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OSONG PUBLIC HEALTH AND RESEARCH PERSPECTIVES

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Vol. 13, No. 5, October 2022

Editorial

313 What measures should be considered in this 2022–2023 winter season
Jong-Koo Lee

Review Articles

316 India's efforts to achieve 1.5 billion COVID-19 vaccinations: a narrative review
Kapil Singh, Ashwani Verma, Monisha Lakshminarayan

328 Effects of medication adherence interventions for older adults with chronic illnesses: a systematic review and meta-analysis
Hae Ok Jeon, Myung-Ock Chae, Ahrin Kim

341 Zika virus as an emerging arbovirus of international public health concern
Samira Vaziri, Siavash Hamzeh Pour, Fateme Akrami-Mohajeri

Original Articles

352 A case-control study of acute hepatitis A in South Korea, 2019
Jung Hee Hyun, Ju Young Yoon, Sang Hyuk Lee

360 Investigation of SARS-CoV-2 lineages and mutations circulating in a university-affiliated hospital in South Korea analyzed using Oxford Nanopore MinION sequencing
Hyaekang Kim, Sung Hee Chung, Hyun Soo Kim, Han-Sung Kim, Wonkeun Song, Ki Ho Hong, Jae-Seok Kim

370 Clinical outcomes of remdesivir-treated COVID-19 patients in South Korea
Mi Yu, Bryan Inho Kim, Jungyeon Kim, Jin Gwack

Brief Reports

377 Presumed population immunity to SARS-CoV-2 in South Korea, April 2022
Eun Jung Jang, Young June Choe, Seung Ah Choe, Yoo-Yeon Kim, Ryu Kyung Kim, Jia Kim, Do Sang Lim, Ju Hee Lee, Seonju Yi, Sangwon Lee, Young-Joon Park

382 Adverse events of the Pfizer-BioNTech COVID-19 vaccine in Korean children and adolescents aged 5 to 17 years
Seontae Kim, Yeseul Heo, Soon-Young Seo, Do Sang Lim, Enhi Cho, Yeon-Kyeng Lee

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Editorial

What measures should be considered in this 2022–2023 winter season

Jong-Koo Lee

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With fewer than 10,000 deaths due to coronavirus disease 2019 (COVID-19) reported a day in the current global pandemic situation, on September 14, the World Health Organization Director-General Tedros Adhanom Ghebreyesus made a rather optimistic statement, "the pandemic is not over, but the end is in sight." Although the number of cases has generally slowed as winter approaches, increases in the case count are being observed in some regions, such as Germany in Europe and China and Japan in the Asia-Pacific region. In Korea, the decrease in the number of patients plateaued, followed by a slight increase in the case count; nearly 50% of the population has been infected, while vaccination coverage is at a very high level (first dose, 87.9%; second dose, 87.1%; and third dose, 65.6.%) [1].

According to a recent community health survey of 10,000 people, 97.8% of participants were antibody-positive. Of these, 57.7% were judged to be antibody-positive due to natural infection rather than vaccination, corresponding to an infection rate about 19.5%p higher than that of 38.2% reported in the same period [2].

Why is it difficult to reach the threshold of traditional herd immunity despite such a high vaccination rate and many natural infections? Contrary to our expectations, immune evasion by the mutant forms of the virus is taking place, and according to a cohort study, 56% of patients infected during the spread of the Omicron variant had asymptomatic cases [3], making it difficult to block transmission. Since COVID-19 does not elicit systemic immunity like measles or smallpox, vaccination or natural infection does not maintain the effect of preventing infection for a long time, and resistance against intervention measures such as vaccination and mask-wearing is also believed to contribute to ongoing spread [4]. Therefore, current vaccination initiatives have no choice but to focus on reducing hospitalization and preventing death rather than on community transmission and eradication through herd immunity.

Therefore, what are our plans for this winter? Seasonal influenza, which had a low incidence in the past 3 years, is increasing. Although the epidemic was almost controlled by social distancing, hand-washing, cough etiquette, and vaccination, it is estimated that seasonal influenza will reoccur as before due to a change in non-pharmaceutical intervention policies this winter. As COVID-19 spreads simultaneously, co-infections will become possible. Therefore, it is necessary to persuade the public that those who have not completed the basic vaccination series and at-risk groups should receive additional vaccinations as soon as possible as follows:

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First, the recent average number of patients is around 20,000 per day, and the fatality rate is lower than before (cumulative fatality rate, 0.11%). Although COVID-19 has not been eradicated, the lower fatality rate reflects the government's targeted measures for high-risk groups, such as an increase in prescriptions for oral medications, additional vaccinations, and early screening of high-risk institutionalized population groups. Nonetheless, excessive optimism about the lower fatality rate is dangerous because the toxicity of the now-prevalent BA.5 variant of concern has not weakened, and the severity of BA.2.75 has not changed.

Secondly, despite publicity initiatives, the vaccination rate is not rising. Deaths from infection among unvaccinated persons and those who have received only the first dose account for 31% of all deaths. Compared to September 23 (i.e., a month ago), the current primary, secondary, and tertiary inoculation rates have hardly changed. The fourth inoculation has been only received by 14.7% (about 7.52 million) of the population, and the additional winter season campaign rate was only 1.6% [1,2]. This reflects a misconception about the formation of hybrid immunity from infection and vaccination against COVID-19. In other words, contrary to the belief that 97.8% of the population is antibody-positive and no further infections will occur, about 10% of those who received the second dose were confirmed to be reinfected [2]. Third and fourth vaccinations can now be mistakenly perceived as unnecessary.

Thirdly, scientific persuasion is needed to address vaccine hesitancy. The Wuhan-based vaccine remains effective at preventing severe cases, and it is necessary to encourage the completion of the basic vaccination series first. Even if a bivalent mRNA vaccine is introduced, people concerned about myocarditis as a side effect must be convinced that it is possible to receive inoculations with a protein subunit vaccine. About 30% of children and adolescents who are not vaccinated are reluctant to be vaccinated because infections may be asymptomatic or mild, or because they have concerns about the cardiac side effects of mRNA vaccines. However, myocarditis is very rare (4.6 per 100,000 in adolescents), and it is necessary to convince them that side effect has a good prognosis [5].

Fourth, as the pandemic has continued, each country has pursued its own unique evidence-based policies, but cooperation between neighboring countries is necessary for cross-border control. In particular, cooperation between Korea and Japan, which is introducing mitigation strategies after vaccination, whereas China adheres to the zero-COVID policy, is important. We must actively engage in health diplomacy on cross-border policies through tripartite ministerial meetings.

Finally, looking back over the past 3 years, we have experienced 3 kinds of limitations in responding to the pandemic. Many people are trying to end the pandemic, but to combat this disease, we must draw upon what we currently know (facts), what we need to know (truths), and what we know and can do (implementation). Although it is vitally important for us to recognize our limitations, and we are trying to reduce the gaps between facts (knowledge), truths, and implementation, the establishment of countermeasures based on scientific evidence remains insufficient. There have been inadequate investments in public health and science, with implications for knowledge and truth, and there has been controversy over the participation and the role of academics and experts in the interpretation of facts. There has also been insufficient procedural justice (accountability for reasonableness) [6] for the implementation of action plans. Thus, we need 3 kinds of improvements.

Notes

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The author has no conflicts of interest to declare.

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Review Article

India's efforts to achieve 1.5 billion COVID-19 vaccinations: a narrative review

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ABSTRACT

The initial case of coronavirus disease 2019 (COVID-19) in India was reported on January 30, 2020, and subsequently, the number of COVID-19-infected patients surged during the first wave of April 2020 and the second wave in the same month of 2021. The government of India imposed a strict nationwide lockdown in April 2020 and extended it until May 2020. The second wave of COVID-19 in India overwhelmed the country's health facilities and exhausted its medical and paramedical workforce. This narrative review was conducted with the aim of summarizing the evidence drawn from policy documents of governmental and non-governmental organizations, as well as capturing India's COVID-19 vaccination efforts. The findings from this review cover the Indian government's vaccination initiatives, which ranged from steps taken to combat vaccine hesitancy to vaccination roadmaps, deployment plans, the use of digital health technology, vaccination monitoring, adverse effects, and innovative strategies such as *Har Ghar Dastak* and *Jan Bhagidari Andolan* (people's participation). These efforts collectively culminated in the successful administration of more than 1.8 billion doses of COVID-19 vaccines in India. This review also provides insights into other countries' responses to COVID-19 and guidance for future pandemics.

Keywords: COVID-19; COVID-19 vaccines; Co-WIN; Vaccination hesitancy

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Introduction

In January 2020, the World Health Organization (WHO) classified coronavirus disease 2019 (COVID-19) as a public health emergency of international concern and declared it a pandemic on March 11, 2020 [1]. As of December 31, 2021 in India, 34,822,040 COVID-19 cases had been confirmed with a case fatality rate of 1.36% after the earliest case was identified in Kerala, India on January 30, 2020 [2]. India, a low- and middle-income country, has a population of about 1.3 billion people and accounts for nearly 18% of the global population [3]. In India, the first wave of COVID-19 cases peaked in September 2020, followed by a distressing second wave that

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began in March 2021 and with the highest peak of more than 414,000 cases on May 7, 2021 [4].

In India, the second wave of COVID-19 overwhelmed the country's health facilities, shattering health workers who became infected [5]. COVID-19 has had a profound impact on public health and the economy [6]. To appropriately respond to COVID-19, a range of containment and mitigation strategies were implemented, with the goal of averting large surges of patients in hospitals and safeguarding the most vulnerable people, such as the elderly and those with comorbidities [7]. Despite national and sub-national containment measures of COVID-19, the testing capacity of over 2.2 million samples within 24 hours to detect and isolate cases [8] and a nationwide vaccination drive, the probability of a third wave is high due to highly contagious mutant strains and variants. The WHO's technical advisory group evaluated the B.1.1.529 variant of COVID-19, initially reported in South Africa, as "Omicron," which has many mutations, and considered this as a variant of concern [9].

As stated by the WHO, ending the COVID-19 pandemic would require equitable access to safe and effective vaccines, which have been shown to be effective and lifesaving [10].

Based on the experience of India from the existing largest immunization program named as 'Universal Immunization Program' (UIP) which targets nearly 26 million infants every year to deliver vaccines against 12 vaccine preventable diseases in the country [11]. India conceptualized to immediately rollout the COVID-19 vaccination program leveraging the existing established infrastructure for the supply, storage and delivery of vaccines to the last mile, under the UIP, where around 600 million doses are administered each year the children every year. The universal immunization program has experiences of implementing large scale immunization campaigns. The country has been carrying out large scale Polio campaigns over more than 2 decades now [12]. Further, World's largest Measles-Rubella Campaign covering more than 324 million children in the age group of 9 months to 15 years, from 2017 through 2020 has been implemented [13]. Data from various studies conducted in India reported MR vaccine coverage ranging from 80% to 90% [14,15], which depicts the implementation and high coverage of vaccination campaigns.

The strength of the UIP made India confident to roll out COVID-19 vaccinations programme on January 16, 2021. By December 31, 2021, more than 1.45 billion vaccine doses had been administered, with 64% of the target population vaccinated with 2 doses and 89% vaccinated with the first dose [16], and the target set by India was to vaccinate 944.7 million adults ages 18 years or older (68.9% of the total population) [17]. However, in light of the emerging threat posed by the Omicron variant, India on December 25, 2021 announced that it would vaccinate children aged 15 to 18 years and administer additional doses to health care workers, frontline workers, and people aged 60 years and above with comorbidities [18].

According to the trends observed in COVID-19 vaccination program in India, India is among the nations with the highest COVID-19 vaccination coverage globally, with 68% of the Indian population fully vaccinated as compared to 0% in January 2021, which is a proportion higher than the global COVID-19 vaccination coverage [10].

This narrative review was undertaken with the goal of summarizing the vaccination strategies adopted by the government of India to contain the COVID-19 pandemic. The findings from this review could be beneficial for other low- and middle-income countries' containment and immunization efforts, enabling more effective decision-making.

Impact on the Health System

This pandemic has placed a huge burden on India's healthcare system, exposing long-standing deficiencies and exacerbating preexisting disparities. In the country, there are currently 5 hospital beds and 9 doctors per 10,000 inhabitants, highlighting the strain on the medical community and health infrastructure [19,20]. The abrupt and unexpected rise in the number of cases, especially in the second wave, led to a major scarcity of medical oxygen [21]. Due to the fear of catching COVID-19 and movement restrictions, supply-side interruptions and reduced health-seeking behavior had a negative impact on the delivery of vital and emergency healthcare services. The number of babies delivered at health care institutions was reduced by 45% [21], raising the risk of infection and maternal complications from risky delivery practices. Making matters worse, more than 80% of the population still lacks adequate health insurance coverage [22].

Materials and Methods

Narrative reviews usually discuss the "state of the art" on a distinct subject from a contextual or theoretical point of view [23]. This narrative review was conducted with the aim of summarizing the government of India's actions and response against the COVID-19 pandemic.

Search Terms and Strategy

A literature search was conducted on March 24, 2022 using the search terms "coronavirus," "coronavirus disease," "COVID-19," and "COVID-19 vaccine" among the government of India's ministries' publications, guidelines, and websites, such as the

Ministry of Health and Family Welfare (MoHFW), Ministry of Home Affairs, Ministry of Women and Child Development, Ministry of Statistics & Programme Implementation, and Ministry of Railways from April 2020 to March 2022. Additionally, United Nations organizations such as the WHO, World Bank, United Nations Development Programme, United Nations International Children's Emergency Fund (UNICEF), and the Asian Development Bank documents were also searched. We also searched websites of non-governmental organizations working in the field of vaccination uptake in India for pertinent documents and publications. In addition to searching the above-mentioned databases, we screened the bibliographies of included studies and located more eligible studies. The searches were executed independently by 2 reviewers on the review team.

Policy documents and guidelines published in the above-identified databases on COVID-19 vaccination in India were included. There were no restrictions on study design for inclusion in the current review. Policies and guidelines for countries other than India were excluded. Documents based on vaccine initiatives other than COVID-19 vaccines were also excluded.

Data Synthesize and Analysis

Based on the review's objectives, data synthesis was carried out in an iterative manner. The information was extracted under the below-given broad qualitative themes that were predetermined by 2 independent authors.

1. COVID-19 vaccination program planning and implementation
2. Policies developed for COVID-19 vaccination
3. Prioritization of beneficiaries for COVID-19 vaccination
4. Vaccine regulations and available vaccine options
5. Vaccine hesitancy and Information, Education & Communication (IEC)campaign
6. Vaccine monitoring and planning
7. Service delivery system
8. Digital health solution for COVID-19 vaccination: Co-WIN
9. Innovations for COVID-19 vaccination
10. Adverse events following immunization

After data extraction, the review team organized and analyzed the data that emerged under broad themes. Following that, a slew of sub-themes emerged. We attempted to go beyond simply describing and summarizing the major elements of the included studies in our analysis. Instead, we attempted to draw comparisons based on similarities and differences between studies, as well as to investigate relationships within the data.

Results and Discussion

Nationwide Vaccination Planning

India developed its COVID-19 vaccination program according to 3 parameters: (1) Epidemiological and scientific evidence; (2) WHO guidelines for COVID-19 vaccines; (3) Best practices on vaccination around the globe.

Based on a methodical edge-to-edge management technique, India's COVID-19 vaccination program was accomplished by the efficient and effective engagement of states/Union Territories and the community. The government of India has been steadfast and assertive in its commitment to the COVID-19 vaccination program, which ranges from expanding research and development capacity to enabling vaccine production to vaccinate every Indian individual at the utmost priority.

- The government of India's vaccination plan is based on scientific methodology that has consisted of the following early and proactive steps since April 2020
- The Task Force for Focused Research on the COVID-19 Vaccine was established in April 2020 to encourage in-house research and development of drugs, diagnostics, and vaccines.
- The National Expert Group on Vaccine Administration for COVID-19 (NEGVAC) was constituted in August 2020 to articulate a comprehensive action plan for vaccination.
- The Empowered Group on Vaccine Administration for COVID-19 was constituted in January 2021 to expedite the optimal utilization of information technology to make COVID-19 vaccination inclusive, transparent, operable, and scalable.

As an essential requirement for COVAX AMC92 countries, India developed a COVID-19 National Deployment and Vaccination Plan (NDVP) [24], and has relied on guidance from the NEGVAC to guide its deployment activities. The NDVP delivers a robust and comprehensive vaccine deployment strategy that incorporates all key aspects as described [25]. To achieve equitable vaccination, the government has developed a number of policies, including free vaccination at public vaccination centers, several registration alternatives, including help for individuals with disabilities, and multiple delivery modes, such as near-to-home outreach camps [26]. India has followed a need-based approach for the country's COVID-19 vaccination program, which was initiated with the vaccination of all healthcare workers. With time, the program was expanded to frontline workers and people

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over the age of 60, followed by the population over the age of 18 years.

The government of India revised the guidelines for direct procurement of vaccine es and inoculation strategies in response to state government recommendations. Effective from May 1, 2021, state governments and the government of India procured COVID-19 vaccines on a 50–50 sharing regime. Vaccines procured through the government of India will be provided to states free of cost for administration to predefined priority groups [27]. The revised guideline dated June 21, 2021 increased the government of India's share of vaccine procurement to 75% of the total vaccines being produced by the manufacturer and stated that the government of India would deliver these vaccines to states and Union Territories free of cost based on predefined allocation criteria [27]. Therefore, government COVID-19 vaccination centers (CVCs) are inoculating citizens for COVID-19 free of charge. The government of India also provides the number of vaccines allocated to states beforehand for robust planning and further peripheral level allocation.

A few states, along with smaller and more rural private hospitals subsequently reported trouble with handling vaccine financing, procurement, and logistics, which slowed the national COVID-19 vaccination program's progress. States were also supposed to make vaccine availability information available at the district and CVC levels in the public domain and to spread vaccine availability information extensively among the local community, enhancing visibility and accessibility for the eligible population. Domestic vaccine makers were provided with an opportunity to provide vaccine doses directly (25% of their production) to private hospitals in order to boost vaccine manufacturing and encourage novel vaccines. Later, the government of India purchased more than 75% of the vaccines and gave them to the states and Union Territories at no cost.

Based on the regime of 2 vaccination doses per person, it was estimated that around 1,889.4 million vaccine doses would be required to vaccinate 68.91% of the Indian population aged 18 years or above (944.7 million people) [17]. On December 25, 2021, it was decided to update the scientific prioritization and COVID-19 vaccination coverage based on the detection of the Omicron variant, which was categorized as a variant of concern by the WHO, scientific global evidence and practices, along with in-house recommendations from the National Technical Advisory Group on Immunisation and Standing Technical Scientific Committee [18]: (1) Inoculation of Covaxin for children aged 15 to 18 years from January 3, 2022. (2) Based on sequencing and prioritization, healthcare workers and frontline workers will receive a precaution dose from January 10, 2022. (3) Based on the doctor's advice, a precautionary dose of the COVID-19 vaccine will be provided to all citizens aged 60 and above with a known comorbidity after the completion of 9 months or 39 weeks following the second dose.

Inoculation with the Corbevax vaccine for children aged 12 to 14 years was planned to start on March 16, 2022, and precautionary doses would be given to all citizens aged 60 years and above on the same date [28]. The priority group-wise vaccine dose requirements are shown in Table 1, and different phases of the COVID-19 vaccination program in India are summarized in Table 2.

Vaccine Regulations

The government has developed regulatory recommendations for vaccine development, with special attention paid to COVID-19 vaccines [29]. Two vaccines, Covishield and Covaxin, manufactured by Serum Institute of India and Bharat Biotech International Limited, respectively, have been a part of the government's COVID-19 national vaccination program since its launch on January 16, 2021. Six other vaccines have been granted approval for emergency use in India. These include:

- Sputnik V (received emergency use authorization [EUA] from the Drugs Controller General of India in April 2021 and is now being administered in India at private vaccination centers)
- Moderna (received an EUA in June 2021 for import and deployment by Cipla)
- Janssen (Johnson & Johnson single-dose vaccine; received an EUA in August 2021)
- ZyCoV-D (DNA-based vaccine approved for emergency use in those aged 12 years and above in August 2021)
- Covovax (protein subunit vaccine; EUA received in December 2021)
- Corbevax (protein subunit vaccine, received an EUA in Dec 2021)

In addition, the government waived the requirement for a bridging trial for these imported vaccines on May 27, 2021 [30]. This will make it easier to receive imported vaccinations and bulk medication materials, as well as make the best use of domestic fill and finish capabilities. Various vaccine options are available in other South Asian countries, such as Afghanistan (Covishield, AstraZeneca [AZD1222], Sinopharm BIBP COVID-19 vaccine, J&J/Janssen Single-Shot COVID-19 vaccines), Bangladesh (AstraZeneca-Covishield), Pfizer, Sinopharm, and Moderna), Bhutan (AstraZeneca-Oxford, Sinopharm, Moderna) [31]. J&J/Janssen, Pfizer, Moderna, and Novovax are the other vaccines approved in the United States and Europe [32,33].

Table 1. Vaccine prioritization and allocation plans by phase

Phase	Commencement date	Priority group	Eligible population (million)	% of total population	No. of doses required (million)[a]
1a	January 16, 2021	Health care workers	10	0.73	20
1b	February 2, 2021	Frontline workers	20	1.46	40
2a	March 1, 2021	Senior citizens (≥ 60 years) & those above 45 years with defined comorbidities	138	10.07	276
2b	April 1, 2021[b]	Population 45–59 years of age	209	15.27	418
3	May 1, 2021	Population 18–44 years of age	597	43.57	1,194
4a	January 3, 2022	Population 15–18 years of age	74	5.41	148
		Total	1,018[c]	74.32	2,037
4b	January 10, 2022	Health care workers and frontline workers	28[d]		28
		Senior citizens (≥ 60 years)	137		137
5	March 16, 2022	Population 12–14 years of age	46	3.39	92
		Total Doses Required		77.71	2,297

[a]Assuming a 2-dose regime (wastage not factored in). [b]Population aged 45–59 years with comorbidities were made eligible for vaccine access on March 1, 2021 along with the priority group of senior citizens (60 years and above) followed by extension of vaccine access to all citizens aged 45 years and above from April 1, 2021. [c]Population aged 15 and above, 76.51% of total population of 1,371 million. Health care and frontline workers are included in their respective age category. [d]As of December 26, 2021, some health care and frontline workers are still receiving their first doses, and 8.387 received first doses in December 2021.

