiologists demonstrated a sharp decline over time. A previous study of patients with CRE, utilizing KDCA data from 2021, revealed that 42.0% of cases occurred in general hospitals and 40.5% in tertiary general hospitals [7]. This finding suggests the potential for tertiary general hospitals to carry out independent epidemiological investigations and IPC measures, provided they possess adequate staffing levels and expertise.

Regarding outbreak location within healthcare facilities, over 40% of outbreaks occurred exclusively within ICUs. A history of ICU admission is generally regarded as a risk factor for CRE [9,15]. In a study by Kim et al. [13] conducted in an ICU, pneumonia and chronic respiratory disease, previous antibiotic use, and history of nasogastric tube placement were identified as risk factors for CPE. This suggests the need for more proactive IPC measures in high-risk groups, with a focus on ICUs during CPE outbreaks. The recent increase in outbreaks occurring simultaneously in ICUs and general wards underscores the importance of IPC measures and ward separation to limit further transmission.

The duration and number of patients associated with each outbreak were significantly greater during the COVID-19 pandemic compared to the pre-pandemic period. This may be due to a decrease in non-urgent healthcare activities not directly related to COVID-19 [12,16]. For instance, regular active surveillance of high-risk groups for CPE might have been limited, as personnel and resources were redirected towards contact tracing, laboratory testing, and isolation of



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COVID-19 patients. Given the need for rapid CPE testing [17], early implementation of epidemiological investigations and IPC measures is also crucial to block further transmission, as well as to avoid prolonging the outbreak and incurring increased disease burden.

The World Health Organization recommends implementing multimodal strategies (consisting of at least 3 and usually 5 elements) across healthcare facilities for the prevention and management of the spread of carbapenem-resistant organisms [11]. Similarly, in the present study, we found that multimodal interventional approaches were concurrently advised following ≥40% of epidemiological investigations of CPE outbreaks in the Republic of Korea, regardless of the type of healthcare facility.

Overall, employee education was the most heavily emphasized measure, along with education for caregivers who frequently interact with patients. For hospitals, environmental cleaning was most commonly recommended; however, no guidance has been made available on monitoring environmental cultures, likely due to specific facility-related circumstances. Interventions to control CPE outbreaks should be tailored to each facility's unique situation, considering available resources and trained staff. In contrast, national guidelines in other countries suggest that acute care hospitals, rather than post-acute care hospitals, should strengthen IPC measures for patients with CRE [3,18]. For effective control of CPE outbreaks, facility-level regulations are crucial, including the implementation of basic IPC measures and outbreak investigation. These regulations should be incorporated into the education and job functions of all employees. Additionally, individual risk factors for CRE should be considered, such as antibiotic use, invasive procedures, and the use of ventilators or urethral catheters [9,19].

Our study had some limitations. The data collected from epidemiological investigation reports may deviate from actual results due to memory bias. Additionally, some CPE-related epidemiological investigations conducted by local governments may not have been reported to the KDCA. Furthermore, we lacked detailed data on the source of infection, antibiotic use, and clinical outcomes, preventing a more in-depth analysis of outbreak-related epidemiological characteristics. However, our study presents a general overview of CPE outbreaks throughout the Republic of Korea since CRE was indicated as a mandatory notifiable disease in this country. Future studies involving detailed data should be conducted to analyze the characteristics of outbreaks responsible for differences in their spread and to consider the effectiveness of combinations of interventions to control CPE transmission.

## Conclusion

We examined the epidemiological features of CPE outbreaks using data from investigations reported to the KDCA, which offered national-level information. Our results indicate that persistent efforts are necessary to manage CPE outbreaks in consideration of their epidemiology.

## Notes

### Ethics Approval

This study received approval from the Institutional Review Board (IRB) of the KDCA (IRB No: 2023-01-02-PE-A) and was conducted in accordance with the principles of the Declaration of Helsinki.

### Conflicts of Interest

The authors have no conflicts of interest to declare.

### Funding

None.