Vaccine Hesitancy

The WHO defined vaccine hesitancy as "delay in acceptance or refusal of vaccines despite availability of vaccine services" [34]. In the near past, vaccine hesitancy has resulted in a 30% rise in measles cases worldwide, including in the USA where measles had been eradicated in 2000 [35]. This prompted the WHO to declare vaccine hesitancy as 1 of the 10 biggest threats to global health. Although India has achieved more than 1.5 billion vaccinations, health care workers and frontline workers have reported general population resistance and apprehension to COVID-19 vaccination in the early stages of the vaccination program, which acted as a critical barrier to service delivery [36]. The COVID-19 Trends and Impact Survey in India has reported a vaccine acceptance rate of 77% among the Indian population and a vaccine hesitancy rate of 23% among respondents, of whom 16% reported "reluctance to vaccine" and 12% reported "not taking COVID-19 vaccines". The 2 major factors associated with hesitancy were "to wait and see if vaccines are safe" and "I think other people need it more than I do right now" [36]. Alternatively, more than three-quarters of men and 73% of women showed a strong willingness for COVID-19 vaccine uptake. An online survey conducted by Chandani et al. [37] in December 2020 in India found that 67% of the participants showed willingness to receive the COVID-19 the vaccine, 23% were not sure, and one-tenth of the participants refused to receive the vaccine. As compared to other South Asian countries, a study conducted by Marzo et al. [38] reported vaccine hesitancy rates in Indonesia (10.2%), Malaysia (18.8%), Myanmar (7.2%), Philippines (7.7), Thailand (52.1%), and Vietnam (3.7%). Another systematic review conducted by Yasmin et al. [39] on COVID-19 vaccine acceptance in the USA reported the COVID-19 vaccine acceptance rate ranged from 12% to 91.4%, demonstrating a huge gap in vaccine uptake. Another multi-country study conducted by Hawlader reported that the vaccine acceptance rate in India was 65.7%, Pakistan (71.5%), Nepal (74%) and Bangladesh (65%) [40]. The government of India has launched a COVID-19 vaccine communication strategy to address vaccine hesitancy and debunk myths and misconceptions related to COVID-19 vaccines [41].

Information, Education, and Communication Campaign on Vaccine Hesitancy in India

United Nations agencies such as UNICEF have developed a series of media campaigns on the following topics in collaboration with the Yale Institute for Global Health, UNICEF, and Facebook [36].

1. Filling information gaps with emphasis on vaccine safety and efficacy: This campaign aimed to fill the information gap by reflecting rigorous testing by scientists and advocacy for the COVID-19 vaccine to prevent the spread of COVID-19.
2. Countering the "wait and see" approach: This time-based approach highlighted the urgency of the COVID-19 vaccine with a message saying, *"Every day you wait to get vaccinated is another day that you could be spreading COVID-19 in your family and community."*

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Table 2. Phases of the COVID-19 vaccination program in India

Phase	Date	Key features
Phase 1	January 16 to February 28, 2021	- Vaccination permitted for HCWs and FLWs. - Procurement arrangement: 100% of vaccine doses procured by the Government of India and provided free of cost to state/UT governments for being administered.
Phase 2a	March 1 to 31, 2021	- Vaccination permitted for persons above the age of 60 years and those above 45 years with defined comorbidities. - Procurement arrangement as in phase 1.
Phase 2b	April 1 to 30, 2021	- Vaccination permitted for all persons above the age of 45 years. - Procurement arrangement as in phase 1.
Phase 3 (liberalized pricing and accelerated national COVID vaccination strategy)	May 1, 2021 to June 20, 2021	- Vaccination permitted for persons aged 18–44 years in addition to priority groups (HCWs, FLWs, persons above the age of 45 years). - Procurement arrangement: • 50% of vaccine doses to be procured by the government of India for being administered by states/UTs to priority groups. • 50% of vaccine doses to be procured by state governments and private hospitals to be administered to persons between 18 to 44 years of age.
Phase 4 (revised guidelines for implementation of the National COVID-19 Vaccination Program)	June 21, 2021 to January 2, 2022	- Permitted population groups remain the same. - However, the government of India will procure 75% of the vaccine doses being produced by the manufacturers in the country. The vaccines so procured will be provided free of cost to states/UTs. These doses will be administered by the states/UTs free of cost to all citizens above 18 years of age as per priority through government vaccination centers. - Domestic manufacturers permitted to provide vaccines to private hospitals only to the ceiling of 25% of their monthly production.
Phase 5a (COVID-19 vaccination of children between 15–18 years)	January 3, 2022	- In addition to the priority group aged 18 years and above, vaccination permitted for children in the age group of 15–18 years. - The only vaccination option would be Covaxin.
Phase 5b (COVID-19 precautionary dose to HCWs, FLWs & 60+ population with comorbidities)	January 10, 2022	- In addition to the priority group aged 15 years and above, a precautionary dose of the COVID-19 vaccine is permitted for HCWs, FLWs, and all persons aged 60 years and above with comorbidities who have received 2 doses of the COVID-19 vaccine. - The prioritization and sequencing of this precautionary dose would be based on the completion of 9 months (i.e., 39 weeks) from the date of administration of the second dose.
Phase 6 (children aged 12–14 years and precautionary dose for 60+ population)	March 16, 2022	- Only the Corbevax vaccine would be used for children aged 12–14 years. - Precautionary doses will be given to all individuals aged 60 years and above. - The prioritization and sequencing of this precaution dose would be based on the completion of 9 months (i.e., 39 weeks) from the date of administration of the second dose.

COVID-19, coronavirus disease 2019; HCW, health care worker; FLW, frontline worker; UT, Union Territory.

3. National pride: With the aim of obtaining social approval for the COVID-19 vaccine through social media, this campaign expressed that India developed an indigenous vaccine that it will share with other countries, with messages such as "Make India #1 in COVID-19 vaccination" and "Don't let India down, get vaccinated against COVID-19."
4. Testimonials and messengers: An analysis from social media showed that vaccinated individuals shared their vaccination testimonies and also encouraged others to get vaccinated.

Vaccination Monitoring and Planning

India is employing a whole-government approach to vaccination deployment, which includes 19 federal ministries of the government of India, state governments, and other government organizations and apex bodies, such as the Indian Council of Medical Research and National Institution for Transforming India (NITI Aayog). Because of their importance, the Prime Minister's office, Parliament, and the Supreme Court, as well as institutional control mechanisms, closely monitor statewide COVID-19 immunization programs. The government has a strong

cascading system of decentralized planning, coordination, and implementation procedures with clearly defined roles and responsibilities at the federal, state, district, and block levels. The NEGVAC was established at the national level and offers guidance on all areas of the vaccination strategy, including equitable vaccine procurement and distribution, delivery systems, prioritizing, and safety surveillance [42]. Task forces have been formed at the state, district, and block levels, with clear budget outlay plans for each level under the leadership of state steering committees. There are also operational control rooms at the state, district, and block levels that operate throughout the day and night. Supervisors are also assigned 3–5 vaccination sites, which they visit twice a day.

With 4 government medical store depots, 37 state vaccine stores, 118 regional vaccine stores, 726 district vaccine stores, and 28,575 sub-district cold chain points located at community health centers, primary health centers (urban and rural), and sub-centers, India has a fully operational cold chain system under the Universal Immunization Programme.

Service Delivery

There are around 234,772 CVCs in India, with 215,927 being government-run and 18,845 being privately run [43] with the provision of providing routine immunization services. The system has considerable human resource capacity, with the option of deploying retired auxiliary nurses and midwives, retired staff nurses or nursing assistants, pharmacists, lab technicians, and nursing students on a temporary basis. Each team must have at least 5 professionals to handle verification, crowd management, ensuring COVID-19-appropriate behavior, vaccination, and observation for any potential adverse events following immunization (AEFIs), as well as a supervisor who oversees 3 to 5 vaccination sites [24]. For vaccination, all private facilities that were enrolled in various insurance plans, as well as any other private facilities that met the operational capacity requirements, were engaged. Furthermore, private-sector experts were included in the state, district, and block-level task forces to strengthen engagement. Private facilities can purchase vaccines directly from the manufacturers (up to 25% of their monthly supply) [34]. On April 11, 2021, the government also issued guidelines for private employers to inoculate their eligible employees through private CVCs (workplace vaccination) [44].

Co-WIN: a Win Over COVID-19

Co-WIN is a comprehensive, cloud-based, end-to-end, and digital platform for planning, implementation, registration, and monitoring of COVID-19 vaccination from the central to peripheral levels [45,46]. Registration for vaccination on this digitalized platform is obligatory to record vaccination data and ensure transparency and accountability. A single digital public portal could also promote awareness, leaving little room for myths, thereby also addressing the issue of vaccine hesitancy with higher precision. India's vaccination drive was initiated with the Co-WIN platform and now includes a beneficiary module covering an online pre-registration system, beneficiary verification, beneficiary ID, vaccination slot booking at centers of choice with the vaccination of choice, second-dose follow-up, and a digital vaccination certificate [46]. Co-WIN is linked with other preexisting government digital platforms such as *Aarogya Setu, Digilocker*, and *Umang* to download vaccination certificates.

The Co-WIN platform also ensures that the following tasks are carried out:

- Verifiable data are available to all vaccinated individuals.
- A second dose of the same vaccine is provided to the beneficiary.
- The time prescribed by the government of India guidelines between both doses should be maintained.
- A vaccine dose is administered to an identifiable individual through verification.
- The platform provides a linkage between beneficiary registrations and vaccine availability for improved planning.
- Available data is useful for future pandemic planning and research.

Furthermore, the digital vaccination data enable the program managers to:

- Monitor the vaccination status of any state, district, or population group in real time.
- Monitor vaccine availability and utilization for improved planning at the national level and below.
- Evaluate vaccine waste and take immediate steps to reduce waste.
- Make it easier to refer individuals to future digital health interventions, such as the administration of booster shots.

Registration without Using the Co-Win Portal

To enable the registration and vaccination of persons without access to a smartphone or the internet, registration of beneficiaries can be done through a common service center. Up to 4 persons can be registered using a mobile phone, allowing the registration of a person by friends and family members. An assisted registration facility is made available through a 1,075 helpline/call center; vaccination slots can also

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be booked by sending the WhatsApp message "book Slot" to MyGovIndia Corona Helpdesk's number (+91-9013151515) [47]. This is further backed up by facilities that provide walk-in registration and vaccination. Furthermore, in areas without internet connectivity, vaccination sessions can still be organized. In such cases, the vaccination records are prepared in reporting formats and entered into the Co-WIN platform for the generation of vaccination certificates. The Co-WIN system receives over a billion visits per day and has recorded 3.1 billion visits per day for booking vaccine slots [48].

Innovations in the Vaccination Drive

The Indian government launched a month-long door-to-door campaign called *Har Ghar Dastak* in November 2021 to encourage people to get fully vaccinated, with the goal of covering all eligible beneficiaries with the first dose and all due beneficiaries with the second dose through reaching out to all missed-out and dropped-out eligible beneficiaries via house-to-house visits [49]. The COVID-19 vaccination drive is being coordinated as a *Jan Bhagidari Andolan* (people's participation) program and has involved stakeholders from various ministries or departments, medical colleges, media houses, non-governmental organizations, professional organizations, civil service organizations, the private sector, youth, and women's networks.

Management of AEFIs

The Co-WIN platform is linked with the WHO-supported Surveillance and Action for Events Following Vaccination (SafeVAC) application for the monitoring of AEFIs [46]. Adverse events are categorized as minor, severe, and serious, and those following vaccination will be reported in Co-WIN either by the vaccinator or by the district immunization officer (DIO). DIOs can access the Co-WIN SafeVAC for serious or severe AEFIs via a single Co-WIN login and then fill out a case report form, preliminary case investigation form, and final case investigation form and submit the materials. Furthermore, all AEFIs must be recorded in AEFI registers at planning units and notified on a weekly basis. This enables the analysis of AEFI cases using both automated data mining and proper statistical approaches to spot alarming trends quickly.

Immunization Waste Management

The biomedical waste management (BMWM) guidelines (2016 and later changes) spell out the requirements for the generation, storage, transportation, disinfection, treatment, and disposal of biomedical waste, which includes vaccination waste [50]. Additional guidance has been provided for BMWM from the COVID-19 immunization program under UIP 2021 [51]. The biomedical waste monitoring software "COVID-19 BWM" was also created for trash generators, carriers, and treatment and disposal facility operators. In the United States, immunization wastage is being reported through VTrckS ExIS (External Information System) interface [52].

Accessibility of Vaccines to the Marginalized, Women, and Hard-To-Reach Areas

MoHFW has issued guidelines for differently abled and senior citizens to get vaccinated at nearby CVCs [26], and some states or municipal corporations provide additional services such as beneficiary transportation [53] for vaccination. Special vaccination sessions are also organized at government CVCs for people such as nomads or migrants, inmates in prisons or mental health institutions, elderly home populations, beggars, residents in rehabilitation centers or camps, and any other identified eligible individuals [54].

Learnings from India's COVID-19 Vaccination Program

India's COVID-19 vaccination program is built on epidemiological evidence, WHO guidelines, and best practices, and it is implemented through a multidimensional approach and active participation of all states and Union Territories. The strategies adopted by India could assist other countries in the implementation of their nationwide vaccination programs in the COVID-19 pandemic or a future pandemic. This may include:

- Prioritization of the eligible population: India initiated COVID-19 vaccination with health care workers, and then expanded vaccination to frontline workers, the population aged more than 60 years, followed by those aged more than 45 years and eventually the population aged 18 years and above [27]. This step-wise approach may assist other countries in prioritizing their population for vaccination programs in ongoing and future pandemics.
- Resource mobilization: (1) The use of trained community health workers, such as accredited social health activists (ASHAs), was critical in mobilizing and connecting the community with the health system. An ASHA is a trained female community health activist belonging to the same village who supports routine immunization and other health services. Recently, the WHO named them global health leaders for providing immunization services during the COVID-19 pandemic in India [55]. (2) Capacity building: Quality training has been provided to health care workers involved in providing immunization services for the successful introduction of COVID-19 vaccines

in India. These training sessions were followed by the nationwide "dry run" conducted in January 2021, which assisted India in preparing for COVID-19 vaccination. (3) Cold chain management: The temperature of COVID-19 vaccines in India needed to be maintained between +2°C to +8°C and stored in walk-in-coolers at state or regional vaccine stores. The cold chain requirement for COVID-19 vaccines in the immunization supply chain can be estimated based on the calculation given in the operational guidelines (Page 91) for COVID-19 vaccination [25].

This is easier said than done, as the last-mile logistics of vaccines in a vast country like India is a difficult task. As an alternative, micro-cold storage, which is known to be quiet, hygienic, portable, without moving parts, and dependable for last-mile vaccine logistics was proposed as a method to deliver vaccines to remote rural areas was also proposed [56].

The manufacturers of vaccines airlifted vaccines in cold boxes with digital temperature tags to 4 major government medical supply depots in Karnal (Haryana), Mumbai, Chennai, and Kolkata, where they are kept in walk-in coolers. The vaccines would then be transported by planes or insulated vans to designated stores in 37 states and Union Territories. The state and Union Territory governments transport them from these 41 centers to temperature-controlled facilities at district-level vaccine stores. Vaccines are stored in ice-lined refrigerators in districts before being transported in cold boxes to distribution centers and then in ice-packed vaccine carriers to vaccination sites. The electronic Vaccine Intelligence Network (eVIN) already monitors the temperature of 29,000 cold chain points in real time [55].

- Use of digital health technology: Other countries may benefit from digital health technologies, such as Co-WIN for planning, implementation, registration, and monitoring of COVID-19 vaccination for current or future pandemics. This system provides support in scheduling sessions and implementing the vaccination process from the central level to the peripheral level.

Wherever possible, virtual training methods were used to train human resources. The newer training modalities emphasized "the new normal" (i.e., mitigation of the risk of transmission). The Integrated Govt. Online Training portal on the Ministry of Human Resources and Development's DIKSHA platform for the capacity building of frontline workers on COVID-19 [57].

- Vaccine hesitancy: India has addressed vaccine hesitancy in a variety of ways [34]. (1) Community engagement with communication approaches to build trust in COVID-19 vaccines. (2) Identification of high-risk groups, areas, and communities known for prior experiences of vaccine hesitancy and the involvement of local leaders to address fear and build trust among those identified. (3) The involvement of influencers at both local and national levels to promote COVID-19 vaccine safety and efficacy. (4) Real-time monitoring of digital media to address myths and misconceptions related to COVID-19 vaccines.

Limitations

This narrative review was conducted while India's COVID-19 vaccination program was still ongoing. New innovations may occur with time; therefore, this review will require a timely update based on the guidelines and policies related to COVID-19 vaccination. This review lacked specific criteria for the selection of articles or documents, and there was no evaluation of the validity of the selected documents. The findings of this review were limited by a lack of quantitative data, as this review reported qualitative data only.

Conclusion

This review summarizes India's proactive response to COVID-19 through different measures such as vaccination planning and initiatives. Vaccination prioritization, resource mobilization, capacity building, addressing vaccine hesitancy, and embracing digital health technology such as CO-WIN played a vital role in achieving 1.5 billion vaccinations in India. The paper, in a nutshell, attempted to capture the vaccination process and strategies used for the implementation of the national COVID-19 vaccination program in India. The country's healthcare system was largely unprepared to cope with the pandemic, but it resorted to efficient and innovative real-time implementation to deal with it.

This review contributes guidance as a document for knowledge sharing, which could support other countries in their fight against this pandemic. This review also reflects India's iterative process of dealing with COVID-19 and provides vital lessons on how to minimize the impact of COVID-19, which will prepare other countries for current and future pandemics. In countries such as India, focusing on social norms and promoting cohesion could be a vital strategy for vaccine hesitancy.

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Notes

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Review Article

Effects of medication adherence interventions for older adults with chronic illnesses: a systematic review and meta-analysis

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ABSTRACT

This systematic review and meta-analysis aimed to understand the characteristics of medication adherence interventions for older adults with chronic illnesses, and to investigate the average effect size by combining the individual effects of these interventions. Data from studies meeting the inclusion criteria were systematically collected in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analysis guidelines. The results showed that the average effect size (Hedges' *g*) of the finally selected medication adherence interventions for older adults with chronic illnesses calculated using a random-effects model was 0.500 (95% confidence interval [CI], 0.342–0.659). Of the medication adherence interventions, an implementation intention intervention (using face-to-face meetings and telephone monitoring with personalized behavioral strategies) and a health belief model–based educational program were found to be highly effective. Face-to-face counseling was a significantly effective method of implementing medication adherence interventions for older adults with chronic illnesses (Hedges' $g = 0.531$, 95% CI, 0.186–0.877), while medication adherence interventions through education and telehealth counseling were not effective. This study verified the effectiveness of personalized behavioral change strategies and cognitive behavioral therapy based on the health belief model, as well as face-to-face meetings, as medication adherence interventions for older adults with chronic illnesses.

Keywords: Aged; Chronic disease; Medication adherence; Meta-analysis; Review

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Introduction

Corrective and effective medications are the best way to manage chronic illnesses. Approximately 50% of older adults in South Korea have at least 3 chronic diseases, increasing the risk of polypharmacy in terms of non-adherence to medications [1,2]. Around 37% of Korean older adults with chronic illnesses take 5 or more medications [2]; among Organisation for Economic

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Co-operation and Development members, South Korea was reported to have the highest consumption of digestive and metabolic medicines and an antibiotic prescription rate 1.7 times higher than average [3].

The estimated rate of adherence to long-term medication regimens is approximately 50.0% in older adults, and this rate is lower in older adults due to numerous comorbidities and consequent polypharmacy [1]. Non-adherence reduces the efficacy of chronic illness treatment [4], and patients with chronic illnesses and low socioeconomic status have shown high rates of medication non-adherence [5]. Older adults reportedly stop taking medications due to complicated drug delivery regimens and high prices [1]. According to a previous study, 74.1% of older adults who take 4 or more medications daily stated that medication regimen complexity was the main barrier to medication adherence. Furthermore, 68.3% of patients over the age of 60 did not know the name of the medications they were taking and were unable to correctly take medications due to lack of knowledge about the disease (63.3%), inadequate knowledge regarding therapy (60.0%), taking many pills at the same time (51.7%), forgetfulness (50.8%), difficulty remembering to take all their pills (48.3%), and difficulty in refilling prescriptions on time (20.0%) [6]. Various factors, such as the patients themselves, medications, health care providers, health care systems, and socioeconomic factors, have been shown to influence medication adherence in older adults. Nonetheless, medication adherence is important for ensuring that therapeutic benefits are delivered to patients [7].

Older adults with chronic diseases living in the community have to take long-term medications, and it can be difficult for the elderly to take their own medications and manage side effects. For this, nursing interventions are needed to help them take medicines correctly. Regarding interventions for promoting medication adherence among patients with chronic illnesses, reminder calls based on medication event monitoring systems are more effective than motivational interviewing, and are also cost-effective [4]. Applying home-based nurse-driven follow-up care for outpatients with hypertension improved the physical component of health-related quality of life, and significantly improved medication adherence and symptom counts [8]. Educational short message services, reminder short message services for medications, and structured telephone support have also been shown to improve self-care behavior, including medication compliance, for patients with chronic illnesses [9]. Text messaging and an interactive voice response intervention to promote adherence among this high-risk group were found to be efficacious [5]. Psychological interventions, such as cognitive behavioral therapy (CBT), including motivational interviewing, also help improve adherence to medication [10].

It is necessary to systematically analyze the characteristics, methods, and effects on outcome variables of various medication adherence programs applied to older adults with chronic diseases, and use these outcomes as a basis for developing effective medication adherence interventions for this population. However, many studies have either not addressed interventions focused on older adults, making it difficult to expect the same effect when applied to this group [4,11,12], or approached medication adherence as part of overall chronic illness management instead of the sole focus [13–15]. Thus, it has been difficult to find strategies to improve medication adherence, which is essential for the management of chronic illnesses, considering the cognitive and physical characteristics of older adults. Therefore, this study aimed to identify the effects of various medication adherence intervention programs for older adults with chronic illnesses to develop effective interventions for evidence-based nursing practice, improve the medication adherence of older adults, and provide directions for future research.

The purpose of this study was to conduct a meta-analysis of the effects of intervention programs related to medication adherence in older patients with chronic illnesses. First, this study aimed to identify the characteristics of intervention programs, assess the methodological quality of medication adherence intervention program studies that were randomized controlled trials (RCTs), analyze the effect size of the medication adherence intervention programs, and evaluate publication bias.

Materials and Methods

Literature Selection Criteria

This study was conducted according to the Cochrane Collaboration's systematic literature review handbook on mediation methods [16], and the guidelines for reporting on systematic literature reviews suggested by the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) group for the intervention method of the Cochrane Collaboration [17]. However, this review study was not registered. The following selection criteria were utilized within the participants, intervention, comparisons, outcomes, timing, setting, and study design (PICOTS-SD) framework.

Selection criteria

Participants

The participants of the studies were older men and women aged 60 years and above who had been diagnosed with 1 or more chronic diseases by a doctor and were taking medications regularly.

Interventions

The types of interventions related to medication adherence included education or information, counseling or psychotherapy, behavioral therapy, social support, or interventions that combined these methods.

Comparisons

The participants were compared with older patients with chronic illnesses who did not receive the medication adherence interventions and were receiving usual care from the hospital or community health centers.

Outcomes

The major outcomes of the intervention were medication adherence and physical and psychological variables related to medication adherence.

Timing

Only results measured immediately after major interventions were included.

Setting

Only interventions conducted on an outpatient basis at a health center, hospital, public hospital's outpatient clinic, general practice, or primary health care unit were included. Interventions conducted while patients were admitted to the hospital were excluded.

Study design

Since the study design has an important effect on the reliability and generalizability of the results of intervention studies, only RCTs were included.

Literature Search and Selection Process

Literature search strategy

The literature search and selection were conducted using electronic databases, targeting papers published in English over the last 10 years until August 11, 2020. We searched Medline and PubMed as electronic databases indexing research in the medical field, as well as the Cumulative Index to Nursing and Allied Health Literature (CINAHL).

Search terms

The following search terms were selected, including Medical Subject Headings (MeSH) for the literature search: "aged" (MeSH) OR "elderly" AND "chronic disease" (MeSH) OR "chronic illness" OR "hypertension" OR "diabetes mellitus" OR "arthritis" for participants, and "medication adherence" (MeSH) OR "medication compliance" (MeSH) for interventions. Searching only for the term "chronic diseases" could have excluded studies on specific chronic diseases, such as hypertension, diabetes, and arthritis; therefore, the search formula was expanded to include the names of major chronic diseases. Search modifiers included full text, RCTs over the last 10 years, English, and humans.

Data selection

All 3 researchers independently participated in the search and data selection process, selected studies based on the selection and exclusion criteria, focusing on the core questions, and conducted discussions to resolve any disagreements. The researchers reached a consensus in all cases.

The final number of studies found based on the search strategy for each database was 706: 56 in Medline, 615 in PubMed, and 35 in CINAHL. Of these, 188 papers were extracted after reviewing the titles and abstracts to exclude duplicate studies, studies on interventions unrelated to the topic, simple drug therapy studies, and studies not including interventions. The core questions were re-examined based on the full text of the extracted studies. As a result, 7 studies were selected, excluding 108 that did not meet the criteria for selecting participants, 9 in which the intervention content did not center on medication adherence, and 64 that did not measure medication adherence as an outcome variable. All 7 studies were included in the meta-analysis after quality assessment (Figure 1).

Ethical Considerations

This study was exempted from review by the Institutional Review Board of Cheongju University, the institution of the lead researcher, to ensure ethical and scientific validity for the overall research (approval number: 1041107-201904-HR-017-01).

Quality Assessment of the Included Studies

To enhance the validity of the research results, a methodological quality assessment was conducted on the 7 studies ultimately selected. Since all 7 studies were RCTs, we used Cochrane's Risk of Bias tool [16], which consists of 7 items, including sequence generation, allocation concealment, blinding of participants, personnel and outcome assessors, incomplete outcome data, selective outcome reporting, and other sources of bias. Each

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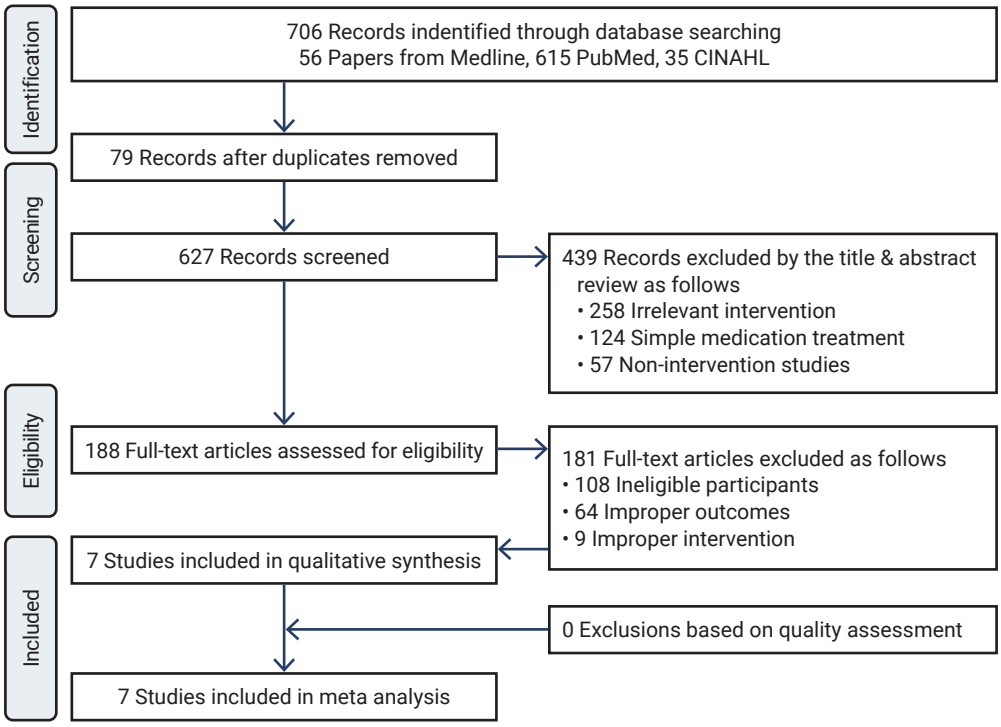

Figure 1. Flow diagram depicting the process of study selection for the meta-analysis.

item is assessed as "yes," "no," or "unclear." Independent quality assessments were conducted by the 3 researchers, whose main fields of study were related to the topics of this study and who were professors of nursing and experienced with systematic literature reviews and meta-analyses. If there was any disagreement regarding an item, the results were determined by sufficient discussion and rigorous re-examination.

Data Analysis

The 7 selected studies were analyzed using the Comprehensive Meta-Analysis 3.0 program (Biostat Inc., Englewood, NJ, USA). After testing for homogeneity between studies through the Q-test, the average effect size was calculated by combining the effect sizes of the individual studies. If the studies were not homogeneous, the average effect size was calculated using a random-effects model that reset the weights considering the variation among participants included in individual studies and the heterogeneity of each study [18]. In the present study, the standardized mean difference, Cohen's *d*, as a measure of effect size, was converted into Hedges' *g*, as Cohen's *d* tends to overestimate the effect size in small samples [19]. A Hedges' *g* value in the range from 0.2 to less than 0.5 indicates a small effect, a value from 0.5 to less than 0.8 indicates a medium effect, and a value of 0.8 or greater indicates a large effect [20]. A visual analysis was performed to test for publication bias using a funnel plot, which was a scatter plot drawn with the treatment effect measured in each study on the x-axis and a scale indicating the precision of the study (number of samples or standard error) on the y-axis. The statistical analysis of asymmetry was performed using Egger regression analysis.

Results

Descriptive Summary of the Included Studies

Table 1 summarizes the characteristics of the 7 studies selected for analysis [21–27]. The following types of medication adherence interventional programs for older adults with chronic illnesses were ultimately selected: an educational program based on the health belief model [21], a remote medication monitoring program [22], a structured pharmacist-led intervention [23], a pharmacist-led care program [24], a complex intervention on prioritizing multiple medications [25], a motivational interviewing program [26], and an implementation intention intervention [27]. All the selected studies except 1 [23] included both male and female participants. Five studies selectively applied interventions to patients with certain chronic illnesses (hypertension, chronic heart failure, chronic obstructive pulmonary disease [COPD], and diabetes), and 2 studies selected participants with "chronic diseases." In all 7 studies, the average age of

Table 1. Descriptive summary of studies included in the meta-analysis

No.	Study	Year of publication	Study design	Participants		Interventions				Interventions for control group	Follow-up	Measured outcomes
				Gender/ chronic diseases	Sample size/mean age (y)	Major type	Program context	Application	Session/ duration			
1	Yazdanpanah et al. [21]	2019	RCT	Both/ hypertension	IG:30/69.1 CG:30/63.9	Educational program	Eight educational sessions based on the health belief model (susceptibility, perceived severity and susceptibility, teaching perceived severity and susceptibility, patient's familiarity with perceived benefits and barriers, promoted self-efficacy, stimulus of cue to action)	Lectures, questions and answers, group discussions, use of desirable role behavior model using supplementary tools and guide sheets	8 sessions /60 min/ for a month	Typical routine services	None	- Medication adherence (MMAS-8)
2	Hale et al. [22]	2016	RCT	Both/Chronic heart failure	IG:13/68.4 CG:16/74.4	Telehealth & counseling (remote medication monitoring system)	The MedSentry medication monitoring system: a remotely monitored electronic device that alerts participants when it is time to take their medications. A monitoring center with advisors who contact participants and caregivers when medications are not taken. The device is installed in the participant's home and data are transmitted to the monitoring center via the internet.	The MedSentry medication monitoring system (device) used several methods to ensure participants take their medications as prescribed (visual cue, audio alarm, etc.)	90 d	Usual medication reminder method	None	- Medication adherence (MOS) - Health status - Depression (PHQ-8) - HRQoL (MLHFQ) - Unplanned hospitalizations - Emergency department visits
3	Abdulsalim et al. [23]	2018	RCT	Male (≥ 94%)/ chronic obstructive pulmonary disease	IG:130/60.6 CG:130/61.1	Structured pharmacist-led counseling intervention	Pharmacist intervention placed emphasis on (1) compliance, (2) smoking cessation, (3) exercise, (4) inhaler use and (5) need for timely follow-up. The counseling sessions (15–20 min) and patient information leaflets emphasized (1) the importance of medication compliance, (2) dose and frequency of medications, (3) need for smoking cessation, (4) simple exercise, (5) proper use of inhaler devices and (6) need for timely monitoring	Pharmacist counseling	6 mo	Standard hospital care	Every 6 mo for 2 y	- Medication adherence (MAQ)

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Table 1. Continued

No.	Study	Year of publication	Study design	Participants		Interventions				Interventions for control group	Follow-up	Measured outcomes
				Gender/ chronic diseases	Sample size/mean age (y)	Major type	Program context	Application	Session/ duration			
4	Korcegez et al. [24]	2017	RCT	Both/type 2 diabetes mellitus	IG:79/61.8 CG:80/62.2	Pharmacist-led educational program	Five face-to-face educational programs with a pharmacist who reviewed medication and treatment plans. Explanation to each patient of the importance of self-monitoring blood glucose, a healthy diet, physical exercise, and smoking cessation and also provision of a different pamphlet during each visit. The pamphlets contained information about type 2 diabetes, complications, medications, treatment goals, and self-care.	Clinical pharmacist's face-to-face education, discussion, recommendations for medication regimens	5 sessions /12 mo	Usual care	None	- Medication adherence (Morisky-Green test) - Hemoglobin A1c, BP, lipid profile, BMI, WC - Self-care activities
5	Muth et al. [25]	2016	RCT	Both/ ≥ 3 chronic conditions	IG:50/75.8 CG:50/75.2	Counseling intervention (complex intervention on prioritizing multiple medications)	Checklist-based interviews with patients on medication-related problems and reconciliation of their medications. Assisted by a computerized decision-support system, discussions of medication intake with patients and adjustments of their medication regimens.	Checklist-based pre-consultation interview, brown bag review, computerized decision support system, physician-patient consultation	5 wk	Usual care	After 6 and 12 wk	- Medication adherence (Morisky-Green test, MAI, MARS) - HRQoL (EQ-5D) - Depression (GDS) - Beliefs in medicine Questionnaire
6	Moral et al. [26]	2015	RCT	Both/chronic diseases	IG:70/75.6 CG:84/76.1	Counseling intervention (motivational interviewing)	MI is a counseling method that involves enhancing a patient's motivation to change behavior. Experimental group providers followed these steps: (1) assessment of ambivalence; (2) exploration of patients' ideas and concerns about their lack of adherence; (3) application of specific interviewing skills for reframing and promoting self-efficacy (using empathy, developing discrepancies, avoiding arguments, confronting barriers and problems, supporting the patient, and others).	Face-to-face motivational interview, counseling	15 min/ 6 mo	Informative personal advice	None	- Medication adherence (Morisky-Green test)

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Table 1. Continued

No.	Study	Year of publication	Study design	Participants		Interventions				Interventions for control group	Follow-up	Measured outcomes
				Gender/ chronic diseases	Sample size/mean age (y)	Major type	Program context	Application	Session/ duration			
7	Trevisan et al. [27]	2020	RCT	Both/type 2 diabetes	IG:45/61.1 CG:45/61.8	Telehealth & counseling (implementation intention intervention)	The intervention was tailored based on the elaboration of action and coping plans, with their respective overcoming strategies. A form specified 3 action plans covering when, where, and how they intended to take their oral anti-diabetic medication over the next 2 months.	Face-to-face meetings, telephone monitoring, in-person behavioral strategies	4 times 15 wk (105 days)	Standard care	None	- Medication adherence (IAGAM) - Hemoglobin A1c

RCT, randomized controlled trial; IG, intervention group; CG, control group; MMAS-8, Morisky Medication Adherence Scale-8; MOS, Medical Outcomes Study; PHQ-8, the 8-Item Patient Health Questionnaire; HRQoL, health-related quality of life; MLHFQ, Minnesota Living with Heart Failure Questionnaire; MAQ, Medication Adherence Questionnaire; BP, blood pressure; BMI, body mass index; WC, waist circumference; MAI, Medication Appropriateness Index; MARS, Medication Adherence Rating Scale; EQ-5D, EuroQol Five Dimension Scale; GDS, Geriatric Depression Scale; IAGAM, Global Evaluation of Medication Adherence.

the participants was 60 years or older, and the number of participants varied from 13 to 130; except for 1 study [22], the number of participants was 30 or more.

All studies were RCTs. There were 3 studies on pharmacist- and physician-led counseling and consultation [23,25,26], 2 on educational programs including lecture lectures [21] and face-to-face education [24], 2 on interventions using group discussion [21,23], and 2 that used medication monitoring systems and telephone monitoring [22,27]. The durations of the programs varied from 1 to 12 months. In most studies, the usual or standard hospital care was applied to the control group, and 2 studies evaluated the results through follow-up. Three studies only measured medication adherence, and 4 studies also evaluated depression, quality of life, and body composition. The Morisky-Green test was the most common tool used to measure medication adherence, as it was used in 3 studies, and other tools included the Morisky Medication Adherence Scale-8 (MMAS-8), Medication Adherence Questionnaire (MAQ), MAI, Medication Appropriateness Index (MAI); Medication Adherence Rating Scale (MARS), Medication Outcomes Study (MOS), Global Evaluation of Medication Adherence (IAGAM).

Quality Assessment of the Included Studies

All 7 studies were RCTs. The qua lity assessment performed using the Cochrane Risk of Bias tool showed that there were 4 studies with sequence generation; 2 studies with allocation concealment; 3 studies with blinding of participants, personnel, and outcome assessors; 7 studies with incomplete outcome data; and 7 studies with selective outcome reporting. The risk of bias was low in all 7 studies. No studies were excluded from the meta-analysis after quality assessment, as there were no cases of a high risk of bias for any item. Three studies were evaluated as "unclear" for sequence generation, 5 for allocation concealment, and 4 for blinding (Figure 2).

Effectiveness of the Medication Adherence Interventions

Effect size of medication adherence by intervention program

In this study, the results of calculating the corrected standardized mean difference (Hedges' *g*) for 7 studies that applied medication adherence interventions for older adults with chronic illnesses are presented as forest plots in Figures 3 and 4. The heterogeneity of all studies—that is, the ratio of the variance between studies to the total variance—was represented by $I^2 = 63.17\%$ ($Q = 16.29$, $p = 0.012$), and the average effect size calculated using a random-effects model, Hedges' *g*, was 0.500 (95% confidence interval

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[CI], 0.342–0.659), indicating a significant effect size. Of the medication adherence interventions, a study [27] that utilized an implementation intention intervention (face-to-face meetings and telephone monitoring with personalized behavioral strategies) had the largest effect size, with a Hedges' *g* of 1.222 (95% CI, 0.619–1.826), and an educational program based on the health belief model [21] was also highly effective, with a Hedges' *g* of 0.883 (95% CI, 0.359–1.407).

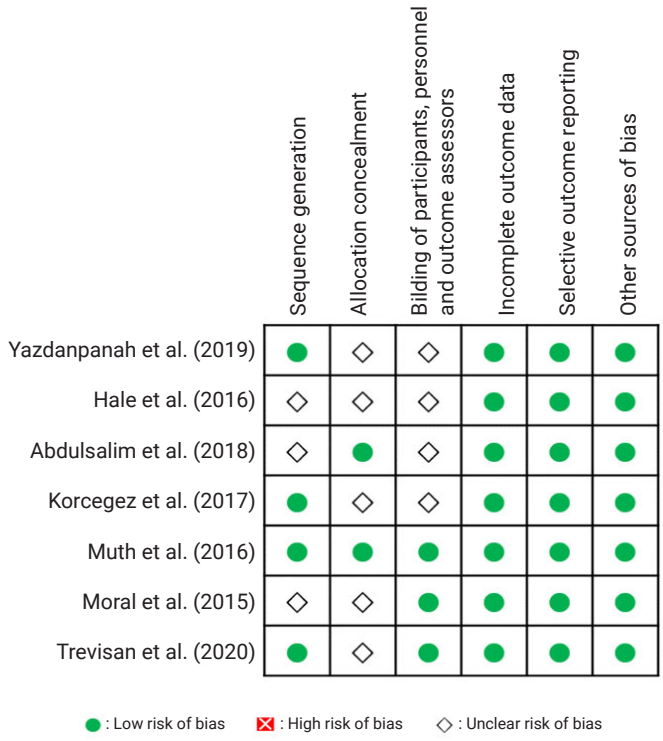

Figure 2. Risk of bias in the included studies.

Effect size according to intervention method

Of the 7 studies, 5 implemented counseling and 2 used education as the major intervention method. Two studies implemented personalized counseling through monitoring with the use of telehealth. Remote intervention methods during a pandemic of an infectious disease such as coronavirus disease 2019 can be highly valuable; therefore, the effects of such interventions were also analyzed in this study.

The average effect sizes of the studies were calculated using a random-effects model. The studies with counseling as a major intervention method had a significant average effect size, with a Hedges' *g* of 0.531 (95% CI, 0.186–0.877; I^2=65.17%; Q=11.48; p=0.022). The studies with education as a major intervention method had a significant average effect size, with a Hedges' *g* of 0.513 (95% CI, −0.157 to 1.184; I^2=77.47%; Q=4.44; p=0.035). The studies with personalized counseling through monitoring with the use of telehealth had a large average effect size, with a Hedges' *g* of 0.717, but this was not statistically significant (95% CI, −0.386 to 1.820; I^2=74.48%; Q=3.92; p=0.048).

Analysis of publication bias

A visual analysis of publication bias was performed using a funnel plot, and Egger regression analysis was performed to objectively interpret the asymmetry of the funnel plot. Egger regression analysis describes the relationship between the effect size and standard error of each study using a regression equation. For the total effect size of the medication adherence intervention programs analyzed in this study, clear asymmetry was not found in the funnel plot. The intercept was 0.65 (t=0.65, p=0.784), indicating that the effect size was not asymmetric.

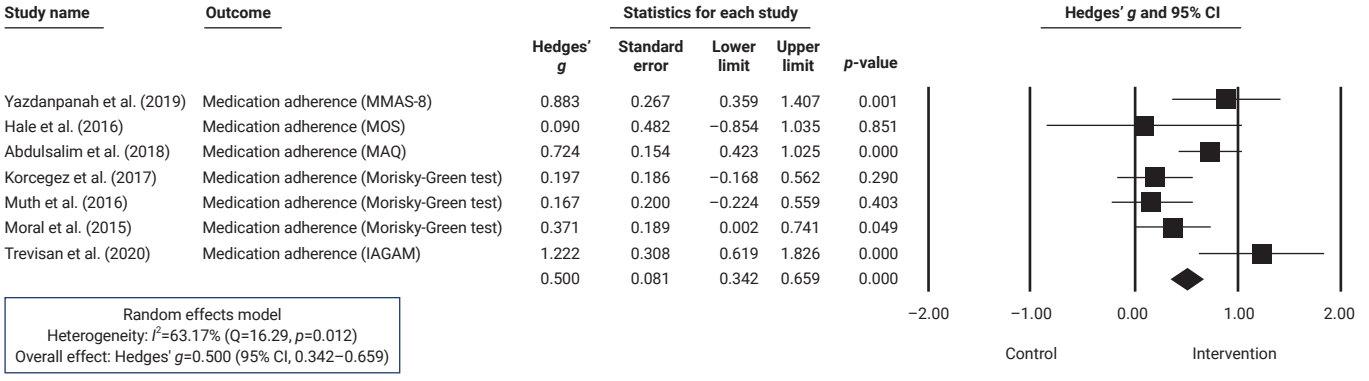

Figure 3. Forest plots of the effects of medication adherence interventions on medication adherence for older adults with chronic illnesses (random-effects model).
CI, confidence interval; MMAS-8, Morisky Medication Adherence Scale-8; MOS, Medical Outcomes Study; MAQ, Medication Adherence Questionnaire; IAGAM, Global Evaluation of Medication Adherence.

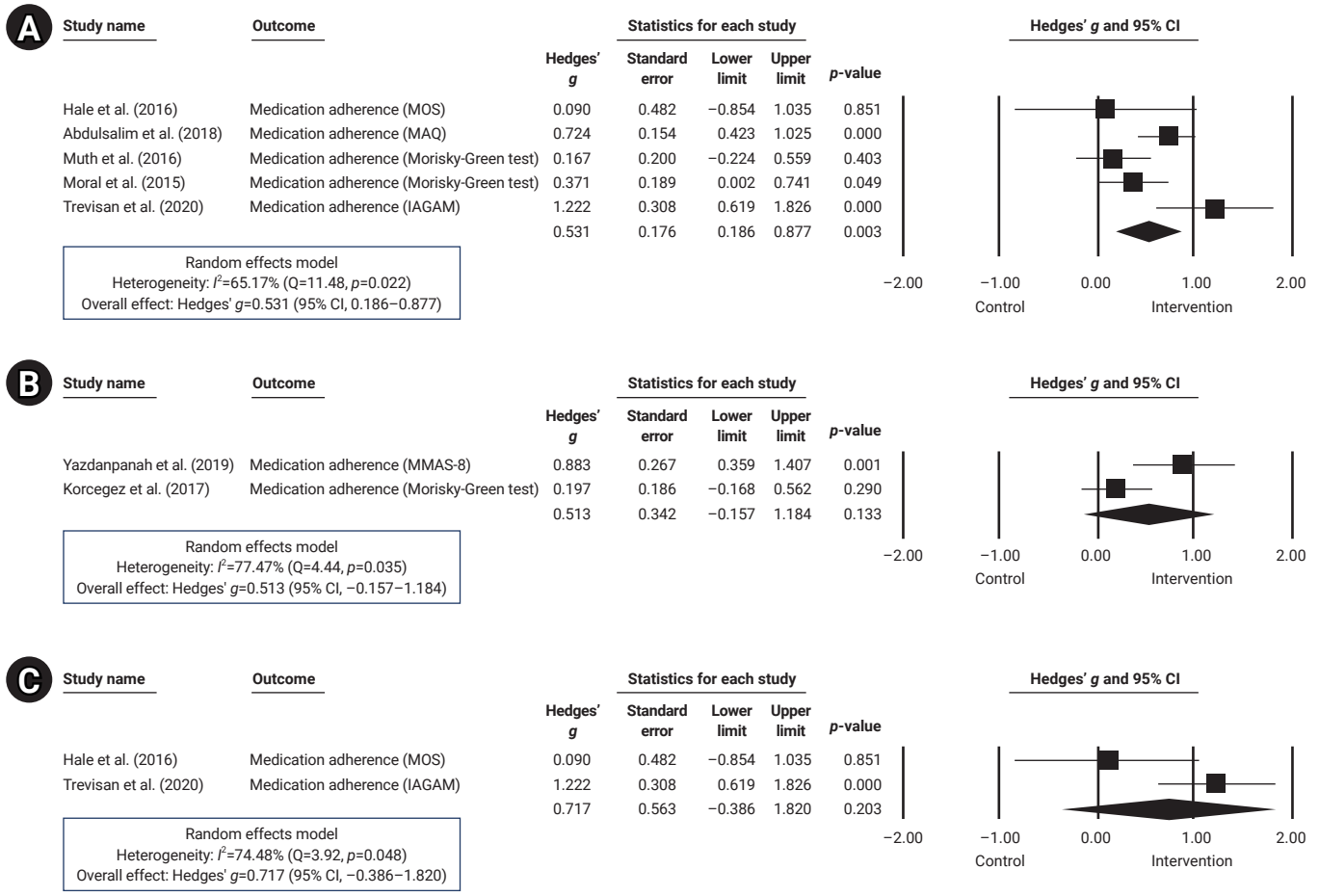

Figure 4. Forest plots of the effects of medication adherence programs according to intervention methods (random-effects model). (A) The effects of medication adherence programs consisting of counseling. (B) The effects of medication adherence programs consisting of education. (C) The effects of medication adherence programs consisting of telehealth and counseling.
CI, confidence interval; MOS, Medical Outcomes Study; MAQ, Medication Adherence Questionnaire; IAGAM, Global Evaluation of Medication Adherence; MMAS-8, Morisky Medication Adherence Scale-8.