### Availability of Data

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

### Authors' Contributions

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

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Short Communication

# Trends of legionellosis reported in Jeju Province, Republic of Korea, 2015–2022

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## ABSTRACT

**Objectives:** The number of reported cases of Legionnaires' disease (LD) in the Republic of Korea surged nationally in 2016; however, in 2022, this number was higher in Jeju Province than the previous national peak. A descriptive epidemiological study was conducted to analyze trends in the incidence of reported LD cases in Jeju Island from 2015 to 2022.
**Methods:** The data for this study were obtained from case reports submitted to the Korea Disease Control and Prevention Agency through its Disease and Health Integrated Management System. The selection criteria were cases or suspected cases of LD reported among Jeju residents between 2015 and 2022. The 95% confidence interval of the crude incidence rate was calculated using the Poisson distribution.
**Results:** Since 2020, the incidence rate of LD in Jeju has risen sharply, showing a statistically significant difference from the national incidence rate. A particular medical institution in Jeju reported a significant number of LD cases. Screening with the urine antigen test (UAT) also increased significantly.
**Conclusion:** Our findings indicate that the rapid increase in cases of LD in Jeju Province since 2020 was due to the characteristics of medical-care use among Jeju residents, which were focused on a specific medical institution. According to their clinical practice guidelines, this medical institution conducted UATs to screen patients suspected of pneumonia.

**Keywords:** Laboratory diagnosis; Legionnaires' disease; *Legionella pneumophila*; Pneumonia

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## Introduction

The leading causative agent of Legionnaires' disease (LD) is *Legionella pneumophilia* serotype 1, which accounts for 2% to 15% of cases of community-acquired pneumonia [1–4]. LD presents as an atypical type of pneumonia because the patient often has no fever and can have extrapulmonary clinical symptoms, such as headache or diarrhea [5–7].

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Although the incidence rate of LD varies widely among countries [8], it has increased significantly worldwide, including in the United States, Europe, and Asia, since 2000 [9–11]. After LD was designated a reportable infectious disease in the Republic of Korea in 2000, the number of reported cases increased from 45 in 2015 to 128 in 2016 [12]. The national reporting rates for the corresponding years were 0.09 and 0.25 per 100,000 people, respectively, representing a 2.7-fold increase over a 1-year period. The 2022 reporting rate in Jeju Province was 6.05 per 100,000 people, the highest rate among local governments and 7.5 times higher than the national rate (0.81 per 100,000) (Figure 1) [13].

While there was a sudden increase in reports of LD nationwide in 2016, an explanation was needed for the surge in reported LD cases in Jeju Province in 2022, as compared to the rest of the nation. Therefore, we conducted a descriptive epidemiological study on trends in the LD reporting rate in Jeju Province from 2015 to 2022.

**HIGHLIGHTS**

The rapid increase in Legionnaires' disease in Jeju Province since 2020 may be related to the patterns of medical use by Jeju residents, which focused on a specific medical institution. The clinical practice guidelines of that medical institution called for the active implementation of urine antigen tests to screen patients suspected of community-acquired pneumonia.

## Materials and Methods

The data for this study were sourced from legionellosis case reports submitted through the Disease and Health Integrated Management System (https://is.kdca.go.kr) of the Korea Disease Control and Prevention Agency (KDCA). For this epidemiological investigation, residents of Jeju Province were selected as study subjects among the cases classified as LD patients or suspected LD patients from 2015 to 2022.

For cases that met the selection criteria, sex, age, occurrence date, reporting institution, test method for LD diagnosis, and route of infection were extracted. Subjects were classified into 2 age groups (< 65 years and ≥ 65 years) based on their age at the time of reporting. The date of LD occurrence was defined as the date of sample collection, and if the date of sample collection was not reported, it was based on the date of reporting at the medical institution. The infection route was divided into nosocomial and non-nosocomial infections based on descriptions in the case report. If the route of infection was unknown, patients in whom suspicious symptoms began at least 2 days after the hospitalization date were considered to have nosocomial infections. Infections acquired in the community or at home without a history of hospitalization were considered non-nosocomial.

To calculate the annual crude incidence rate (CIR) of LD, we used the annual mid-year population based on the resident