Discussion

This study conducted a systematic review and meta-analysis to integrate and analyze the results of RCTs that investigated the effectiveness of medication adherence-related intervention programs for older patients with chronic illnesses. Quality assessments with the Cochrane's Risk of Bias tool were performed for the 7 selected studies, and all showed a low risk of bias. However, 3 studies were assessed as unclear for sequence generation, 5 as unclear for allocation concealment, and 4 as unclear for blinding of participants, personnel, and outcome assessors. The types of medication adherence interventions for older adults with chronic illnesses applied in the 7 selected studies included an educational program based on the health belief model [21], a remote medication monitoring program [22], a structured pharmacist-led intervention [23], a pharmacist-led care program [24], a complex intervention on prioritizing multiple medications [25], a motivational interviewing program [26], and an implementation intention intervention [27].

Yazdanpanah et al. [21] used the health belief model for older adult patients, based on the assumption that their belief in the effectiveness of prescribed medications would determine their medication adherence and use of appropriate medications. The program aimed to raise awareness about the possibility and severity of the corresponding diseases, induce behavioral triggers, and inspire confidence in behaviors, considering the perceived benefits and disadvantages of behavioral changes. Changes in the beliefs of older adults in the low-rate medication adherence stage resulted in a significant improvement in medication adherence post-intervention [21]. The remote medication monitoring program implemented by Hale et al. [22] applied telemonitoring and telehealth

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medication adherence technologies, and was reported to be a helpful intervention to improve patient self-management and quality of patient care; furthermore, it reduced health care utilization and expenditures for patients with chronic diseases requiring complex medication regimens.

Medication adherence telehealth interventions have been reported to act as patient education systems to enhance health literacy, pharmacist consultations, phone-based adherence assessments and positive behavior encouragement, and electronic reminders, thereby improving medication adherence [28]. It is necessary to monitor the health status of older adults with chronic illnesses in real time for regular administration of medications and health management, as well as to provide customized health management information accordingly. Therefore, telephone-based intervention methods can replace some face-to-face meetings between patients and medical staff in the context of chronic disease management and help maintain the quality and quantity of care.

Abdulsalim et al. [23] reported that enhancing patient self-efficacy as part of self-management education was important to promote long-term adherence. Self-efficacy is a key factor that influences human motivation and behavior, and the most important factor in determining the relationship between knowledge and behavior [29]. Furthermore, self-efficacy can play an important role in changing medication adherence habits into desirable behaviors and sustaining them. Older adults could experience physical and cognitive difficulties with the daily intake of specialized and complex medications, resulting in low self-efficacy and confidence in relation to proper medication adherence. Participation from pharmacists, who are experts on medication, in shared decision-making during the initial and regular follow-up visits helped improve patient self-efficacy associated with taking medications and augmented the partnership between patients and physicians, thereby facilitating adherence, improving patient outcomes, and diminishing economic and social burdens [23]. The pharmacist-led care program educated patients regarding correct medication use, reinforced treatment adherence, and developed their knowledge on drug therapy and health conditions [24].

According to Moral et al. [26], a face-to-face motivational approach in primary care could help older patients with chronic diseases receiving polypharmacy treatment improve treatment adherence to a greater degree than usual care for providing information and advice. Motivational interviewing is a counseling method that involves enhancing a patient's motivation to change behavior [30]. Moral et al. [26] used (1) assessment of ambivalence, (2) exploration of patients' ideas and concerns about their lack of adherence, and (3) application of specific interviewing skills to reframe and promote self-efficacy (e.g., empathy, developing discrepancies, avoiding arguments, confronting barriers and problems, and supporting the patient) through motivational interviewing as an experimental intervention, and obtained significant results. The strategies reported by Trevisan et al. [27] strategies for coping planning encouraged patients to anticipate barriers to taking their medication and formulate strategies to overcome them. Cognitive-behavioral coaching to improve patients' coping ability is an integrated approach that combines cognitive, behavioral, and imaginary problem-solving techniques and strategies within a cognitive-behavioral model to achieve realistic goals set by the patient [31]. This is expected to be helpful in promoting medication adherence in older adults, as it can help them overcome real problems and address the emotional, psychological, and behavioral difficulties that hinder their performance and goal achievement.

Of the 7 studies, 5 selectively applied interventions to patients with certain chronic illnesses (hypertension, chronic heart failure, COPD, and diabetes), and 2 selected participants with "chronic diseases." There were 3 studies on pharmacist- and physician-led counseling and consultation [23,25,26], 2 on educational programs including lectures [21] and face-to-face education [24], 2 on interventions that used group discussions [21,23], and 2 that used medication monitoring systems and telephone monitoring [22,27]. Individual counseling and consultation methods were generally tailored to the characteristics and severity of chronic diseases, with varying precautions for administration. Routine monitoring of daily drug administration was required, and educational methods involving lectures by experts and group discussions with individuals with chronic diseases were effective, given older adults' general level of knowledge about medications and the need to provide accurate information on new medications. In most of the selected studies, usual or standard hospital care was provided to the control group, and 2 studies evaluated the results through follow-up.

Considering the total effect of the applied medication adherence intervention programs, taking medications is important for older adults with chronic illnesses, and interventions beyond usual or standard hospital care are required. It is important to evaluate long-term effects in chronic disease management; therefore, follow-up to assess program effectiveness needs to be considered as an important component in program development. The Morisky-Green test, which was used in 3 studies, was the most commonly used tool to measure medication adherence; other tools included

the MMAS-8, MAQ, and IAGAM. The Morisky-Green test evaluates whether patients forget to take medication, are careless about taking medication, or stop taking medication when their health status improves or worsens [32]. According to Roy et al. [6], levels of medication adherence may differ according to the measurement tool used to assess older adults taking multiple medications. Thus, when selecting high-risk groups for medication adherence, careful selection of assessment tools is necessary.

For the 7 studies included in the systematic review, the total effect size was medium (Hedges' $g = 0.500$), which was statistically significant when calculated using a random-effects model in consideration of heterogeneity. Of the medication adherence programs, the implementation intention intervention applying face-to-face meetings and telephone monitoring with individualized behavioral strategies [27] and the educational program based on the health belief model [21] were highly effective, with Hedges' g values of 0.8 or higher. The most effective interventions related to medication adherence reported in previous studies were tailored to the client and included aspects of counseling (e.g., education, motivational interviewing, CBT) [33]. The implementation intention intervention [27] was tailored with an elaboration of action and coping plans and their respective strategies. Kim [34] reported that older adults with chronic illnesses who took many medications, but did not know their exact administration methods or purpose of medication use, misused medications by re-using them after the expiration date, sharing them with others, or arbitrarily changing the timing of administration. However, compliance with medication adherence can be improved only if interventions are applied in a way that depends on physical, psychological, and functional factors for each older patient [35]. This should be followed by the use of other adherence-targeting interventions tailored to patients' individual needs. It is also necessary to identify older adults' health beliefs regarding taking medications, understand the obstacles in changing those beliefs, and devise strategies to adjust them.

Based on the results of the effect size analysis according to intervention method, face-to-face meetings had a significant effect, whereas education and meetings via telehealth did not. In particular, neither interventions focused on face-to-face education [24] nor monitoring via telehealth [22] had significant effects. However, both education based on the health belief model [21] and telehealth with utilization of CBT were found to be effective interventions for older adults with chronic illnesses [27]. Thus, intervention programs for older adults with chronic illnesses should mainly utilize face-to-face meetings, while education based on the health belief model and CBT can enhance interventions' effects. However, since only a small number of studies were ultimately selected for review, it is difficult to generalize the results of this meta-analysis. As another limitation of this study, it was conducted according to the PRISMA guidelines for reporting systematic literature reviews, but this review was not registered.

Conclusion

This study conducted a meta-analysis based on a systematic literature review of RCTs for medication adherence programs applied to older patients with chronic illnesses conducted in the last 10 years. Of the 7 medication adherence programs, an implementation intention intervention based on face-to-face meetings and telephone monitoring with individualized behavioral strategies and an educational program based on the health belief model were highly effective. Meeting face-to-face was found to be a more effective method than education and meeting via telehealth for implementing medication adherence intervention programs for older adults with chronic illnesses. Future studies should devise intervention strategies with impacts on physical and psychological health related to medication adherence in older adults for integrated health management.

In this study, we determined the characteristics and application methods of interventions that are helpful in improving medication adherence in older patients with chronic illnesses. We confirmed that interventions including individualized behavior modification strategies and cognitive behavioral coaching strategies based on health beliefs could be helpful in improving medication adherence among older adults.

Notes

Ethics Approval

This study was exempted from a review by the Institutional Review Board of Cheongju University, the institution of the lead researcher, to ensure ethical and scientific validity for the overall research (approval number: 1041107-201904-HR-017-01).

Conflicts of Interest

The authors have no conflicts of interest to declare.

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Availability of Data

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

Authors' Contributions

Conceptualization: HOJ; Methodology: HOJ; Data curation: HOJ, MOC,

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AK; Formal analysis: HOJ, MOC, AK; Supervision: HOJ; Software: HOJ; Validation: HOJ; Investigation: HOJ; Funding acquisition: HOJ; Project administration: HOJ; Resources: HOJ; Visualization: HOJ; Writing original draft: HOJ; Writing-Review & Editing: HOJ, MOC, AK.

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Review Article

Zika virus as an emerging arbovirus of international public health concern

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ABSTRACT

Zika virus (ZIKV) was identified in 1947 in a rhesus monkey during an investigation of the yellow fever virus in the Zika Forest of Uganda; it was also isolated later from humans in Nigeria. The main distribution areas of ZIKV were the African mainland and South-East Asia in the 1980s, Micronesia in 2007, and more recently the Americas in 2014. ZIKV belongs to the *Flaviviridae* family and *Flavivirus* genus. ZIKV infection, which is transmitted by *Aedes* mosquitoes, is an emerging arbovirus disease. The clinical symptoms of ZIKV infection are fever, headache, rashes, arthralgia, and conjunctivitis, which clinically resemble dengue fever syndrome. Sometimes, ZIKV infection has been associated with Guillain-Barré syndrome and microcephaly. At the end of 2015, following an increase in cases of ZIKV infection associated with Guillain-Barré syndrome and microcephaly in newborns in Brazil, the World Health Organization declared a global emergency. Therefore, considering the global distribution and pathogenic nature of this virus, the current study aimed at reviewing the virologic features, transmission patterns, clinical manifestations, diagnosis, treatment, and prevention of ZIKV infection.

Keywords: *Aedes*; Arboviruses; Flavivirus; Microcephaly; Zika virus

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Introduction

Zika virus (ZIKV) is an arbovirus transmitted by *Aedes* species mosquitoes. ZIKV was initially identified in 1947 in a febrile sentinel rhesus monkey in the Zika Forest of Uganda, near Lake Victoria [1–3]. In the beginning of 1948, ZIKV was also detected in *Aedes africanus* mosquitoes in the same forest [4]. Therefore, the name ZIKV originated from the geographical area where it was initially isolated. The virus is classified in the family *Flaviviridae*, and it is highly similar to other members of the family, such as the yellow fever virus (YFV), Japanese encephalitis virus (JEV), and West Nile virus (WNV) [5–7].

Serologic studies have also proven human infection [3]. During studies in the early 1950s, ZIKV was also detected in humans in Nigeria [8]. In 1956, an *in vitro* study indicated that

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artificially fed *Aedes aegypti* mosquitoes can transmit the virus to mice and monkeys [9,10]. Some serologic evidence of human ZIKV infection in several African and Asian countries emerged from 1951 to 1981 [11]. The virus was limited to a narrow African/Asian niche until 2007, when an outbreak in Micronesia was first documented [12]. Further outbreaks also happened in the Pacific Island nations from 2013 to 2014, and since 2015 it has been reported in Central and South America [13–15].

The symptoms of people infected with ZIKV are usually mild and very general, including increased blood temperature, cutaneous rash, headache/malaise, nonpurulent conjunctivitis, arthralgia, myalgia, and gastrointestinal impairment; the symptoms continue for several days and then disappear [6,15]. The high rates of primary microcephaly and Guillain-Barré syndrome (GBS) associated with ZIKV infection in Brazil have raised concerns that the virus circulating in these regions is a rapidly developing neuropathic, teratogenic, emerging infectious public health threat [7,16]. According to a World Health Organization (WHO) announcement on February 1, 2016, the ZIKV infection outbreak represented a "public health emergency of international concern" (PHEIC) [17]. Based on international health regulations, a PHEIC is an extraordinary global event associated with public health risk, which requires international coordination due to the worldwide spread of a disease [18]. Therefore, considering the global emergence and pathogenic nature of this virus, the current study aimed at reviewing the virologic features, transmission pattern, clinical manifestation, diagnosis, treatment, and prevention of ZIKV infection.

Virology and Pathogenesis

ZIKV is an arbovirus in the family *Flaviviridae*, genus *Flavivirus*, which phylogenetically and antigenically is most closely related to the Spondweni virus. It is an enveloped virus comprising a single-stranded RNA genome with a positive polarity of approximately 11 kb [19,20]. Three lineages have been discovered with the aid of phylogenetic examinations: 1 Asian and 2 African lineages (African I and African II) [21,22]. All lineages originated from the same source in Uganda in the early 20th century [22]. The virus's RNA includes its complete open reading frame (ORF) sequence. The ORF encodes a polyprotein comprising 3 structural components (capsid [C], premembrane [prM], and envelope [E]) and 7 nonstructural proteins (Table 1; Figure 1) [23–31]. The E and prM proteins are the surface particles of the virus, and the C protein and the genomic RNA molecule make up the nucleocapsid [6,32,33]. Existing information about the pathogenesis of ZIKV is adequate; however, the main immunological and pathological knowledge about the effects of viral proteins on the host is derived from the results of studies on clinically important flaviviruses that tend to cause central nervous system infections; such as dengue virus (DENV), WNV, tick-borne encephalitis virus, JEV, YFV, and St. Louis encephalitis virus [33]. While ZIKV has a significant sequence similarity to the other human flaviviruses, it shows substantial differences in pathology. Clinically, unlike related flaviviruses, such as WNV and DENV, which can infect neural cells but either target mature neurons (WNV) or elicit a less cytotoxic response (DENV), ZIKV exhibits a clear tropism for proliferative neural cells, often with cytotoxic effects [34]. ZIKV can be transferred to humans through mosquito bites, or by injecting the virus into the skin and submucosa of a mammalian host. Therefore, the skin and mucous membranes play an important role in preventing the spread of infection. Human skin cells, such as keratinocytes and fibroblasts, are susceptible to the infection and replication of ZIKV [19].

Binding of the viral envelope protein and uptake of particles into susceptible cells are necessary for ZIKV infection, which proceeds through specific cell receptors such as AXL, DC SIGN, Tyro3, and TIM-1. ZIKV activates the transcription of Toll-like receptor 3 (TLR3), MDA5, RIG-I, and interferon-stimulated genes such as OAS2, ISG15 and MX1, characterized by strongly enhanced beta-interferon gene expression [19,35]. Recent studies have shown that the depletion of AXL reduces ZIKV infection of cultured fibroblasts and astrocytes [34]. Furthermore, previous studies on developing fetal brain cells in humans observed that these cells are highly enriched with AXL receptors, making them susceptible to ZIKV infection [36]. According to studies on DENV infection, primary ZIKV infection may induce apoptosis in the infected cells, allowing it to evade the innate immune response and boosting the primary release of viral particles [37]. Consequently, both DENV and ZIKV increase replication by autophagy; however, pharmacological modulation was achieved using 3-methyladenine, an autophagosome formation inhibitor that decreases the copy number of viruses in infected fibroblasts [7,19]. ZIKV is not the only flavivirus that triggers apoptosis and autophagy. For example, both DENV and WNV can trigger caspase activation to induce apoptosis [34]. Murine model studies on the inoculation of ZIKV to mouse brains showed that ZIKV-induced autophagy can be assumed to play a pivotal role in the pathogenesis of primary microcephaly [38]. Findings of the Carlos Chagas Institute of Parana Fiocruz indicated that ZIKV can pass through the placenta. The potential mechanism of ZIKV trans-placental transport is that the antibodies generated from a previous flavivirus infection

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Table 1. Important proteins of ZIKV and their functions

Protein	Function/possible effect on the host	Reference
C	Interaction with RNA for nucleocapsid assembly/Protein C is involved in post-transcriptional regulation in host cells and virus-associated neurological diseases. In addition, ZIKV C protein can form a stable complex with Ras-GAP SH3 domain-binding protein 1 (G3BP1) and caprin-1 to block the formation of stress granules in the host cell; in human neural progenitor cells, it induces ribosomal stress and apoptosis.	[23,24]
PrM	Consolidation, contribution to the E protein folding and releasing process/Possible related factor in severe dengue virus pathogenicity, increasing the immature virions' infectious effect because of anti-PrM antibodies. It also induces cellular oxidative stress and autophagy leading to cell death.	[25]
E	Receptor attachment protein, fusion protein/Main protein for inducing neutralizing antibodies against virus infection.	[24,26]
NS1	RNA replication/Transfer to host cell membrane and release into the extracellular space, innate immune system signaling pathways regulator; anti-NS1 antibodies could damage platelets and endothelial cells; C4 complement antagonist.	[27,28]
NS2A	RNA synthesis and viral formation/Host cell death by triggering apoptotic factors, IFN antagonist. In addition, NS2A can directly mediate the degradation of adhesion junction proteins, thereby destroying mammalian cortical neurogenesis.	[29]
NS2B	Serine protease assembly with NS3/ZIKV NS2B can inhibit the phosphorylation of TBK1 to suppress IFN-β production.	[24,27]
NS3	Serine protease effect in complex with NS2B; possess RNA helicase and triphosphatase activities/Host cell apoptosis, microRNAs modulator, one of the targets of the cytotoxic T cell response, downregulation of the host immune response by inhibiting the induction of IFN and downstream IFN-stimulated genes.	[24,28]
NS4A	RNA replication/Human type I IFN signaling pathway blocker, autophagy-inducing factor, anti-death effect on host cells during infection.	[24,30]
NS4B	RNA replication/NS4B can combine with TBK1 to inhibit the production of type I IFN; and stress granules modulator.	[24,31]
NS5	Methyl transferase, RNA guanylyl transferase, RNA-dependent RNA polymerase (RdRP), RNA synthesis and capping / Human type I and III IFN signaling pathway blocker, inhibits the production of IFN-β and inhibits the expression of IFN-stimulated genes.	[24,28]

ZIKV, Zika virus; C, capsid; prM, premembrane; E, envelope; IFN, interferon.

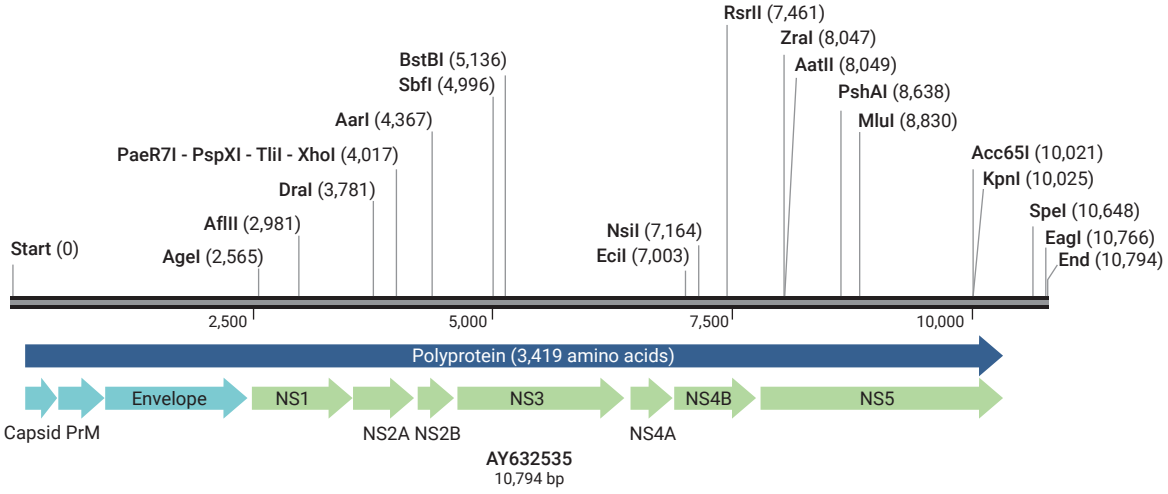

Figure 1. Schematic representation of the Zika virus genome and the cutting site of different restriction enzymes.
NS, non-structural protein.

bind to ZIKV particles in the maternal blood and could cross the villous trees to reach the fetal vessels by infecting neonatal Fc receptor (FcRn)-bearing cells [7,39–41]. *In vitro* neuropathogenesis studies have demonstrated that human neural progenitor cells (hNPCs) of the developing fetus are effectively infected by ZIKV. ZIKV-infected hNPCs can be another explanation for ZIKV infection of the fetal central nervous system, leading to brain abnormalities including microcephaly [42–44]. A recent *in vitro* study revealed that the expression of 11 microcephaly-related genes (*CDK5RAP2, MCPH1, CASC5, WDR62, ASPM, CENPJ/CPAP, STIL, CEP135, CEP152, ZNF335*, and *PHC1*) was reduced in ZIKV-associated microcephaly tissues. All of these genes regulate the cell cycle and cell death, and it is likely that the

decreased expression of these genes is an indirect effect of ZIKV infection and that prenatal infection with this virus stops the cell cycle, leading to apoptosis and differentiation defects in the developing nervous system [34].

Epidemiology and Transmission

Primary virological and serological studies indicated that ZIKV infection was limited to African and Asian countries from the 1950s to the 1980s [9,45,46]. Endemic circulation of the virus has been reported in some Asian countries such as Thailand, Indonesia, Peninsular Malaysia, Cambodia, Philippines, and Borneo, as well as in passengers from endemic areas (Table 2) [1–4,8,10–14,17,22,47–50]. Within a 60-year period from 1947 to 2007, Asia and Africa were the only areas with serological and entomological reports [11,51,52]. In 2007, the first outbreak outside of Africa and Asia was reported from Yap Island, Micronesia, in the western Pacific Ocean, north of Papua New Guinea, with 49 confirmed cases based on immunoglobulin M (IgM) seropositivity, and 73% of the residents infected with ZIKV were 3 years of age or older [5,12]. From 2013 to 2014, the Western Pacific islands of French Polynesia, Easter Island, and New Caledonia became the next endemic areas [13]. In March 2015, the first molecularly confirmed case of ZIKV infection was identified in Brazil. The first report of the WHO on ZIKV transmission was published in May 2015 in mainland South America; the possible explanation was that the virus was transmitted during the Va'a World Sprint Championship canoe race in Rio de Janeiro, Brazil, in August 2014 [22]. The phylogeny of the Brazilian strain was similar to that of the French Polynesian one in 2013-2014, both belonging to the Asian lineage. After the May 2015 introduction of the ZIKV in Brazil, it spread rapidly across Brazil and the Americas [47]. On January 28, 2016, 26 countries in the Americas reported autochthonous cases of ZIKV infection and on February 1, 2016, the WHO declared a PHEIC [53]. Outbreaks of ZIKV infection peaked in 2016 and decreased significantly during 2017 and 2018 in the Americas. However, in the South-East Asia Region, in May 2017, 4 ZIKV-positive cases confirmed by reverse transcription-polymerase chain reaction (RT-PCR) were reported from India (Gujarat, 3; Tamil Nadu, 1). From September to November 2018, the largest Indian ZIKV outbreak was reported from the states of Rajasthan and Madhya Pradesh. In total, 159 cases (64 pregnant women) and 130 cases (42 pregnant women) were confirmed as ZIKV-positive by RT-PCR in the states of Rajasthan and Madhya Pradesh, respectively [48]. ZIKV continues to develop and spread silently throughout the world in the form of asymptomatic infections. In July 2021, India reported a ZIKV outbreak in Kerala, the first outbreak activity in South-East Asia Region since the outbreak in Rajasthan, India, in 2018. Extensive testing identified at least 70 PCR-confirmed cases of ZIKV disease by August 2021 [49,50]. Accurate and up-to-date epidemiological

Table 2. Overview of global Zika virus outbreaks (1947 to date)

Year	Location/country	Event	WHO Regional Office	References
1947–1948	Uganda	Discovery of ZIKV in febrile sentinel rhesus monkey and isolation of ZIKV from *Aedes* mosquito	AFRO	[1–4]
1952–1953	Nigeria, Tanzania, Uganda	Isolation of ZIKV from human	AFRO	[3,8]
1950s–1980s	Bangladesh, Borneo, Burkina Faso, Cameroon, Gabon, Indonesia, India, Malaysia, Philippines, Thailand, etc.	Sporadic cases of ZIKV infection in African and Asian countries	AFRO, SEARO, WPRO	[10,11]
2007–2009	Yap Island, Micronesia	First outbreak ZIKV outside of Africa and Asia	WPRO	[12]
2013–2014	Cook Islands, Easter Island, French Polynesia, New Caledonia, etc.	ZIKV outbreak in the Western Pacific Region	WPRO	[13]
2015–2016	Brazil, Columbia, El Salvador, Mexico, United States of America, Venezuela and Caribbean countries	ZIKV outbreak in the Americas	Region of the Americas/ Pan American Health Organization	[14,17,22,47]
2017–2018	India	Biggest ZIKV outbreak in India	SEARO	[48]
2019	France (Var department)	First case of autochthonous ZIKV disease in Hyeres, Var department, France	European Region	[49]
2020	Lao People's Democratic Republic	One probable case of ZIKV-associated neonatal microcephaly	WPRO	[49]
2021	India	ZIKV outbreak in India	SEARO	[49,50]

ZIKV, Zika virus; AFRO, African Region; SEARO, South-East Asia Region; WPRO, Western Pacific Region.

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data on ZIKV are limited in many parts of the world. Most ZIKV infections are asymptomatic, and if they do occur, symptoms are generally mild and non-specific, and therefore may not be detected or reported. However, as of December 2021, 89 countries and regions have recorded autochthonous mosquito-borne transmission of ZIKV, and it was distributed in all WHO regions except the Eastern Mediterranean Region (Figure 2). The current status of ZIKV transmission and spread indicates that it has the potential to re-emerge as an epidemic [54].

ZIKV is epizootic and enzootic in African non-human primates, the main natural reservoir. The bite of contaminated *A. aegypti* and *A. albopictus* mosquitoes, found in most parts of America (including the United States), is the primary source of transmission to humans. These mosquitoes also transmit chikungunya, DENV, and YFV [55]. The geographic distribution of *A. aegypti* globally coincides with the areas of DENV transmission. In rare cases, *A. albopictus* can be involved in DENV epidemics. Other *Aedes* species such as *A. africanus, A. furcifer, A. taylori*, and *A. luteocephalus* are likely vectors in Africa and Asia [56]. Because of the adaptations of mosquitoes to the climatic conditions of urban and rural regions, their omnipresence in many tropical and subtropical countries, anthropophilic behaviors, the invasion of European and North American residential areas by the mosquitoes, and the potential of mosquitoes to carry other arboviruses, the 2 species of *A. aegypti* and *A. albopictus* pose the greatest threats to most countries. *Aedes* species spreading ZIKV live in different countries of the world; therefore, outbreaks can probably spread the infection in currently unaffected countries [18,57].

An infection occurs when a human is bitten by a contaminated mosquito. In addition to mosquitoes, other routes of ZIKV transmission are possible, although the epidemiologic significance of ZIKV transmission seems unlikely under natural circumstances. It has been suggested that direct transmission can take place from primates to humans through animal bites [55,58]. ZIKV is detectable in the saliva of 19.2% of infected people, although its epidemiologic features should be established [59]. Sexual transmission has been recorded, and the presence of viral RNA was detected using PCR in semen up to 60 days from the occurrence of clinical symptoms, indicating that the virus could persist in the male genitalia for much longer than in the peripheral blood [60–62]. Perinatal and congenital infections can also happen. The possibility of transmission through transplantation and transfusion is a further major clinical and public health concern [63].

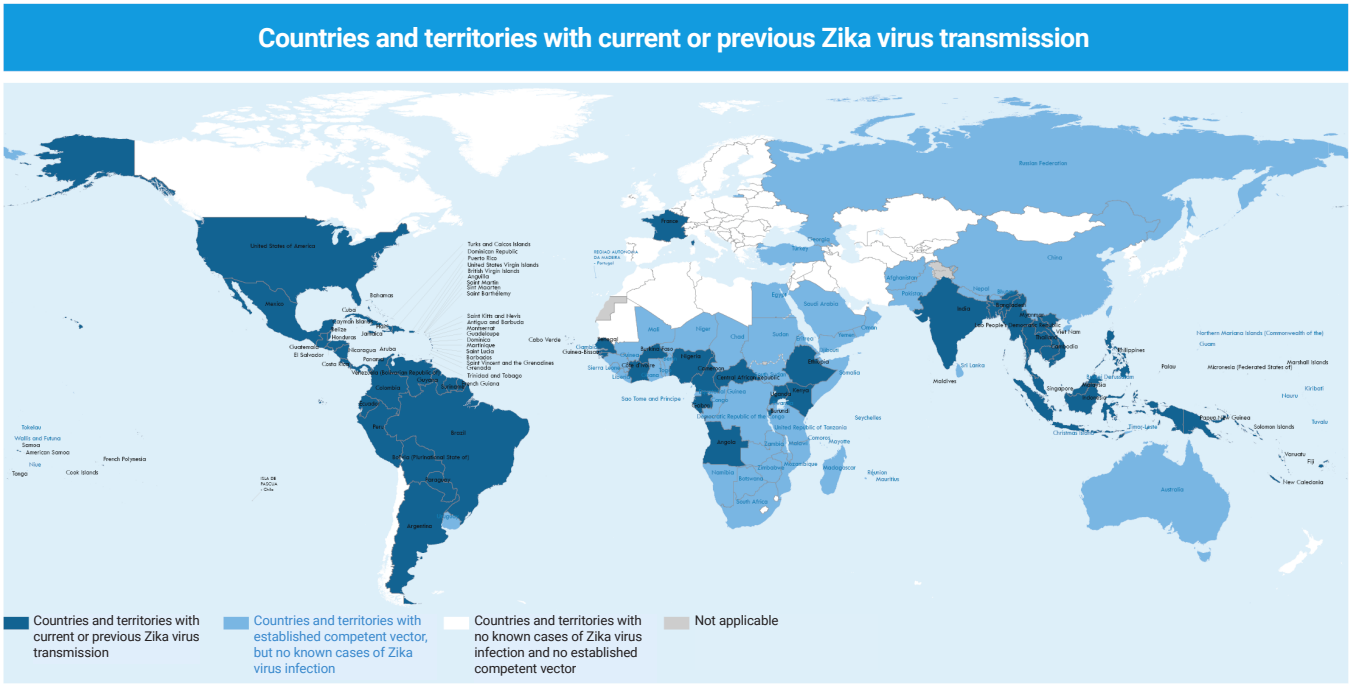

Figure 2. All countries and territories that have or have had Zika transmission.
Content source: World Health Organization (as of February 2022; https://cdn.who.int/media/docs/default-source/documents/emergencies/zika/map-of-countries_with_zika_transmission_feb2022.pdf?sfvrsn=802a352a_5).

Clinical Manifestations

The clinical manifestation of ZIKV infections is non-specific and often mistaken for other flaviviral infections such as DENV and chikungunya. ZIKV and DENV coexist in many developing countries, where there is limited access to health resources and virus-specific diagnostics are not readily available. The co-circulation of both viruses poses challenges for healthcare providers in differentiating between the 2 infections. These infections have similar clinical features, including fever, conjunctivitis, maculopapular rash (which can be pruritic), and joint pain; which usually appear within about 2 to 12 days after the mosquito bite. The clinical manifestations of the disease may last from several days to a week [33,64]. Early differentiation of ZIKV and DENV infections is important for the prognosis and subsequent monitoring and follow-up of these patients. Although ZIKV infection is self-limiting, in contrast, severe DENV infection leads to a debilitating disease that can cause capillary leakage, electrolyte imbalances, organ impairment, and in some cases death [65]. A study in Singapore showed that patients with DENV infection had significant thrombocytopenia, transaminitis, and monocytosis. Conversely, ZIKV patients had normal platelet, aminotransaminase, and monocyte levels, which can help distinguish DENV from ZIKV [66]. ZIKV only affects one-fifth of the population, and hospitalization-requiring severe disease and death are rare; the signs and symptoms of the disease are relatively mild [67]. The main clinical manifestations during the Yap outbreak were a maculopapular rash (90%), arthritis/arthralgia (65%), fever (65%), conjunctivitis (55%), myalgia (48%), headache (45%), retro-orbital pain (39%), edema (19%), and vomiting (10%) [12]. There is a possible association between maternal ZIKV infection and microcephaly in newborns, as well as developmental ocular abnormalities; in addition, there have been some reports about infected adults with neurologic conditions such as GBS [68]. During the outbreak in French Polynesia, higher rates of GBS were reported; specifically, the incidence of GBS during the outbreak was 20 times higher than in non-outbreak periods [69]. In 62% of Brazilian GBS patients during the outbreak, the ZIKV symptoms were similar. The most remarkable and surprising consequence of ZIKV infection is its possible association with inborn abnormalities, especially microcephaly. Intrauterine or neonatal death is possible. The number of infants with congenital microcephaly became 20 times higher after the epidemic commencement, with over 1,200 cases reported during 2015 (99.7 per 100,000 live births) [33].

Diagnosis

Specific ZIKV diagnostic algorithms for adults and children have been proposed by the US Centers for Disease Prevention and Control (US-CDC). ZIKV is classified as a human pathogen hazard group 3 and biosafety level 2 microorganism by the UK Advisory Committee on Dangerous Pathogens and the US-CDC, respectively [70,71]. To diagnose ZIKV infection, the routine method is to detect viral RNA in serum samples of cases in the acute phase of the disease using RT-PCR, as well as other specific anti-ZIKV serum antibody tests [72]. The isolation of ZIKV from animals or mosquitoes is another method for diagnosing the disease [72]. The virus can be cultured in some cell lines such as Vero and LLC-MK2, or by intracerebral inoculation of suckling mice [33]. Although these methods can help virological investigations, they are unfeasible in many medical laboratories. Serological tests such as the enzyme-linked immunosorbent assay (ELISA) or immunofluorescence are also used. An IgM antibody response in primary ZIKV-infected patients has been reported; however, a cross-reaction with other flaviviruses may make the diagnosis difficult [72,73]. If the assay result is positive, a plaque-reduction or neutralization test should be conducted to measure virus-specific neutralizing antibodies and discriminate among cross-reacting antibodies produced during primary flavivirus infections [74]. RT-PCR of clinical samples (often the peripheral blood) is the most common laboratory test for diagnosing acute ZIKV infection. RT-PCR is a sensitive method for the accurate differentiation of the ZIKV from other species of flaviviruses with similar manifestations. This is particularly valuable in areas with concurrent circulation of arboviruses as a common phenomenon. Genotyping is also practical for this purpose [75]. After the emergence of the disease, the viremic period can last for 1 to more than 11 days [76]. Based on the Yap outbreak in 2007 in a series of 17 patients, the serum viral load was rather low, ranging from 930 to 728,800 (mean, 21,495) copies/mL [5]. A viral load of 338,797 copies/mL was reported in blood samples collected on day 11 after the incidence of clinical symptoms [5]. Furthermore, saliva, urine, and semen are good specimens to detect ZIKV RNA in some patients, and the sensitivity of RT-PCR for saliva samples is considerably higher than that of blood (57.1% vs. 28.1%) [59,76]. Diagnostic flavivirus infection testing should be performed using acute-phase sera samples collected immediately after the incidence of disease, and the latter samples should also be obtained 2 to 3 weeks after the first blood drainage [10].

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Treatment

No vaccines or medications are available to prevent or treat ZIKV infections. There is also no specific antiviral treatment for controlling severe and fatal outbreaks [77]. Treatment is primarily supportive, and symptoms can be generally improved or ameliorated by the aid of fluids, rest and oral sedatives, and antipyretics for reducing fever and pain; however, because of the risk of bleeding, aspirin and other non-steroidal anti-inflammatory drugs can be used only when DENV infection has been excluded [78,79]. Healthcare centers should adequately apply standard precautions as well as further mosquito-proofing actions. Healthcare workers who care for Zika patients are recommended to use insect repellents and carry out mosquito avoidance behaviors. Given that ZIKV causes a range of congenital diseases, including microcephaly in newborns and GBS in adults, it is necessary that women, especially those who wish to become pregnant, be vaccinated. Several different ZIKV vaccine candidates using different platforms have now been developed and tested in preclinical and clinical trials. These include live virus vaccines, viral vector vaccines, inactivated vaccines, nucleic acid vaccines (DNA and RNA vaccines), virus-like particle vaccines, and subunit protein vaccines. Each of these vaccine platforms induces humoral and/or cell-mediated immune responses to varying degrees. Given the current facts, it may be necessary to develop more than 1 type of Zika vaccine. For example, inactivated vaccines are usually safe and could be administered to pregnant women as well as women of childbearing age. However, multiple doses and the use of adjuvants may be required to induce stronger and longer-lasting protection. Live attenuated vaccines can be used in men, children, and the elderly. However, they can induce toxic inflammatory responses by potentially reverting to virulent forms, or may be less effective due to pre-existing immunity to the vector virus. DNA or subunit vaccines are generally considered safe for use in all target populations, including pregnant women. The most advanced vaccine candidates to date include nucleic acid-based vaccines (DNA vaccines) that encode the PrM and E proteins of the H/PF/2013 strain of ZIKV (VRC-ZKADNA090-00-VP and VRCZKADNA085-00-VP) [54,80]. *In vitro* studies applying small interfering RNA, therapeutic antibodies, and molecules targeting nonstructural proteins (especially NS3 and NS5 proteins) are still in progress, but no antivirals have yet been introduced for specific therapies against flaviviral infections (except hepatitis C virus). There are a few available drugs, including tetracycline, chloroquine, amodiaquine, and mefenamic acid, with *in vitro* inhibitory effects against flaviviruses (particularly DENV); however, their potential clinical benefits has not yet been confirmed [33,81].

The WHO reported that about 80% of people in developing countries rely on traditional drugs for their primary health care needs [82]. About 855 traditional medicines used in the world are obtained from crude plant extracts [83]. Medicinal plants are a crucial therapeutic aid for various viral diseases [48,84–90]. Medicinal plants might be effective antimicrobial compounds because they have no or low toxicity. The use of polyphenol-rich medicinal plants and their purified compounds as potential antiviral therapies has been recently explored. Several phytochemical families, including alkaloids, flavonoids, polyphenolics, coumarins, terpenoids, and saponins, have already been described as exerting antiviral activity against numerous enveloped RNA viruses, including flaviviruses. Several studies have shown that a polyphenol from green tea (epigallocatechin gallate) and curcumin inhibit ZIKV and DENV infection. Recent *in vitro* studies have also shown that *Doratoxylon apetalum* and *Psiloxylon mauritianum* extracts prevented ZIKV and DENV infection by inhibiting the entry of the virus into human cells [91–96].

Prevention

The primary measure to prevent and control ZIKV infection is to avoid the bites of virus-infected mosquitoes. To control ZIKV infection, the following measures should be taken: the use of insect repellent, careful hand hygiene, protection of mucous membranes, wearing shirts with long sleeves and long pants impregnated with permethrin, prevention and elimination of standing water bodies with the risk of mosquitoes' laying eggs, reduction of outdoors activities overlapping with the time of maximum biting activity of mosquitoes, installing window and door screens, and the application of certain mosquito control programs [97–99]. A cohort study in southern Puerto Rico that began in 2018 examined risk factors for ZIKV-related infection. Among 4,035 participants tested for ZIKV, 651 (16%) had evidence of a recent infection. Infection prevalence increased with older age, from 7% among 1- to 10-year-olds up to 19% among 41- to 50-year-olds. Males had a higher risk of Zika infection prevalence than females. The prevalence of ZIKV infection also decreased with the presence of home screens and air conditioning [100]. The European Centre for Disease Prevention and Control and the US-CDC recommend avoiding traveling to virus-infected areas for pregnant mothers and those who are planning pregnancy. Sex education and the use of condoms are also important to prevent sexually transmitted diseases. Considering that the risk of sexual transmission of ZIKV is relatively high,

visitors to endemic areas are recommended to maintain sexual abstinence or practice safe sex [18,98,99].

Since there is no information about the duration of viremia and viral shedding in bodily fluids such as semen, urine, and saliva, it is also not clear how long precautions should be considered for further empirical verification. Some studies suggested the use of contraceptive penile caps 28 days after returning from endemic areas for asymptomatic travelers, and 6 months after recovery if the patient was still symptomatic [33]. Based on CDC recommendations, protection should be taken during vaginal, anal, and oral intercourse with male partners via proper preventive measures during travel and after returning from endemic regions; in particular, pregnant women are advised to abstain from sex with men who have returned from endemic regions [34,98]. Furthermore, some reports have described the transmission of ZIKV via blood transfusion. Thus, as an effective preventive measure, individuals who have recently returned from ZIKV-affected areas should be prevented from blood and organ donation. The safe disposal of sharp objects contaminated with blood and body fluids in medical centers is another infection control measure. It is particularly important to clean and sterilize non-disposable medical instruments after each use [20].

Conclusion

ZIKV, an arthropod-borne flavivirus, is an emerging infectious disease with the potential to cause a serious global threat to public health. ZIKV infection typically causes a mild and self-limiting disease in otherwise healthy people. However, if ZIKV infection occurs during pregnancy, it can cause fetal abnormalities. Therefore, according to recent PHEIC declarations by the WHO, ZIKV is unique in its ability to lead to congenital anomalies. At present, serologic (ELISA) and molecular (RT-PCR) testing are used to diagnose ZIKV infection. No specific drug or vaccine is available for ZIKV infection, and treatment is supportive based on reducing the symptoms of the disease. Given the current facts, it may be necessary to develop more than 1 type of Zika vaccine. For example, an inactivated vaccine would be needed for pregnant women and perhaps women of childbearing age, while a live attenuated vaccine could be used in men, children and the elderly. DNA or subunit vaccines may be safer and lead to longer immunity. Still, protection against mosquito bites is the most effective way to prevent ZIKV infection.

Notes

Ethics Approval
None.

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

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Availability of Data
All data generated or analyzed during this study are included in this published article.

Authors' Contributions
Conceptualization and design: SV, SHP, FAM; Data curation: SV, SHP; Supervision: FAM; Validation: SHP, FAM; Visualization: SV, SHP; Writing-original draft: all authors; Writing review & editing: all authors; Final approval of the version to be published: all authors.

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Original Article

A case-control study of acute hepatitis A in South Korea, 2019

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ABSTRACT

Objectives: We aimed to reconfirm the source of hepatitis A virus (HAV) infection through epidemiological and genotype investigations of individual cases in a 2019 outbreak in South Korea.
Methods: We investigated food intake histories, associations with hepatitis A, and genotypes of HAV in 31 patients with hepatitis aged 20 to 49 years registered in the integrated disease and health management system during December 1–7, 2019 (case group) and in 35 sex- and age-matched people without a history of HAV vaccination or infection among patients' families and colleagues (control group).
Results: The consumption of salted clams was a significant factor (odds ratio, 4.33; 95% confidence interval, 1.32–14.18) in the risk factor analysis of food intake history. HAV genotypes were analyzed in 24 of 31 patients. Type IA and type IIIA were found in 23 and 1 cases, respectively.
Conclusion: Salted clams are considered to have been the source of HAV infection at 49 weeks of the HAV outbreak in 2019; this result was consistent with that of a previous epidemiological investigation conducted by the Korea Disease Control and Prevention Agency in September 2019. Therefore, monitoring of the production and distribution of salted clams needs to be continued.

Keywords: Disease outbreaks; Hepatitis virus A; Korea; Virus diseases

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Introduction

Hepatitis A is a waterborne and foodborne infectious disease caused by hepatitis A virus (HAV). HAV is an RNA virus classified into the genus *Hepatovirus* within the family *Picornaviridae*.