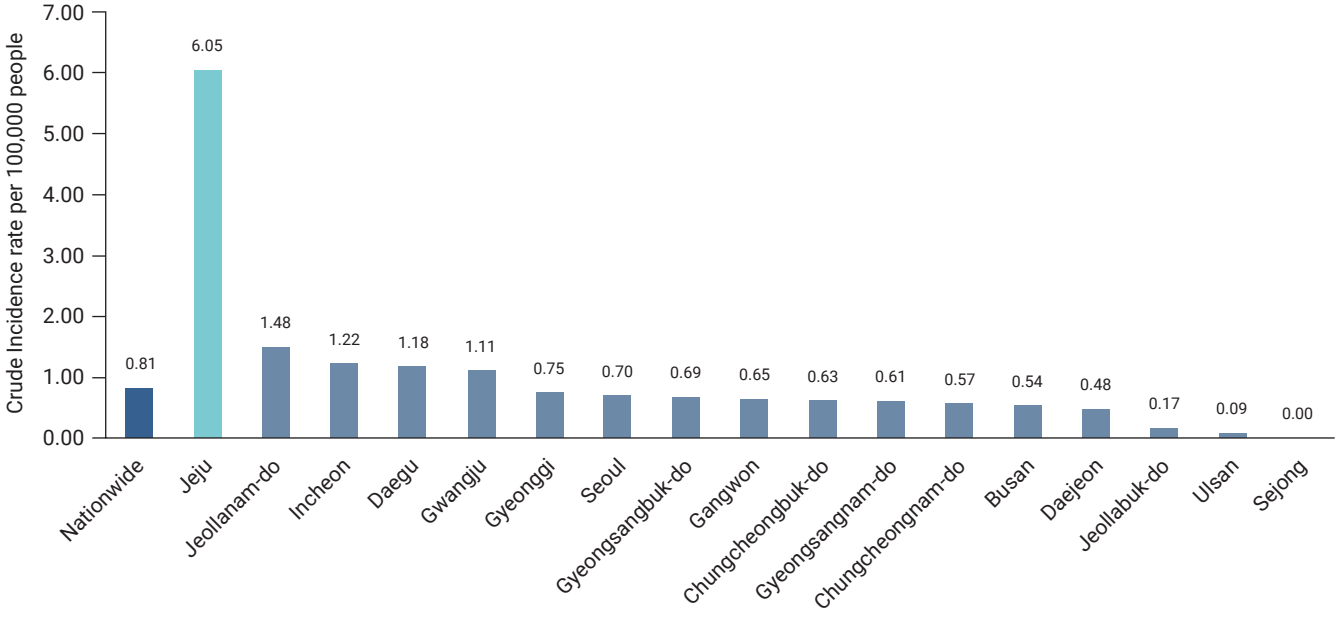


**Figure 1.** Nationwide crude incidence rates of reported legionellosis in the Republic of Korea in 2022.



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registration used by the KDCA [13]. The 95% confidence interval (CI) of the CIR was calculated by applying the Poisson distribution. The 2-sample t-test, chi-square test, and Fisher exact test were performed to evaluate differences in the characteristics of related variables between the classified groups. STATA ver. 17.0 (Stata Corp.) was used for the analysis, and $p$-values $< 0.05$ indicated statistical significance.

This study was approved for exemption by the institutional review board (IRB) of Jeju National University as a study utilizing secondary data (JJNU-IRB-2023-019).

## Results

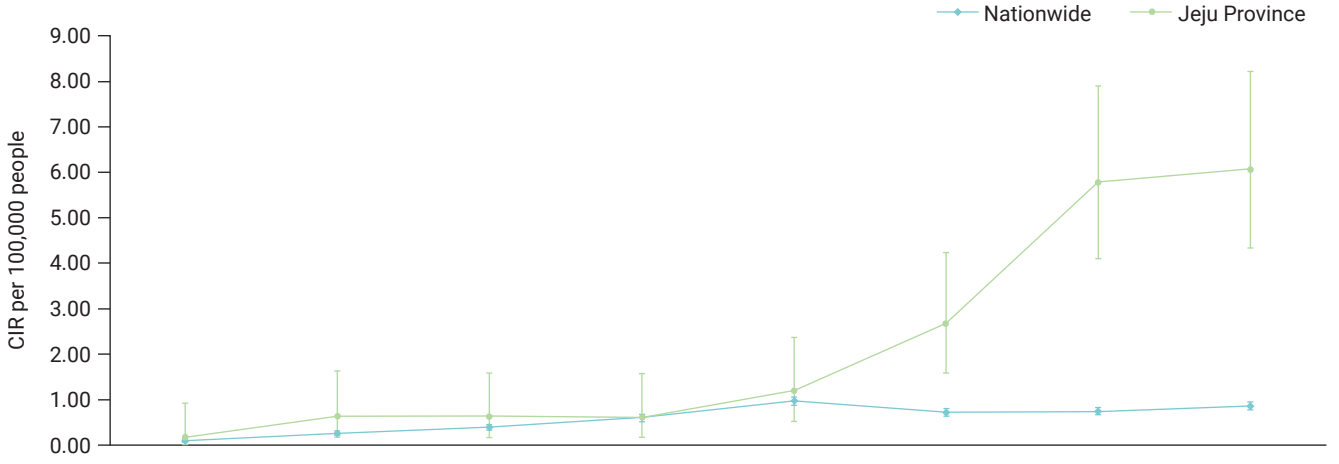
We analyzed 119 patients who met the selection criteria. The distribution of occurrences and the CIR by year is shown in Figure 2. Since 2020, the incidence rate of LD in Jeju Province has risen sharply, showing a statistically significant difference from the national incidence rate. In 2022, the LD incidence rate was the highest in Jeju Province and was 7.5-fold higher than the national incidence rate (6.05/0.81). Although there was no significant difference between the sexes in the distribution of incidence rates by year, the incidence rate in the older group ( ≥ 65 years) was significantly higher after 2020 (Table 1).