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HAV has only 1 serotype and 7 genotypes, of which types I, II, III, and IV are found in humans. Type I is distributed worldwide, with type IA mainly found in North America, Korea, China, Japan, and Taiwan and type IIIA observed in India, Sri Lanka, Nepal, Malaysia, and the United States [1,2].

HAV outbreaks occur due to the consumption of undercooked contaminated food or contaminated drinking water [3]. Raw foods such as frozen strawberries, scallops, pomegranate seeds, chives, and raw oysters, especially shellfish, are sources of HAV infection. As evidenced by the 290,000 infections caused by contaminated shellfish in Shanghai, China in 1988 [4] and 292 infections caused by the consumption of Philippine scallops in a sushi restaurant in Hawaii, USA in 2016, hepatitis A infections caused by the ingestion of shellfish have been occurring on an ongoing basis since the 1970s [5,6]. In addition, there was a recent case of occurrence owing to polluted groundwater in a park in South Korea (hereafter, Korea) in 2017 [7].

Hepatitis A was classified as a national notifiable infectious disease in Korea in 2010, and mandatory surveillance was initiated. After the occurrence of 5,521 cases in 2011, approximately 1,000 to 2,000 cases have occurred every year. In 2019, there was a large-scale outbreak of hepatitis A in 17,598 people, with an incidence rate of 33.95 per 100,000 people. Furthermore, 3,906 and 3,989 cases were reported in 2020 and 2021, respectively [8].

The 2019 hepatitis A epidemic epidemiological investigation conducted by the Korea Disease Control and Prevention Agency confirmed that salted clams were the source of infection in 21 of 26 cluster outbreaks as of August 2019. According to the results of 2 case-control studies, the intake rate of salted clams in the case group was 59 times and 115 times higher than that in the control group, respectively, suggesting that the main source of infection was salted clams [9,10]. In those investigations, the genotype analysis of HAV in patients and salted clams, which were suspected to be the source of infection during the 2019 hepatitis A outbreak epidemiological investigation, showed that the viruses were highly similar (i.e., type IA).

Based on the investigation results, on September 11, 2019, the Korea Disease Control and Prevention Agency confirmed that the main cause of the hepatitis A outbreak was contaminated salted clams. Therefore, it was recommended via the media to stop eating salted clams until safety was ensured. After that, the number of hepatitis A cases, which was 660 cases per week, steadily decreased. Therefore, when we conducted the investigation in the 49th week after the outbreak, only 63 cases (approximately 10%) were reported [8,9].

However, as individual infections continued to occur in the fourth quarter of 2019, it became necessary to determine whether the reason for the newly developed individual infections was salted clams or other infectious agents. Therefore, the source of infection due to food intake was evaluated in this case-control study of hepatitis A cases reported in the 49th week of 2019, approximately 2 months after it was recommended to stop eating clams (in the 37th week). This time point was chosen considering the incubation period of HAV.

This report was also intended to inform the public regarding the risk of HAV infection through the intake of salted seafood produced without heating.

Materials and Methods

Study Subjects

Hepatitis A epidemiological survey data registered at medical institutions using the Korea Disease Control and Prevention Agency's integration system from December 1 to December 7, 2019 were analyzed.

Among 63 cases reported to the integrated disease and health management system during the abovementioned period, we identified 41 patients with hepatitis A among adults aged over 20 years who were diagnosed with hepatitis A based on clinical symptoms consistent with hepatitis A, HAV IgM detected in blood samples and specific genes detected in samples (such as blood, feces, or rectal swabs), while excluding cases of delayed reporting and cases for which epidemiological investigations were completed.

The control group included adults aged over 20 years who had established contact with patients during the same period. Among the patients' families or colleagues, those who reported that they had no history of hepatitis A and had never been vaccinated against hepatitis A were selected with consideration of sex and age. However, there was a possibility that hepatitis A could be transmitted to them via contact with patients or exposure to the same infectious agents. Therefore, in this study, we monitored the occurrence of hepatitis A from the last exposure date to the maximum incubation period of 50 days to confirm that HAV infection did not take place.

In addition, people aged ≥50 years, who have HAV antibody positivity rates ≥90%, were excluded from the investigation on the basis of the results of a recent study on the prevalence of anti-HAV antibodies [10,11]. As a result, 31 and 35 people in the patient and control groups, respectively, were finally selected.

Study Methods

Epidemiological investigation (survey)

The responsible public health center and the Korea Disease Control and Prevention Agency reported patients' clinical symptoms, isolation and management measures, food intake history, physical contact with infected persons, and contact tracing according to the management guidelines for waterborne and foodborne infectious diseases. In particular, the food intake history investigated the consumption of uncooked raw foods such as raw shellfish, various types of salted fish, and sashimi; frozen fruits such as strawberries, raspberries, and blackberries; and drinking water, including mineral water and groundwater. If there was an intake history of salted clams, the reason for intake was investigated [12].

Risk factor analysis

A case-control study was conducted by selecting hepatitis A patients aged 20 to 49 years who were reported from December 1 to 7, 2019 for the case group and family and work colleagues of patients for the control group. Our study considered HAV-contaminated food or drinking water intake as a risk factor.

HAV genotype analysis

The HAV genotypes of the case group were identified by the responsible Public Health and Environment Research Institute and were compared with the genotype distribution in the epidemiological investigation results obtained in September 2019.

Data analysis

IBM SPSS ver. 21.0 (IBM Corp., Armonk, NY, USA) was used for data analysis. The general characteristics of individuals in the patient and control groups are presented as frequencies and percentages, and the significance level was set to <0.05 using the chi-square test. In the case-control group study, odds ratios (ORs) and 95% confidence intervals (CIs) were obtained using the Excel 2013 program (Microsoft Corp., Redmond, WA, USA). In addition, this study was approved by the Institutional Review Board (IRB) of Seoul National University (IRB No: E2202/001-003).

Results

General Characteristics

The case group included 14 men (45.2%) and 17 women (54.8%), whereas the control group included 10 men (28.6%) and 25 women (71.4%). The average age of the individuals was 38.3 years, which was not significantly different from the average age of all hepatitis A patients reported through the Korea Disease Control and Prevention Agency's integration system in 2019 [8]. Among the total participants, the percentage of those in their 40s was the highest (28 patients, 42.4%), followed by those in their 20s and 30s (19, 28.8%), respectively. No significant differences in the ratios were found with respect to sex and age in the patient and control groups (Table 1).

Hepatitis A in the case group occurred in 9 cities and provinces, most commonly in Gyeonggi Province (15 cases, 48.4%) and in Seoul metropolitan city (5 cases, 16.1%). In the control group, there were 18 people in Gyeonggi Province and 4 in Seoul metropolitan city. There was no significant difference in the distribution of residence areas between the patient and control groups (Table 1).

Epidemic Curve and Occurrence Characteristics

Thirty-one patients in the case group developed symptoms between November 18 and December 5, 2019. The average period from symptom onset to the report date was 7.8 days (minimum, 0 days; maximum, 15 days). The average period from symptom onset to the date of diagnosis was 6.0 days (minimum, 0 days; maximum, 15 days). The most frequent date of symptom onset was November 29, 2019 (6 patients,

Table 1. General characteristics of cases and controls

Characteristic	Case ($n=31$)	Control ($n=35$)	p
Sex			0.162
Male	14 (45.2)	10 (28.6)	
Female	17 (54.8)	25 (71.4)	
Age (y)			
20–29	6 (19.4)	13 (37.1)	0.111
30–39	9 (29.0)	10 (28.6)	0.967
40–49	16 (51.6)	12 (34.3)	0.155
Region (city or province)			
Seoul	5 (16.1)	4 (11.4)	0.578
Gyeonggi-do	15 (48.4)	18 (51.4)	0.888[a]
Busan	-	1 (2.9)	
Daegu	1 (3.2)	2 (5.7)	
Incheon	1 (3.2)	2 (5.7)	
Daejeon	2 (6.5)	2 (5.7)	
Sejong	1 (3.2)	1 (2.9)	
Gangwon-do	2 (6.5)	2 (5.7)	
Chungcheongbuk-do	-	1 (2.9)	
Chungcheongnam-do	3 (9.7)	1 (2.9)	
Jeollabuk-do	1 (3.2)	-	
Gyeongsangbuk-do	0 (0)	1 (2.9)	

Data are presented as n (%). The p-value is based on the chi-square test.
[a]Since the numbers except for the two regions (Seoul and Gyeonggi-do) were too small, the other regrions from Busan to Gyeongsangbuk-do were comparerd by summing them up.

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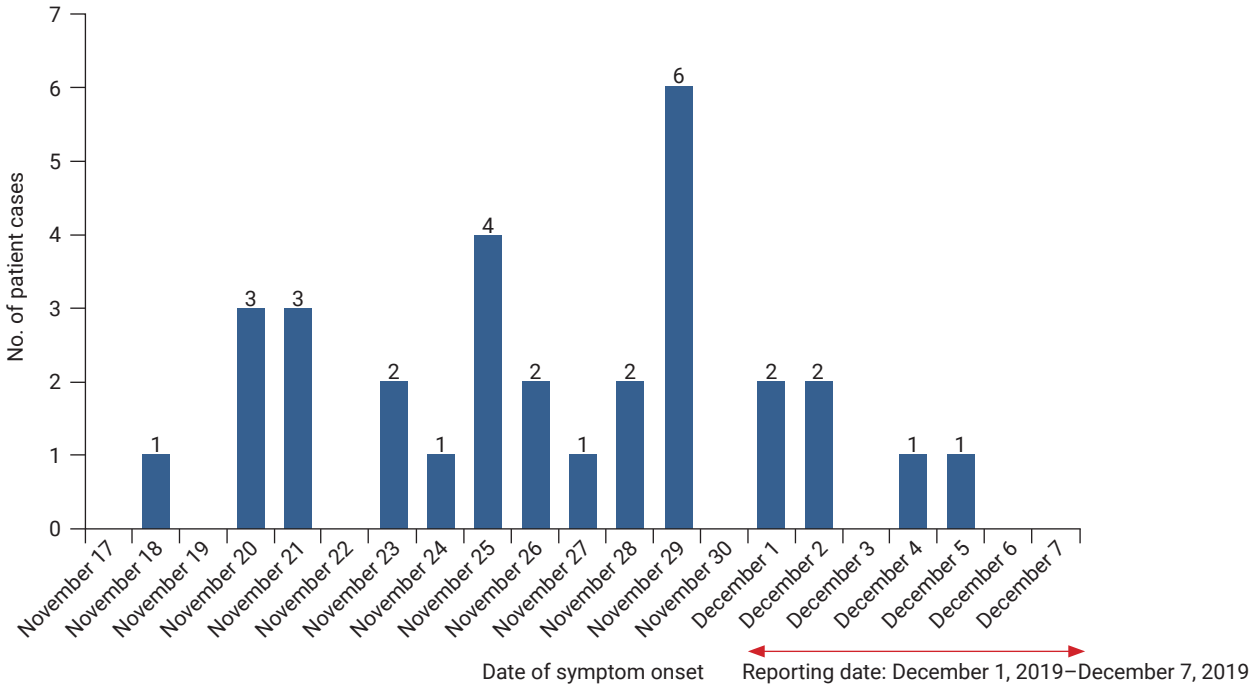

Figure 1. Epidemic curve for hepatitis A patients in the 49th week of 2019.

19.4%), after which symptom onset continued to occur in 1 to 3 patients per day during the outbreak period (Figure 1).

The symptoms included fever of 38°C or higher (21 cases, 67.6%), nausea (19 cases, 61.3%), and a feeling of fatigue (18 cases, 58.1%), which were consistent with those reported before as the most common symptoms in the analysis of the 2017 epidemiological survey (i.e., fever, nausea, and severe fatigue/weakness). However, no cases of jaundice were reported in this study, unlike the previously reported jaundice incidence rate of approximately 40% [13].

Risk Factor Analysis

The intake of salted clams (OR, 4.33; 95% CI, 1.32–14.18) 15 to 50 days before the onset of symptoms was significant in the food intake analysis (Table 2).

In the case group, among patients with an intake history of salted clams, 13 (41.9%) purchased salted clams from a side-dish store near their residence, 8 (61.5%) purchased clams from a nearby market, and 5 (38.5%) consumed salted clams served as a side dish at a restaurant. Five patients (38.5%) reported being aware that salted clams were the probable source of HAV infection. Eight patients (61.5%) responded that they were unaware that salted clams were the probable source of HAV infection in 2019.

Five individuals with an intake history of salted clams in the control group purchased them from a nearby side-dish store and consumed them at home. Among them, 2 (40.0%) reported that they had heard about the recommendation to avoid eating salted clams through the news but ignored it because they judged that it would be safe to eat them from October to November, and 3 people (60.0%) responded that they were not aware of the recommendation.

Laboratory Test Results

The HAV genotype was identified in 24 of 31 patients. Type IA was detected in 23 patients, and type IIIA was detected in 1 patient.

Discussion

The number of patients with hepatitis A, which had reached 659 cases per week by the 34th week of the 2019 outbreak, decreased to 63 in the 49th week of 2019 after the recommendation to stop eating salted clams on September 11, 2019 (in the 37th week). In this study, we determined whether the source of infection in each case was still salted clams, even after recommending the public to stop consuming salted clams.

The incidence rate was high in Seoul and Gyeonggi Province, which accounted for 64.5% of the case group. This reflects the fact that patients with hepatitis A in Seoul and Gyeonggi Province accounted for 48.6% of all patients in 2019. The number of patients rapidly decreased after the recommendation to stop eating salted clams in the 39th week in Daejeon, Sejong, and Chungcheong Province, which had high crude incidence rates [8].

Table 2. Association of illness with foods

Variable	Case (*n* = 31)	Control (*n* = 35)	OR (95% CI)
Raw shellfish			
Oysters	3/28	5/30	0.64 (0.14–2.94)
Cockles	1/30	0/35	NA
Clams	1/30	0/35	NA
Raw fish			
Raw fish	9/22	5/30	2.45 (0.72–8.35)
Sliced raw octopus	1/30	1/34	1.13 (0.07–18.92)
Shrimp	1/30	1/34	1.13 (0.07–18.92)
Salted fish			
Salted clams	13/18	5/30	4.33 (1.32–14.18)
Salted guts of hairtail	1/30	0/35	NA
Salted squid	1/30	3/32	0.36 (0.35–3.61)
Frozen fruits	0/31	0/35	NA
Groundwater	0/31	0/35	NA

Data are presented as *n* of people who reported consuming the food/*n* of people who reported not consuming the food.
OR, odds ratio; CI, confidence interval; NA, not available.

According to the results of the food intake history investigation to identify the source of infection, the intake rate of salted clams among the patients was 4.33 times (95% CI, 1.32–14.18) higher than that of the control group.; Therefore, after analyzing the data, this study revealed that salted clams were the source of infection. This finding is consistent with the study results reported by Seo et al. [14], who suggested that raw shellfish intake was a risk factor for hepatitis A, and the epidemiological investigation results published by the Korea Disease Control and Prevention Agency in September 2019 [15]. The genotypes of 87.5% of the 179 human samples and 80.4% of the 8 salted clam samples related to the cluster that occurred in 2019 were type IA. and the genotypes of HAV in the case group who ingested salted clams were all type IA, which was consistent with the results of a previous study [16].

Salted clams are bivalves that obtain nutrients by constantly filtering seawater. Therefore, when seawater is contaminated with viruses, the viruses may be concentrated inside the clam. In addition, because seawater along the coast, where sewage can flow in, can be continuously polluted, raw shellfish (including salted fish consumed raw) can be a source of HAV. It has been reported that HAV was detected in 8.9% of collected shellfish in Italy. HAV has also been detected in 3.8% of clams collected from fish farms or stores in Thailand. Therefore, this study considered salted clams as the source of infection in the 49th week of 2019 [17,18].

After the epidemiological investigation by the Korea Disease Control and Prevention Agency in September 2019, the Ministry of Food and Drug Safety inspected 136 salted clam products distributed in Korea in September 2019. The virus was detected, and the products were recovered and discarded in 44 cases, including 30 domestic and 14 Chinese salted clam products. In addition, domestic products were ordered to be inspected before sale to ensure that only products without viruses could be sold, and customs inspections were enforced for salted clams imported from China [19]. Regarding the distribution of salted clams, salted clams consumed in the patient and control groups were provided as side dishes at restaurants or were purchased from side-dish stores from the end of September to early November 2019 according to the epidemiological investigation results

Although mandatory surveillance and test orders were being implemented, the intake rate of salted clams in the case group was 4.33 times higher than that in the control group in this study. Moreover, a cluster infection of hepatitis A was reported in 6 people who consumed salted clams in April 2020. Therefore, cases of hepatitis A caused by salted clams continued to occur [20].

Compared with other products, there is a larger number of salted clams in products with the same serial number; therefore, clams that were omitted from sampling during the test may have been contaminated with HAV. Considering that HAV was detected in domestic products during product inspections in September 2019 and in raw clams collected at the Boryeong clam farm in Chungnam in December 2019, it is likely that contamination along Korea's coast has occurred. Therefore, there is a possibility of HAV contamination of salted clams produced in Korea [21].

In addition, as salted clams are salted food products, the storage period is extended. Therefore, it is possible that

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consumers would continue to consume contaminated salted clam products without discarding the products they had individually purchased before the products were recalled. Moreover, in this study, more than 60% of people who ate salted clams were unaware that salted clams, an unheated food, could be contaminated. Therefore, it was assumed that individual cases of hepatitis A continued to occur because of the possibility of contamination of individual clams, as described above, and the continuous ingestion of contaminated salted clams without the awareness of relevant details owing to the lack of publicity.

In the food intake history investigation, sashimi intake, in addition to the consumption of salted clams, was higher in the case group than in the control group, although the difference was not statistically significant, and sashimi was identified as a probable source of infection. An investigation of the dietary history of patients with hepatitis A in Korea during the incubation period in 2017 found that these patients consumed a large proportion of raw vegetables/salads, followed by fresh fruit/fresh fruit juice, sashimi/sushi, steak tartare, raw oysters, and marinated raw crabs, with sashimi in the third place. The prevalence of norovirus infection, a waterborne and foodborne infectious disease caused by the ingestion of seafood caught in contaminated seawater, has also been reported.

HAV has been reported in approximately 1% of fish and shrimp harvested from the Persian Gulf, confirming that sashimi can also be a source of infection [13,22,23]. Therefore, in addition to salted clams, which have already been identified as infectious agents, existing probable sources of infection such as raw shellfish, including sashimi and oysters, and the intake of other raw foods should continue to be investigated and managed.

This study had limitations. First, the age group was selected by reviewing the general antibody positivity rate. However, considering that the antibody positivity rate of individuals in their 40s was 68% to 69%, anti-HAV immunoglobulin G tests were not performed in the control group, since there could have been cases wherein people were not infected with HAV even if they consumed contaminated salted clams. Therefore, the risk may appear lower than the actual level. Nevertheless, this study identified salted clam consumption as a significant risk factor (OR, 4.33; 95% CI, 1.32–14.18), clearly indicating that salted clams were the source of infection. Second, we requested cooperation from local governments to inspect restaurants and vendors. However, it was impossible to inspect the food because the salted clams had already been discarded, were not recorded in account books, or could not be collected because they were sold out a long time ago. Similarly, sashimi was not considered a significant source of infection even though sashimi was consumed by many subjects in addition to salted clams. However, like clams, fish also live in polluted waters, and sashimi is raw food. Therefore, the risk of infection from sashimi cannot be excluded. Nevertheless, no further investigation regarding foods related to sashimi intake was conducted. Finally, because HAV has a long incubation period and the infection can develop 1 to 2 weeks before the onset of symptoms, individuals' memory may not have been accurate during the survey. In addition, salted clams were already known as a source of infection through the media in September. Therefore, there may have been a recall bias toward reporting intake of salted clams or salted seafood.

Conclusion

In the study by Ki et al. [24], the reasons for the 2019 hepatitis A outbreak were identified as a decrease in the level of adult herd immunity, a change in Korean food culture, a weak public health system, and a lack of effective coordination of public health policies. The occurrence of infections caused by shellfish intake was likely because of the age of patients with a low antibody retention rate and changes in eating habits [12].

Recently, in Korea, people in their 20s, 30s, and 40s have been shown to have low HAV antibody positivity rates because they have not acquired immunity after birth naturally or through vaccination. However, their intake of salted seafood, raw clams, and raw fish is higher in the context of the social activities of this group. Therefore, it is thought that HAV infection from salted clams reflected this increased risk of infection. In addition, it was assumed that the hepatitis A outbreak continued in December 2019 because of the possibility of contamination of coastal beaches, the inherent limitation of the inspection process that all of the clams in imported and domestic salted clam products cannot be tested, and the continued intake of salted clams owing to the lack of publicity after the recommendation to discontinue consumption.

The 2019 hepatitis A epidemic epidemiological investigation in Korea confirmed once again that salted shellfish, which is an unheated product, can be a source of HAV infection, as well as raw shellfish consumption. Therefore, the monitoring of imports, production, and sale of salted clams should be continued. In addition, in order to effectively investigate and manage HAV, which has a long incubation period, education including salt foods is needed for raw food types that can be a source of infection. In addition, it is necessary to actively promote information on the probable sources of infection, personal hygiene management, and safe food intake to prevent HAV infection in the future.

Notes

Ethics Approval

This study was approved by the Institutional Review Board of Seoul National University (IRB No: E2202/001-003) and performed in accordance with the principles of the Declaration of Helsinki.

Conflicts of Interest

The authors have no conflicts of interest to declare.

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Availability of Data

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

Authors' Contributions

Conceptualization: JHH, SHL; Data curation: JHH; Formal analysis: JHH; Investigation: JHH, SHL; Methodology: JHH, SHL; Project administration: all authors; Resources: JHH; Software: JHH; Supervision: JYY; Validation: JYY; Visualization: JHH, SHL; Writing-original draft: all authors; Writing-review & editing: all authors.

Additional Contributions

We thank all the local government infectious disease managers.

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Original Article

Investigation of SARS-CoV-2 lineages and mutations circulating in a university-affiliated hospital in South Korea analyzed using Oxford Nanopore MinION sequencing

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ABSTRACT

Objectives: Despite the introduction of vaccines, treatments, and massive diagnostic testing, the evolution of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has continued to overcome barriers that had slowed its previous spread. As the virus evolves towards increasing fitness, it is critical to continue monitoring the occurrence of new mutations that could evade human efforts to control them.

Methods: We performed whole-genome sequencing using Oxford Nanopore MinION sequencing on 58 SARS-CoV-2 isolates collected during the ongoing coronavirus disease 2019 pandemic at a tertiary hospital in South Korea and tracked the emergence of mutations responsible for massive spikes in South Korea.

Results: The differences among lineages were more pronounced in the spike gene, especially in the receptor-binding domain (RBD), than in other genes. Those RBD mutations could compromise neutralization by antibodies elicited by vaccination or previous infections. We also reported multiple incidences of Omicron variants carrying mutations that could impair the diagnostic sensitivity of reverse transcription-polymerase chain reaction-based testing.

Conclusion: These results provide an understanding of the temporal changes of variants and mutations that have been circulating in South Korea and their potential impacts on antigenicity, therapeutics, and diagnostic escape of the virus. We also showed that the utilization of the nanopore sequencing platform and the ARTIC workflow can provide convenient and accurate SARS-CoV-2 genomic surveillance even at a single hospital.

Keywords: Nanopore sequencing; Republic of Korea; SARS-CoV-2; SARS-CoV-2 delta variant; SARS-CoV-2 Omicron variant

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Introduction

Since its first emergence in December 2019, severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has rapidly spread globally, and 4 months later the World Health Organization officially declared it a pandemic [1]. Since then, over 500 million human cases, including over 6 million deaths, have been reported worldwide so far, yielding several variants of interest (VOIs) and variants of concern (VOCs). The first case in South Korea was reported in January 2020, followed by a rapid increase in reported cases, which led to the first wave peak in February 2020 [2]. There have been several rises in the number of new infections in South Korea [2], including the latest surge of Omicron subvariants. Despite the strict restrictions on human activity and the introduction of vaccines and treatments, the evolution of the virus has continued to overcome barriers that had previously slowed its spread. The highest number of infections caused by new emerging variants has always exceeded the previous high, and the recent Omicron peak reached about 80 times higher than the previous Delta peak in South Korea [3].

During the course of the pandemic, more than 10 billion genome sequences of SARS-CoV-2 have been gathered worldwide, leading to the discovery that its continuous evolution is the fundamental driving force behind the prolonged pandemic [4]. Several genomic surveillance studies have also revealed that the accumulation of mutations has been heterogeneous along the genome and multiple genetic sites, such as the genes coding for the S and N proteins, were under positive selection [5,6]. As the virus evolves towards increasing fitness, it is necessary to continue monitoring the occurrence of new mutations that could increase infectivity or transmission efficiency, especially in response to these human efforts to control them.

In this study, we performed whole-genome sequencing using Oxford Nanopore MinION on 58 SARS-CoV-2 isolates collected during the ongoing coronavirus disease 2019 (COVID-19) pandemic (the 2nd, 4th, and 5th waves of infections) at a university-affiliated hospital in South Korea and tracked the emergence of mutations of certain variants responsible for the massive spikes in South Korea. Our results provide an understanding of the temporal change of variants and mutations that have been circulating in South Korea and the potential contribution of the evolving mutations on antigenicity, therapeutics, and diagnostic escape of the virus. We were also able to demonstrate that the utilization of the nanopore sequencing platform and the ARTIC workflow could provide convenient and accurate SARS-CoV-2 genomic surveillance even at a single hospital.

Materials and Methods

Sample Collection and Diagnostics

Nasopharyngeal and oral swab specimens from suspected cases were collected as part of routine surveillance at Kangdong Sacred Heart Hospital, Seoul, South Korea. RNA was extracted using a STARMag Universal Cartridge Kit (Seegene Inc., Seoul, Korea), and real-time reverse-transcription polymerase chain reaction (RT-PCR) with Seegene Allplex SARS-CoV-2 assay (Seegene Inc.) on a Bio-Rad CFX96 thermal cycler (Bio-Rad Laboratories, Hercules, CA, USA) was performed. Among samples that tested positive, those collected from June 2020 to September 2020 (Wuhan-type epidemic), November 2021 to December 2021 (Delta epidemic), and February 2022 to April 2022 (Omicron epidemic), which coincided with the 2nd, 4th, and 5th waves of the pandemic in South Korea, were subjected to whole-genome sequencing (Figure 1; Table S1).

Amplicon-Based Whole-Genome Sequencing

We performed whole-genome sequencing on 58 SARS-CoV-2 isolates following the ARTIC nCoV-2019 sequencing protocol. The cDNA synthesis and PCR amplification were performed according to the ARTIC amplicon sequencing protocol, using cDNA synthesis Automix (Seegene Inc.) in combination with the ARTIC nCoV-2019 V3 amplicon set. The PCR products were treated with a ligation kit (SQK-LSK109; Oxford Nanopore Technologies, Oxford, UK) and a barcoding kit (EXP-SFB001; Oxford Nanopore Technologies). Libraries were sequenced with the Oxford Nanopore MinION device using ONT R9.4.1 flow cells (Oxford Nanopore Technologies) for 12 hours.

Generation of Consensus Genomes and Mutational Profiling

For the construction of consensus sequences, the recommended ARTIC bioinformatics workflow (https://github.com/artic-network/fieldbioinformatics) was used. Generated sequences were manually assessed to verify the mutations called by the ARTIC pipeline. The genomes were classified into PANGO lineages using Pangolin v.4.0.6 [7], and mutation annotation was performed using Nextclade (https://clades.nextstrain.org) and Coronapp (http://giorgilab.unibo.it/coronannotator/). The genome sequences used for comparison were retrieved from the GISAID database (https://www.gisaid.org/) on April 6, 2022. Sequences were aligned using ClustalW 1.2.1 [8], and a maximum-likelihood phylogenetic tree was constructed using FastTree 2.1 [9] with 1,000 bootstrap replications. The Wuhan-Hu-1 sequence (RefSeq: NC_045512.2) was used as a reference genome and for rooting the tree as an outgroup.

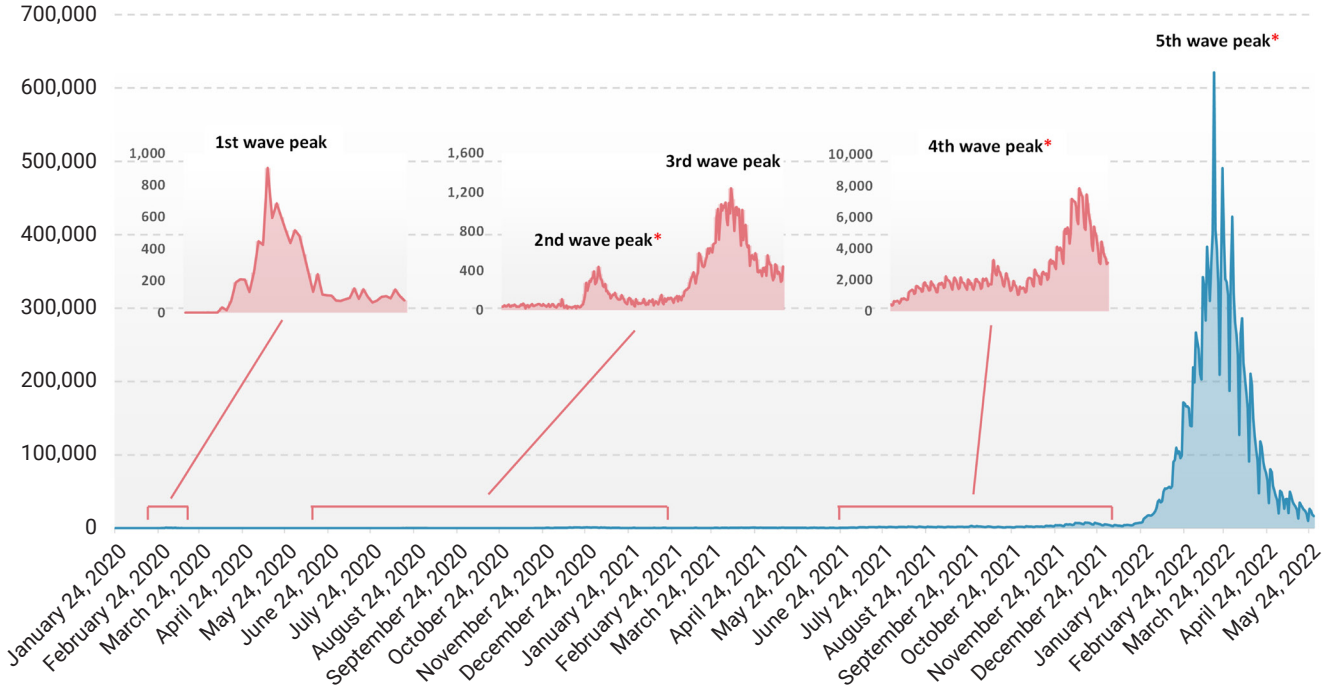

Figure 1. Daily new confirmed cases and time series of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) waves in South Korea. Daily cases of SARS-CoV-2 in South Korea between January 20, 2020 and May 27, 2022 and 5 large waves are shown. The specimens used for analysis in this study were collected during the 2nd, 4th, and 5th waves, which are highlighted with asterisks.

The tree was visualized using Interactive Tree of Life ver. 5 (https://itol.embl.de). Antibody escape was calculated using an escape calculator for the SARS-CoV-2 receptor-binding domain (RBD) [10].

Ethics Approval

This study was approved by the Institutional Review Board (IRB) of Kangdong Sacred Heart Hospital, Seoul, South Korea (IRB No: NON2021-001-001) and performed in accordance with the principles of the Declaration of Helsinki.

Results

Temporal Changes of SARS-CoV-2 Variants in South Korea

The ARTIC protocol generated 250,686±45,498 raw reads, totaling approximately 109±19 Mbp of sequences for each sample. The mean read qualities ranged between 11.6 and 13.9 (Table S1). All 58 sequenced samples showed at least 85% of the genome covered at least 20-fold, and 48 samples had more than 95% coverage (Table S2). Fifty-seven samples with at least 90% coverage were used in the subsequent whole-genome comparison (Table S1). In total, 6 SARS-CoV-2 lineages were identified in the 58 samples based on Pangolin [7] and Nextclade [11]. The samples collected between June 2020 and September 2020 (second wave of infections) were assigned to the B.1.497 (20C) lineage, and the samples collected between November 2021 and December 2021 (4th wave) belonged to the Delta VOC, which consisted of AY.69 (21I) and AY.122.5 (21J) (Table S1). Twenty-eight samples collected between March 2022 and April 2022 (5th wave) belonged to the Omicron VOC, including 11, 8, and 9 classified as BA.1.1 (21K), BA.2 (21L), and BA.2.3 (21L), respectively. The BA.2 and BA.2.3 lineages are currently the major causes of ongoing cases in South Korea [3]. The B.1.497 lineage had an average of 14.7 mutations, and the number of synonymous and non-synonymous mutations was similar on average (Figure S1; Table S3). However, an average of 45.1 and 44.4 mutations were identified in the 2 Delta subvariants, and the number of non-synonymous mutations was more than twice greater than that of synonymous mutations (Figure S1; Table S3). For the 3 Omicron subvariants (8 intact BA.1.1, 3 BA.2, and 5 BA.2.3 sequences were considered), the average numbers of mutations were 61.9, 66.7, and 70 for BA.1.1, BA.2, and BA.2.3 respectively, and the differences among them were also mainly due to the accumulation of non-synonymous mutations (42.1, 47, and 49.4 on average) (Figure S1; Table S3). The differences in the accumulation of non-synonymous and synonymous mutations were greater

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in the S region, compared to the other gene regions (Figure S1). As the virus evolved, while the number of synonymous mutations maintained below 7 in the S gene, non-synonymous mutations markedly increased to an average of 28, 22, and 23 in BA.1.1, BA.2, and BA.2.3, respectively (Figure S1).

The divergence between lineages was the greatest in the spike protein. The BA.1.1 subvariant contained about 32 new mutations in the spike encoding region compared to the Delta variants, and the BA.2 and BA.2.3 subvariants gained about 9 new mutations (T19I, A27S, G142D, S371F, V213G, T376A, D405N, R408S, and 24–26 deletion) compared to BA.1.1 (Tables S2, S3). Meanwhile, the 2 subvariants lacked 14 mutations, including 69–70 del, 142–144 del, and 211 del. Although most of the amino acid changes in the spike were fixed at the individual level, KD-Cov-O19 carried 2 unique mutations, L5F and H49Y (Tables S2, S3).

Impacts of the Emergence of Mutations on Infectivity and Therapeutics

As evident from Figure 2 and Table S4, the differences

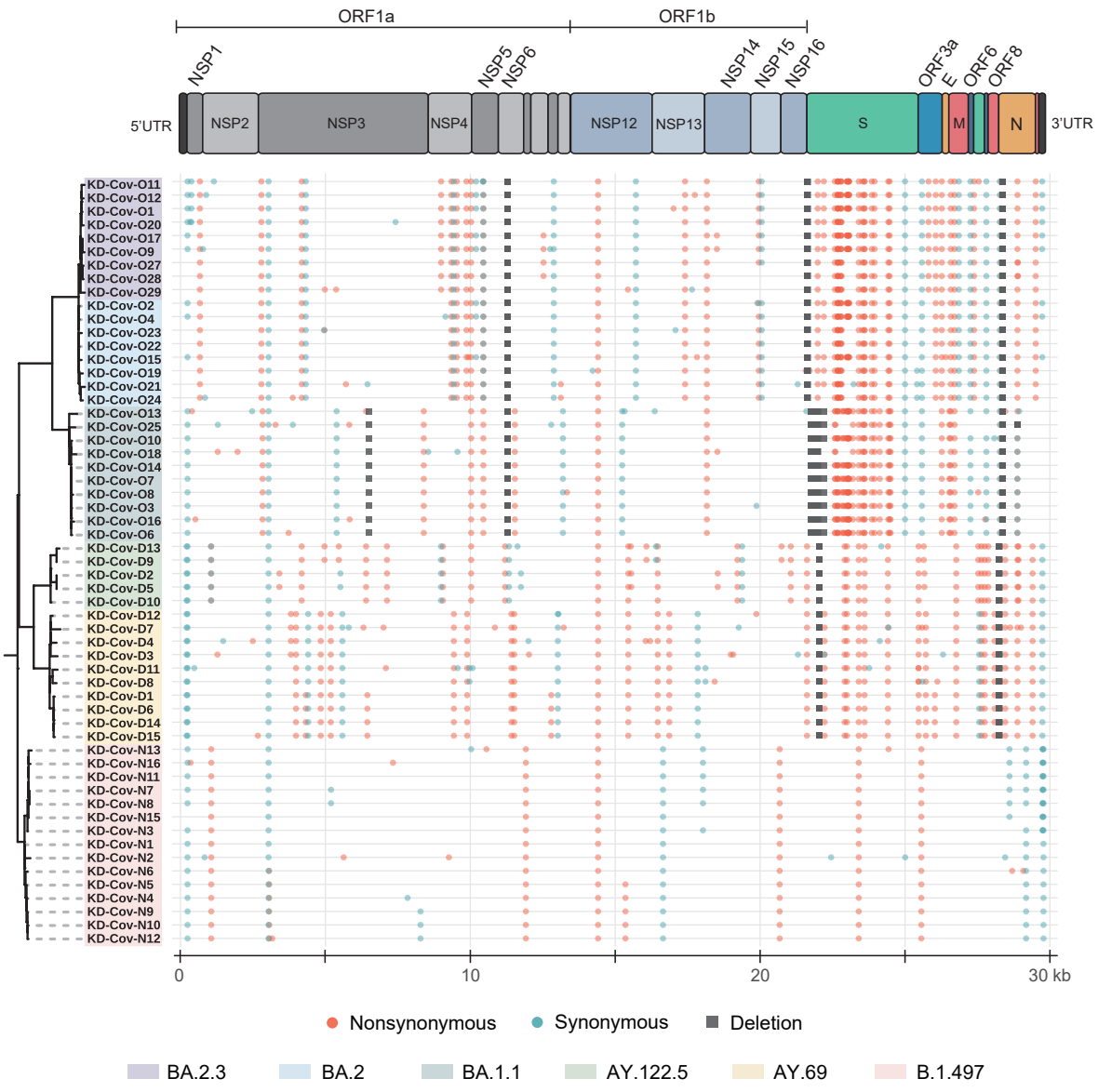

Figure 2. Genome-wide mutational profiling of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) isolates. This figure illustrates genome-wide patterns of mutations in 6 SARS-CoV-2 lineages responsible for the major waves in South Korea. A maximum-likelihood phylogenetic tree was constructed to show the relationship between the isolates, and the tree labels were colored based on the lineages. Each colored circle and square represent different types of mutations, located according to their actual position in each genome.

among lineages were more pronounced in the spike gene. While the B.1.497 possessed only 1 fixed mutation in the gene, 6–7 and 27–31 fixed mutations were identified in genomes of the Delta (AY.122.5 and AY.69) and the Omicron (BA.1.1, BA.2, and BA.2.3) variants, respectively. Markedly, the majority of the mutations gained by the Omicron variants were located in the RBD region of the gene, which had 7.5–8 times more substitutions (16 for BA.1.1 and 15 for BA.2 and BA.2.3) than the Delta subvariants in the region, and all these substitutions were non-synonymous changes. Of the 16 changes in Omicron BA.1.1 and 15 changes in the Omicron BA.2 and BA.2.3 subvariants in the RBD, 8 (K417N, G446S, E484A, Q493R, G496S, Q498R, N501Y, and Y505H) and 6 (K417N, E484A, Q493R, Q498R, N501Y, and Y505H), respectively, mapped to the positions proposed to be critical for binding to human ACE2 [12], and the residues remained unchanged in other lineages (Figure 3A).

The antibody-escape calculator [10] estimated that the combination of the RBD mutations of the Delta subvariants reduced the fraction of binding antibodies to below 0.9 (Figure 3C). The mutations that emerged in the Omicron variants could lead to more immune escape by dropping the fraction to 0.5 (BA.1.1) and 0.6 (BA.2 and BA.2.3), and the difference between these subvariants was induced by additional R346K, N440K, G446S, and G496S mutations in the BA.1.1 lineage (Figure 3D, E).

In the M_{pro} coding region, which is an important antiviral drug target of Paxlovid (Pfizer) for treatment of the virus, 1 B.1.497 isolate (KD-Cov-N13) was observed to have a change in the 168 position, and 2 AY.69 isolates, D7 and D11, harbored M264I and a synonymous change in the 10078 nucleotide position, respectively (Table S3). The BA.1.1 lineage carried 1 mutation (P132H), and 4 types of substitution (synonymous changes in the 10198, 10432, and 10447 nucleotide positions and P132H) were observed in BA.2 and BA.2.3. The substitution at the 10432 position occurred only in KD-Cov-O11, BA.2.3, which had the most substitutions in the NSP5 region among our isolates.

The Effect of the Emergence of Mutations on Diagnostic Sensitivity

Routine diagnostic testing has been performed at our diagnostic facility since the beginning of the SARS-CoV-2 pandemic. However, since February 2022, we have observed a few cases (KD-CoV-25, 26, 27, 28, and 29) showing discrepant results in target gene detection with a commercial assay (Allplex SARS-CoV-2 assay) which targets N, E, and RNA-dependent RNA polymerase (RdRP)/S gene fragments. KD-Cov-O25 and O26, a mother-child pair, showed N gene drop-out, despite having cycle threshold (Ct) values below 25 for both the E and RdRP/S genes (Table 1). In the KD-Cov-O27 and O28 samples, another mother-child pair, the Ct values for N and the other 2 (E and RdRP/S) differed by about 5 cycles, and regarding KD-Cov-O29, the Ct value for RdRP/S was 8 cycles higher than those of the E and N genes (Table 1). Deletions were identified in position 28877-28894, leading to the deletion of 6 amino acids (203–208 del) in the N protein of the KD-CoV-O25 and O26 pair. The KD-CoV-O27 and O28 pair carried an A208V mutation (C28896T) in the protein, overlapping the deleted region of the above-mentioned isolates. The only change observed in the KD-Cov-O29 genome was an additional M657T mutation (T15437C) in NSP12 compared to BA.2.3 isolates with normal Ct values. Although information on the primers and probes used in commercial SARS-CoV-2 assays is not generally disclosed, the mutations observed in the above cases may affect the RT-PCR diagnostic efficacy of the Allplex SARS-CoV-2 assay. To date, a total of 1,281 cases with deletions in the 203-208 position were reported on GISAID (10,140,904 deposited N gene sequences as of April 6, 2022). Interestingly, this deletion has been sporadically occurring in Canada, the USA, Brazil, Germany, Italy, and several other countries since its first appearing on GISAID in early 2020 (EPI_ISL_3717678, Isolation: India, March 19, 2020) before the emergence of Omicron. Furthermore, it was not specific to the Omicron variant and was also observed in Alpha, Delta, Gamma, Omicron, and other lineages. It was most prevalent in the USA and Brazil (397 and 186 instances, respectively). However, in South Korea, the deletion was first observed in January 2022 in the genome sequence of the Omicron BA.1.1 variant on GISAID and has maintained a low frequency (7 instances/ 11,785 Omicron sequences). It has also been exclusively observed in the Omicron subvariant (BA.1.1) so far in South Korea. The A208V mutation has been observed in 4,447 genome sequences, and the majority of them originated from the USA (1,009) and England (897).