The epidemiological characteristics of reported cases before and after a sharp change in the incidence rate (before 2019 and after 2020) were compared (Table 2). With the increased number of cases (from 21 to 98) the mean age at occurrence differed significantly (63.8 vs. 76.8 years) ($p < 0.001$ by two-sample t-test). There was no significant difference between the sexes or routes of infection. One medical institution reported a significantly higher number of LD cases than other institutions ($p < 0.05$ by the chi-square test), and the urine antigen test (UAT) was used significantly more frequently as the test method at that institution ($p < 0.05$ by the Fisher exact test).

## Discussion

In this study, we found that the patient age in cases of LD in Jeju Province increased from 2020 onwards, while the distribution of sex and route of infection did not change significantly. We also found that intensive case reporting arose from a specific medical institution where application of the UAT had also increased.

If the occurrence of a particular disease increases in a community, possible changes in reporting guidelines, increases in disease awareness, and the introduction of a new test method should be considered before deciding whether the incidence of the disease *per se* has increased [10,14,15]. First, in our context, the possibility of an increase due to changes in reporting guidelines could be preferentially excluded, as the diagnostic criteria for reporting in the KDCA's *Legionella* management guidelines for 2012, 2016,




| Year | 2015 | 2016 | 2017 | 2018 | 2019 | 2020 | 2021 | 2022 |
|---|---|---|---|---|---|---|---|---|
| Cases in Jeju (*n*=119) | 1 | 4 | 4 | 4 | 8 | 18 | 39 | 41 |
| Jeju CIR (95% CI) | 0.16 (0.00–0.91) | 0.63 (0.17–1.62) | 0.62 (0.17–1.58) | 0.60 (0.17–1.55) | 1.20 (0.52–2.36) | 2.68 (1.59–4.23) | 5.77 (4.10–7.89) | 6.05 (4.34–8.21) |
| Nationwide CIR (95% CI) | 0.09 (0.06–0.12) | 0.25 (0.21–0.30) | 0.38 (0.33–0.44) | 0.59 (0.53–0.66) | 0.97 (0.88–1.05) | 0.71 (0.64–0.79) | 0.74 (0.67–0.82) | 0.85 (0.77–0.93) |

**Figure 2.** Annual crude incidence rates (CIR) of legionellosis in Jeju Province and nationwide in the Republic of Korea.
CI, confidence interval.

**Table 1.** Annual crude incidence rate of legionellosis by sex and age groups in Jeju Province, Republic of Korea, from 2015–2022

| Year | Sex | | Age group (y) | |
|---|---|---|---|---|
| | Male | Female | <65 | ≥65 |
| 2015 | 0.32 (0.01–1.80) | 0 | 0.19 (0.00–1.05) | 0 |
| 2016 | 1.26 (0.34–3.22) | 0 | 0.55 (0.11–1.61) | 1.16 (0.03–6.36) |
| 2017 | 0.61 (0.07–2.21) | 0.62 (0.08–2.24) | 0.18 (0.00–1.00) | 3.33 (0.68–9.62) |
| 2018 | 0.90 (0.19–2.63) | 0.30 (0.01–1.69) | 0 | 4.28 (1.15–10.82) |
| 2019 | 1.78 (0.65–3.88) | 0.60 (0.07–2.17) | 0.88 (0.28–2.04) | 3.09 (0.63–8.92) |
| 2020 | 3.25 (1.62–5.82) | 2.09 (0.84–4.31) | 0.88 (0.29–2.05) | 12.77 (6.70–21.53) |
| 2021 | 7.97 (5.25–11.59) | 3.56 (1.84–6.22) | 0.89 (0.29–2.06) | 31.72 (21.72–43.83) |
| 2022 | 6.78 (4.30–10.17) | 5.32 (3.16–8.41) | 1.60 (0.73–3.03) | 28.47 (19.33–39.90) |

Data are presented as crude incidence rate (95% confidence interval).

**Table 2.** A comparison of epidemiological characteristics in reported cases of legionellosis between 2015–2019 and 2020–2022 in Jeju Province, Republic of Korea

| Characteristic | Total (*n*=119) | 2015–2019 (*n*=21) | 2020–2022 (*n*=98) | *p* |
|---|---|---|---|---|
| Age (y) | 74.53±14.84 | 63.81±16.12 | 76.83±13.57 | <0.001*** |
| Sex | | | | 0.225 |
| Male | 77 (64.7) | 16 (76.2) | 61 (62.2) | |
| Female | 42 (35.3) | 5 (23.8) | 37 (37.8) | |
| Hospital | | | | <0.05* |
| A | 102 (85.7) | 14 (66.7) | 88 (89.8) | |
| B | 3 (2.5) | 2 (9.5) | 1 (1.0) | |
| C | 10 (8.4) | 3 (14.3) | 7 (7.1) | |
| D | 2 (1.7) | 1 (4.8) | 1 (1.0) | |
| Other | 2 (1.7) | 1 (4.8) | 1 (1.0) | |
| Diagnosis | | | | <0.05* |
| UAT | 91 (76.5) | 12 (57.1) | 79 (80.6) | |
| UAT+culture | 3 (2.5) | 0 (0) | 3 (3.1) | |
| UAT+PCR | 10 (8.4) | 3 (14.3) | 7 (7.1) | |
| PCR | 15 (12.6) | 6 (28.6) | 9 (9.2) | |
| Route | | | | 0.817 |
| Nosocomial | 19 (16.0) | 3 (14.3) | 16 (16.3) | |
| Non-nosocomial | 100 (84.0) | 18 (85.7) | 82 (83.7) | |

Data are presented as mean±standard deviation or *n* (%).
UAT, urine antigen test; PCR, polymerase chain reaction.
*$p<0.05$, ***$p<0.001$.

2018, 2019, and 2020 had not changed [12]. Second, in terms of increased awareness of LD, it is plausible that both the public and healthcare professionals had gained interest in pneumonia due to the sudden outbreak of coronavirus disease 2019 in 2020 [16]. However, since this change in interest was a nationwide phenomenon, it is not likely to explain the increased reporting of LD from Jeju Province as compared to the rest of the country. Last, the hypothesis that the increase in reported LD patients was due to the introduction of a new testing method is likely to be valid according to the simultaneous variability hypothesis-setting method [14], since the number of reports based on positive UAT results changed markedly around 2020.

Since the development of a method for detecting urinary *L. pneumophilia* antigen in late 1990 [17], the UAT has become a major diagnostic method for LD worldwide [18] due to its easy handling and rapid diagnosis [19]. Amid these changes, the incidence rate of LD in the United States surged by 192% and 286% in 2009 and 2014, respectively, relative to the incidence rate in 2000 [15,20]. In Europe, the incidence rate was 2.6 times higher in 2015 than in 2000 [21,22]. In addition, the incidence rate in Hong Kong was 5.7 times higher in 2015 than in 2005. As discussed above, the predominant interpretation of these findings is that the rapid increase in the incidence rate of LD since 2000 reflects the introduction of the UAT [15,23–25]. This



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interpretation is notably supported by the fact that 97% of all cases in the United States were diagnosed by means of the UAT, while there was no change in the distribution of infection routes [15]. Therefore, it can be interpreted that the rapid increase in the reporting rate of nationwide LD since 2015 was also an effect of the introduction of the UAT. In our study, as seen in the United States [15], 87.4% of all cases were diagnosed via the UAT (104/119), while the distribution of infection routes in Jeju Province did not change (Table 2). Thus, the impact of the UAT introduction can explain the 37.8-fold (6.05/0.16) increase in the incidence rate from 2015 to 2022 in Jeju Province (Figure 2).

It has also been argued that the number of LD patients increased rapidly after the introduction of the UAT, which led to diagnoses of more LD cases that had been missed previously [18]. In other words, due to the microbiological characteristics of LD pathogens, the incidence rate of LD before introducing the UAT method was underestimated [11,15,20]. LD is an atypical type of pneumonia, which often is not associated with fever and shows extrapulmonary clinical symptoms, such as headache or diarrhea, making it difficult to diagnose [6,7]. However, due to the high sensitivity of the UAT used in screening, the period from symptom onset to diagnosis was shortened by 5 days [26], and the mortality rate also decreased rapidly [24].

If the UAT enabled the diagnosis of patients who would otherwise have been missed, it could explain why the reporting rate of Jeju Province was the highest among local governments in the Republic of Korea, for the following 3 reasons:

First, a main finding of this study is that 88 of 98 LD cases reported in Jeju Province after 2020 were from a specific medical institution. In other words, that medical institution diagnosed and treated 90% of LD cases among Jeju residents.

Second, in accordance with the Treatment Guidelines for Pneumonia in the Republic of Korea [27], the abovementioned medical institution had been performing the UAT for early diagnosis and initial antibiotic selection for all patients with suspected community-acquired pneumonia who required hospitalization. By actively performing UATs, with a sensitivity of 80% and specificity of 95% or higher [17], the diagnosis rate of LD, an atypical type of pneumonia, increased. This also supported a main finding of the present study—namely, that the age of confirmed LD patients had significantly increased since 2020. The reason for this finding is that individuals ≥65 years of age have more underlying diseases than those <65 years and have a relatively low clinical suspicion of pneumonia and a positive rate of general blood tests [28].

Third, on October 7, 2019, the abovementioned hospital switched the UAT method from immunochromatographic assay-based UAT (ICT-UAT) to fluorescence immunoassay-based UAT (FIA-UAT). Since the examiner directly reads the results with the ICT-UAT method, subjective reading errors can result in false negatives. In contrast, in the FIA-UAT method, a scanner reads the results automatically [29] and can more sensitively diagnose faint bands that are difficult to distinguish with the eyes [19,30]. Hence, the fact that the hospital used the more sensitive FIA-UAT, which reduced false negative errors from the beginning of October 2019, supports the rapid increase in the number of LD cases since 2020.

There were some limitations in this study. First, 10 cases that were finally classified as "non-LD" cases after further epidemiological investigation were excluded. Thus, the possibility of late exclusions should be considered among the subjects selected as LD cases. However, since the subject selection process took place in March 2023, the possibility of further exclusions of non-LD cases in the final selection is likely to be extremely low. Second, to obtain the incidence rate of LD in Jeju Province, participants were limited to patients with addresses in Jeju Province, in accordance with the reporting guidelines of the KDCA, which manages cases according to their address [12]. However, one LD-diagnosed case was included while residing in another region, although their address was in Jeju Province. Since such cases can occur in all local governments nationwide, it was not intentionally excluded from statistical comparison. Third, among the 119 selected subjects, the route of infection was unknown in 26 cases (21.8%). Therefore, we first defined nosocomial infections based on the epidemiological investigation and treated all others as non-nosocomial infections. Since it was difficult to distinguish between community-acquired and domestically-acquired infections in patients with an unknown route of infection, as pointed out in the guidelines of the KDCA [12], the 2 routes were grouped together and classified as non-nosocomial infections. In addition, since all selected cases were sporadic occurrences, 1 travel-related infection case was also classified as a non-nosocomial infection.

In conclusion, the rapid increase in the number of LD cases reported in Jeju Province was probably due to the pattern of medical-care use among Jeju residents, which was focused on a particular medical institution. Concurrent and active implementation of the UAT by that medical institution to screen patients suspected of community-acquired pneumonia in accordance with their treatment guidelines reduced false negatives. Thus, rather than inferring that the LD incidence rate after 2020 actually increased as compared

to rates before 2019, it is more likely that some cases were not reported before 2019 due to missed diagnoses. Patients with actual LD were actively diagnosed after 2020 due to the introduction of the FIA-UAT. To confirm this hypothesis, epidemiological studies comparing and analyzing UAT use and pneumonia-related patterns in medical centers of other local governments will be required in the future. Moreover, as the proportion of LD in community-acquired pneumonia is expected to be higher than previously thought, more active infection control for LD should be implemented.

## Notes

### Ethics Approval

This study was approved for exemption by the IRB of Jeju National University as a study utilizing secondary data (JJNU-IRB-2023-019).

### Conflicts of Interest

The authors have no conflicts of interest to declare.

### Funding

This study was supported by the 2023 Education, Research, and Student Guidance grant funded by Jeju National University.

### Availability of Data

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

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phrp
OSONG PUBLIC HEALTH AND RESEARCH PERSPECTIVES

# Instruction for authors

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*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

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Please refer to the following examples.

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  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.
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**NOTICE:** These recently revised instructions for authors will be applied beginning with the February 2023 issue.

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