Discussion

In this study, we performed whole-genome sequencing on 58 SARS-CoV-2 isolates collected during the ongoing COVID-19 pandemic at a single hospital to track the emergence of mutations of certain variants responsible for the massive spikes in South Korea. The differences among lineages were more pronounced in the spike gene, especially in the RBD region. Since changes in the RBD region may substantially change the antigenicity and susceptibility to pre-existing antibodies [12,13], mutations of emerging viruses in this region should be closely monitored. The new mutations gained by the Omicron variants were mostly located in the

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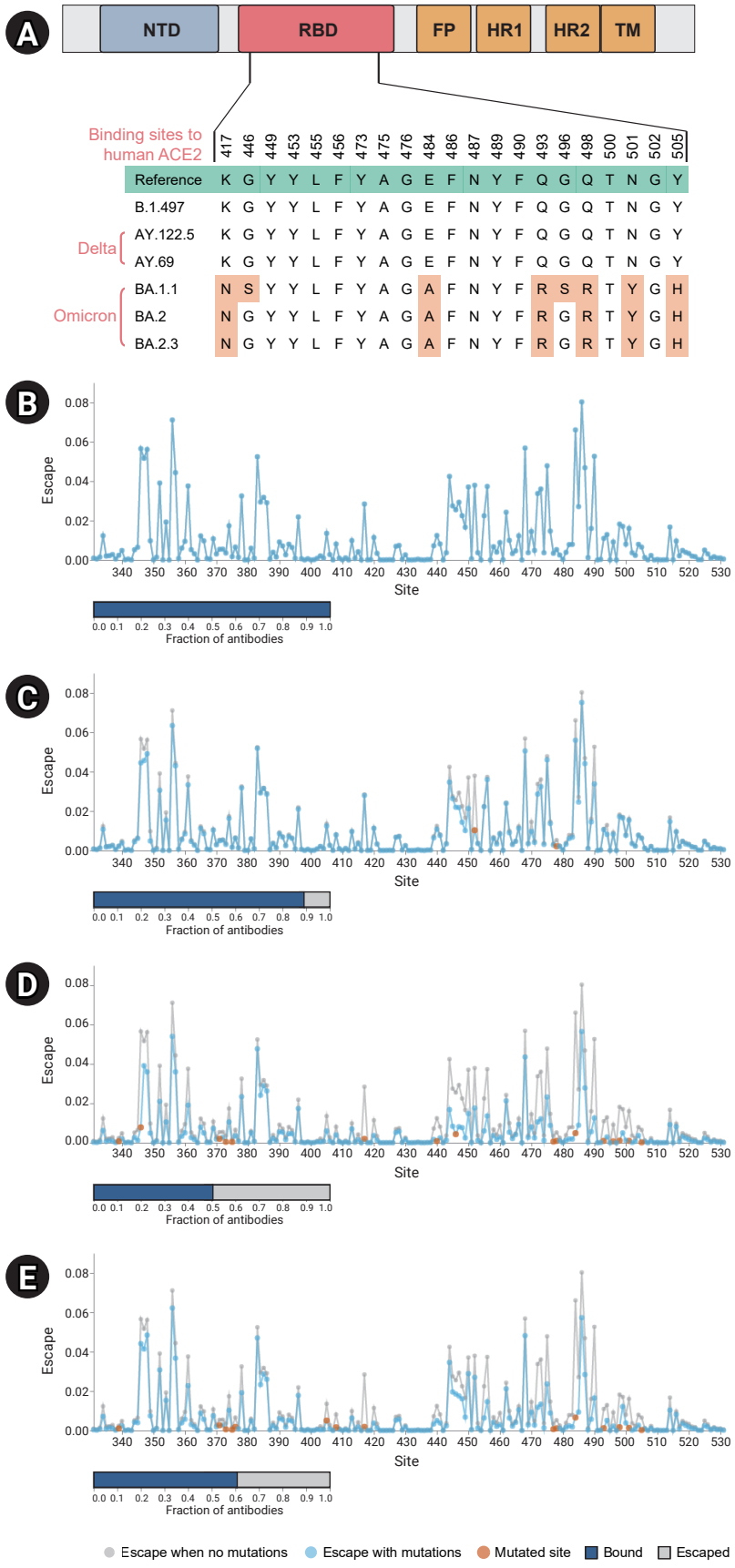

Figure 3. Mutations in the spike protein receptor-binding domain (RBD) may affect binding to human ACE2 and antibodies. (A) Differences in amino acid residues of known binding sites to human ACE2. (B–E) Antibody escape map for 33 neutralizing antibodies targeting RBD. The blue line shows escape mediated by mutations at each site, and the gray line represents the original escape map in the absence of mutations. The orange circles represent each mutation. The bar graphs show the total antibody binding remaining after combinations of mutations occurred. (B) B.1.497, (C) AY.122.5 and AY.69, (D) BA.1.1, (E) BA.2 and BA.2.3.
NTD, N-terminal domain; FP, fusion peptide; HR1, heptad repeat 1; HR2, heptad repeat 2; TM, transmembrane domain.

Table 1. Ct values for specimens with the Allplex SARS-CoV-2 assay and potentially associated mutations

Sample name	Pair	Sampling date	Ct value E	Ct value RdRP	Ct value N	Mutation (nucleotides)	Mutation (amino acids)
KD-Cov-O25	Child 1	February 14, 2022	20	21	ND	del 28877-28894	N:del 203-208
KD-Cov-O26	Parent 1	February 24, 2022	23	24	ND		
KD-Cov-O27	Child 2	April 1, 2022	21	21	25	C28896T	N:A208V
KD-Cov-O28	Parent 2	April 1, 2022	20	20	26		
KD-Cov-O29	NA	April 13, 2022	26	34	26	T15437C	NSP12:M657T

Ct, cycle threshold; RdRP, RNA-dependent RNA polymerase; ND, not detected; NA, not available.

critical binding sites to human ACE2. Interestingly, G446S and G496S were exclusively detected in BA.1.1. Another study reported that G496 was the residue introducing the most significant effects on the RBD-ACE2 interaction [14], and the G496S mutation was also suggested to reinforce or generate chemical bonding at the interface, along with G446S and N501Y [15]. Of the mutually detected mutations in the 3 Omicron subvariants, a previous study showed that Q493R and N501Y, along with S477N, formed a new interaction with human ACE2, which enhanced the binding of the Omicron variant to human ACE2 [16]. The Y505H mutation did not seem to have an impact on binding [17].

We then analyzed how the emerging RBD mutations could compromise neutralization by antibodies elicited by vaccination or natural infection, using a recently developed escape calculator tool that utilized a deep mutational scanning approach. Previous studies demonstrated that the calculator correlated well with experimentally measured neutralization titers [10]. The results indicated that the combination of RBD mutations that emerged in the Omicron variants could lead to more immune escape compared to the previous lineages. The difference between the Omicron subvariants was induced by additional R346K, N440K, G446S, and G496S mutations in the BA.1.1 lineage (Figure 3D, E). Motozono et al. [18] showed that Omicron BA.1 with the G446S mutation, located adjacent to NF9 epitope, showed greater inhibition of replication by vaccine-induced T cells as a result of enhanced presentation and recognition of the antigenic peptide on the spike protein. As shown in Figure 3B–E, the mutation at position 484 was among the largest drivers of antigenic changes [19]. In a study using 19 monoclonal antibodies, substitutions at this position occurred the most frequently [20], and all amino acid changes to A, K, Q, P, D, and G reduced recognition by antibodies [20,21]. The E484A mutation detected in Omicron variants also ablated neutralization by bamlanivimab, a therapeutic monoclonal antibody [22]. The E484K mutation carried in Beta, Gamma, Zeta, Eta, and Theta variants [23] is also well known for its capability of reducing antibody binding, and it emerged in a patient during the use of monoclonal antibodies or convalescent plasma therapy [24].

Rapid emergence of new variants with higher mutation loads also raises concern for the clinical effectiveness of currently used treatments. The non-monoclonal antibody therapeutics currently approved and used to treat SARS-CoV-2 are nirmatrelvir (an antiviral component of Paxlovid), remdesivir, and molnupiravir. Nirmatrelvir inhibits M_{pro}, and both remdesivir and molnupiravir are RdRP inhibitors. According to previous studies, there are 26 binding site amino acid residues in NSP5 with nirmatrelvir, and key interaction sites were discovered [25,26]. Interestingly, the P168S mutation identified only in KD-Cov-N13 was located at this site, but the sample was collected in September 2020, which indicates that the mutation was not driven by selective drug pressure. Although other substitutions were not located in the direct binding site, the synonymous change in the 10198 nucleotide position, frequently detected in lineages BA.2 and BA.2.3, was located in the proximity of the S2 binding pocket of nirmatrelvir [25]. P132H, one of the most prevalent NSP5 variants, was also detected in all the Omicron isolates in this study, but several studies have shown that it is unlikely to affect nirmatrelvir binding affinity, as the residue is located in a flexible turn [27,28]. We speculate that no mutations affecting Paxlovid resistance have occurred in this study period. In addition, no mutations were detected in RdRP residues that interact with remdesivir or molnupiravir [29,30].

Paxlovid has been globally used since it was authorized by the Food and Drug Administration in December 2021. Research has shown that although certain mutations such as P132H, G15S, and K90R have become frequently reported, the binding and inhibitory effects of nirmatrelvir were still not compromised by those variants [31]. Nonetheless, it is obvious that, with the advent of the Omicron variant, the frequency and number of substitutions in the NSP5 region have markedly increased compared to earlier VOCs and VOIs, and the fact that several mutational changes have been occurring at the inhibitor binding sites, albeit at a relatively low frequency [26], indicates that continuous genomic monitoring and characterization of those mutations

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in the protease sequence should be performed.

After the Omicron variant emerged in South Korea, we observed a few mutations affecting the detection of the N gene. By carrying these mutations, the virus may have the ability to evade detection, thus having selective advantages such as increased transmission [32]. Recurrence of the mutations in the same genetic region across various lineages during the course of the SARS-CoV-2 pandemic also implies certain beneficial roles of the mutation. The 203–208 del mutation is positioned in the linker region, which links the N-terminal and C-terminal of the N protein. Previous studies have suggested that this deletion might impact phase separation, promoting the function of the region and possibly provides advantages in the packaging and replication process of the virus [33–35]. The N gene was generally considered a highly conserved region and has been used for the target region of several RT-PCR diagnostic kits [36]. However, recent genomic surveillance studies have shown that this gene, particularly the linker region, is one of the least conserved regions in the SARS-CoV-2 genome [33,35,37].

There also have been reports of similar detection failure problems in several diagnostic kits. A mutation in the E gene (C26340T) was reported to affect E gene detection by the Cobas SARS-CoV-2 assay (Roche Inc., Basel, Switzerland) [38] in 2020. Furthermore, C29200A [39] and G29179T [40] mutations in the N gene were observed to impair the sensitivity of Xpert Xpress SARS-CoV-2 assay (Cepheid Inc., Sunnyvale, CA, USA) in 2020. In early 2021, Zannoli et al. [32] collected VOC B. 1.17 specimens showing N gene drop-out using the Allplex SARS-CoV-2 assay, which resulted from the 207–208 deletion or 208-209 indel. Furthermore, more than 100 specimens, mostly Gamma variants, with impaired N gene detection by the GeneFinder Kit were reported by Lesbon et al. [33], and 3 different mutations in the gene were identified as associated mutations, including 202–207 deletion, between April 2020 and July 2021. The constant occurr ence of these mutations could affect the diagnostic sensitivity of RT-PCR-based testing and lead to an increase in false-negative results, especially in samples with a low viral load or in single target assays. Therefore, continuous monitoring of the mutations and the consequent sensitivity of various diagnostic kits is crucial for maintaining accurate diagnostics.

The results provided in this study will contribute to an understanding of the potential impacts of the emerging mutations on evading global efforts to control the virus, thus underlining the need for continual genomic surveillance and characterization of the evolution of SARS-CoV-2. Although whole-genome sequencing plays a key role in pandemic surveillance, the clinical adoption of sequencing has been limited by several aspects, such as higher costs, technical and bioinformatics expertise, and time for implementation. In this respect, the present study showed that utilization of the nanopore sequencing platform and the ARTIC workflow could offer rapid, cost-effective, and reliable sequencing of SARS-CoV-2 samples even at a single hospital. This strategy can serve as a method for increasing the national genomic surveillance capacity for SARS-CoV-2 and other future pathogens in pandemics and epidemics by enabling private labs, academia, and other regional institutions to actively engage in surveillance.

Supplementary Material

Table S1. Information on the SARS-CoV-2 specimens used in this study and sequencing statistics; **Table S2.** Coverage depths of each amplicon; **Table S3.** Mutations that occurred in each genome of 58 SARS-CoV-2 isolates; **Table S4.** Distribution of mutations in the spike proteins of 58 SARS-CoV-2 isolates. Positions that are highlighted in yellow represent regions with low sequencing depths; **Figure S1.** Comparison of the number of non-synonymous and synonymous mutations in each genetic region. Supplementary data are available at https://doi.org/10.24171/j.phrp.2022.0183.

Notes

Ethics Approval

This study was approved by the Institutional Review Board (IRB) of Kangdong Sacred Heart Hospital, Seoul, South Korea (IRB No: NON2021-001-001) and performed in accordance with the principles of the Declaration of Helsinki.

Conflicts of Interest

The authors have no conflicts of interest to declare.

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Availability of Data

The datasets generated during the current study are available in the NCBI GenBank accession no. ON797335-ON797392.

Authors' Contributions

Conceptualization: JSK, HK; Data curation: HK; Formal analysis: HK, HySK; Funding acquisition: JSK; Investigation: SHC, HySK; Methodology: SHC, JSK; Project administration: JSK; Resources: JSK; Software: HK; Supervision: KHH; Validation: HaSK, WS; Visualization: HK; Writing–original draft: HK, JSK, SHC, HySK, HaSK, WS, KHH; Writing–review & editing: all authors.

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Original Article

Clinical outcomes of remdesivir-treated COVID-19 patients in South Korea

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ABSTRACT

Objectives: This study analyzed the clinical outcomes of remdesivir treatment in coronavirus disease 2019 (COVID-19) patients in South Korea.
Methods: This retrospective cohort study involved the secondary analysis of epidemiological data. Among patients diagnosed with COVID-19 from July 2, 2020 to March 23, 2021 (12 AM), 4,868 who received oxygen therapy and were released from isolation after receiving remdesivir treatment were assigned to the treatment group, and 6,068 patients who received oxygen therapy but not remdesivir were assigned to the untreated group. The study subjects included children under the age of 19. The general characteristics and severity were compared between the groups. Differences in the time to death and mortality were also compared.
Results: In the untreated group, the hazard ratio [HR] for mortality was 1.59 (95% confidence interval [CI], 1.40–1.80) among patients aged ≥70 years and 2.32 (95% CI, 2.00–2.69) in patients with severe disease in comparison to the treatment group. In a comparison of survival time among patients with severe disease aged ≥70 years, the HR for mortality before 50 days was 2.09 (95% CI, 1.77–2.46) in the untreated group compared to the treatment group.
Conclusion: Patients with remdesivir treatment showed better clinical outcomes in this study, but these results should be interpreted with caution since this study was not a fully controlled clinical trial.

Keywords: Antiviral; Clinical outcomes; COVID-19 treatment; Remdesivir

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Introduction

Remdesivir (Veklury; GILEAD, Foster City, CA, USA), a therapeutic agent for coronavirus disease 2019 (COVID-19), is an antiviral medication that contains nucleoside analogs, which have a similar structure to adenosine triphosphate molecules, and inhibits RNA polymerase. Through this inhibitory activity, remdesivir inhibits the replication of severe acute respiratory syndrome

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coronavirus 2 (SARS-CoV-2), which is an RNA virus that causes COVID-19 [1].

Remdesivir was initially developed to treat Ebola virus disease in Western Africa in 2013–2016. After the start of the COVID-19 pandemic in early 2020, Gilead Sciences began conducting clinical trials to assess the effect of remdesivir on SARS-CoV-2 and reported animal experiment results suggesting that remdesivir can be used for Middle East respiratory syndrome coronavirus and severe acute respiratory syndrome coronavirus [2–4].

In May 2020, the United States Food and Drug Administration (FDA) granted an emergency use authorization for remdesivir based on a clinical trial conducted by the National Institute of Allergy and Infectious Disease (NIAID), in which remdesivir reduced the recovery period of confirmed COVID-19 patients by 31% (from 15 to 11 days) compared to the placebo group. Remdesivir was subsequently approved for emergency use for COVID-19 in South Korea [5].

In early May 2020, in South Korea, the instantaneous reproduction number of COVID-19 increased from 0.2 to 1.8 in about 2 weeks after social distancing was relaxed, and it remained at about 1 until early July. This was due to the effect of cluster outbreaks in Daegu and North Gyeongsang Province [6]. As the number of confirmed cases increased, it tbbecame important to prepare countermeasures for the treatment of confirmed cases.

In October 2020, following the release of an interim clinical study report, the NIAID reported that remdesivir reduced the recovery period by 5 days in a clinical trial involving hospitalized patients with COVID-19. The researchers reported that the remdesivir-treated group had fewer deaths than the placebo group, although the difference in mortality was not statistically significant. Based on other relevant studies, the United States FDA officially approved the use of remdesivir for the treatment of COVID-19 [7,8].

On October 15, 2020, the World Health Organization published the report of a clinical trial assessing the effects of 4 medications, including remdesivir, in 11,266 patients admitted to 500 hospitals in 30 countries from March 2020 to early October 2020. It was reported that remdesivir did not reduce the hospitalization period or mortality, raising controversy regarding the effectiveness of remdesivir against COVID-19 [9].

A study on the effect of remdesivir conducted among 101 COVID-19 patients admitted to 20 medical facilities across South Korea reported that while early remdesivir administration prevented symptoms from worsening in patients with severe COVID-19, remdesivir did not significantly affect fatality, recovery time, and the percentage of recovered patients [10]. In a study of 2,374 soldier patients treated with remdesivir, remdesivir did not affect fatality and hospitalization time [11].

The Central Disease Control Headquarters of South Korea have been supplying remdesivir free of charge to medical facilities to treat severe COVID-19 patients since July 2, 2020 and have been monitoring their clinical outcomes on a daily basis. This study aimed to measure the effect of remdesivir treatment on severe COVID-19 patients by comparing time to death and the hazard ratio (HR) for mortality between the treatment and untreated groups.

Materials and Methods

Subjects

Treatment group

In total, 4,868 confirmed COVID-19 patients from July 2, 2020 to March 23, 2021 who were on oxygen therapy with remdesivir treatment were included. The period of this study was chosen as an interval with minimal effects from vaccination and COVID-19 mutations. The study subjects included 5 children under the age of 19 who received remdesivir treatment.

Untreated (control) group

A total of 6,068 confirmed COVID-19 patients in the same period who were on oxygen therapy without remdesivir treatment were assigned to the untreated group.

Definitions

Severity

In accordance with the domestic eligibility criteria for remdesivir treatment, COVID-19 patients who met the following clinical criteria were selected: (1) evidence of pneumonia on a chest radiograph or chest computed tomography, (2) room air oxygen saturation ≤94%, and (3) patients on oxygen therapy (excluding those on a mechanical ventilator or extracorporeal membrane oxygenation). Severity was divided into severe and mild. Severe cases were defined as patients who received noninvasive ventilation or high-flow nasal oxygenation. Mild cases were defined as patients who received oxygen therapy (less than 15 L of oxygen per minute) with nasal prongs or a facial mask. Severity was classified according to the definitions used in existing papers and the use or non-use of a respiratory machine [12].

Case fatality rate

The case fatality rate was defined as the proportion of

deaths among confirmed COVID-19 cases.

Survival time

For deceased patients, survival time was defined as the time from COVID-19 diagnosis to death. For survivors, it was defined as the time from COVID-19 laboratory confirmation to the time of follow-up (March 23, 2021).

Study Period

This study period was from July 2, 2020 (when remdesivir was introduced) to March 23, 2021. This period was selected to minimize the impact of changes in the virus's properties that could affect clinical outcomes. In other words, this period was not meaningfully affected by the Delta and Omicron variants.

Statistical Analysis

Clinical information, including sex, age, oxygen therapy, and comorbidities (yes or no), was collected from basic epidemiological investigation data from the COVID-19 Information Management System of Korea Disease Control and Prevention Agency (KDCA) and from the COVID-19 Patient Information Management System of the Health Insurance Review and Assessment Service. The chi-square test or Fisher exact test was used to examine the differences in demographic distributions between the treatment and untreated groups. The Kaplan-Meier estimator, the log-rank test, and a Cox proportional-hazard regression model were used to examine the differences in time to death between the 2 groups. All statistical analyses were performed using Microsoft 365 Excel (Microsoft Corp., Redmond, WA, USA), Rex (Rexsoft, Seoul, Korea) and R ver. 3.6.3 (The R Foundation, Vienna, Austria).

Ethics Approval

This study was exempted from review by the Institutional Review Board of the KDCA (IRB No: 2021-11-01-PE-A).

Results

Demographics

In total, 10,936 patients—4,868 in the treatment group and 6,068 in the untreated group—were included in this study. The 2 groups showed overall differences in the general demographics. The percentage of male patients was higher in the treatment group, with 2,666 males (54.8%), than in the untreated group, with 3,033 males (50.0%; $p < 0.001$) The patients were divided into two 2 groups using the median age of the treatment group (70 years). The percentage of patients aged ≥70 years was higher in the treatment group (48.2%) than in the untreated group (25.4%; $p < 0.001$). Furthermore, 3,358 patients (69.0%) had mild COVID-19 and 1,510 (31.0%) had severe COVID-19 in the treatment group, while 5,501 patients (90.7%) had mild COVID-19 and 567 (9.3%) had severe COVID-19 in the untreated group. The percentage of severe cases was significantly higher in the treatment group than in the untreated group ($p < 0.001$). The percentage of patients with comorbidities was higher in the treatment group (67.6%) than in the untreated group (55.4%, $p < 0.001$). In total, 4,306 patients (88.5%) recovered and 562 (11.5%) died in the treatment group, while 5,518 patients (90.9%) recovered and 550 (9.1%) died in the untreated group. The percentage of deceased patients was significantly higher in the treatment group than in the untreated group ($p < 0.001$; Table 1).

Survival Analysis

The survival analysis was adjusted for age and severity to minimize impact of underlying differences in general demographics between the treatment and untreated groups. Age was divided into <70 years and ≥70 years, and severity was categorized as mild and severe. Severe cases aged ≥70 years were analyzed separately.

Patients aged <70 years

The differences in survival time among 7,047 patients aged <70 years were estimated. Approximately 77.0% and 84.0% of treated and untreated patients survived after 50 days, respectively. The treatment group had a higher survival rate than the untreated group for patients aged <70 years ($p < 0.001$; Figure 1). The HR for mortality was 0.46 in the untreated group (95% confidence interval [CI], 0.34–0.62) compared to the treatment group for patients aged <70 years; reflecting a significantly lower mortality risk than in the treatment group (Table 2).

Patients aged ≥70 years

Survival time was compared among 3,889 patients aged ≥70 years. Approximately 68.0% and 65.0% of the treated and untreated patients survived after 50 days, respectively. The treatment group had a higher survival rate than the untreated group ($p < 0.001$; Figure 1). The HR was 1.59 (95% CI, 1.40–1.80) in the untreated group compared to the treatment group for patients aged ≥70 years, and this difference was statistically significant (Table 2).

Mild cases

The differences in survival time among 8,859 mild cases were estimated. Approximately 76.0% and 82.0% of treated and untreated patients survived after 50 days, respectively;

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Table 1. General demographics of the treatment and untreated groups

Characteristic	Treatment group	Untreated group	*p*-value
Count	4,868 (100)	6,068 (100)	
Sex			< 0.001
Male	2,666 (54.8)	3,033 (50.0)	
Female	2,202 (45.2)	3,035 (50.0)	
Age (y)			< 0.001
< 70	2,523 (51.8)	4,524 (74.6)	
≥ 70	2,345 (48.2)	1,544 (25.4)	
Severity			< 0.001
Mild	3,358 (69.0)	5,501 (90.7)	
Severe	1,510 (31.0)	567 (9.3)	
Comorbidities			< 0.001
Yes	3,289 (67.6)	3,364 (55.4)	
No	1,579 (32.4)	2,704 (44.6)	
Outcome status			< 0.001
Recovery	4,306 (88.5)	5,518 (90.9)	
Death	562 (11.5)	550 (9.1)	

Data are presented as *n* (%).

the difference in survival time between the 2 groups was not statistically significant ($p = 0.88$; Figure 1), with an HR of 0.98 (95% CI, 0.80–1.21) in the untreated group compared to the treatment group (Table 2).

Severe cases

Survival time among 2,077 severe cases was compared between the treatment and untreated groups. Based on survival curves, 25.0% of treated survivors did not survive after 40 days, and 25.0% and 50.0% of untreated patients did not survive after 18 and 43 days, respectively. About 65.0% and 45.0% of the treated and untreated patients survived after 50 days, respectively. The treatment group had a higher survival rate than the untreated group ($p < 0.001$; Figure 1). The HR was 2.32 (95% CI, 2.00–2.69) in the untreated group compared to the treatment group (Table 2).

Severe cases aged ≥70 years

Differences in survival time among 1,261 severe cases aged ≥70 years were estimated. A quarter (25.0%) of treated patients did not survive after 21 days, and 25.0% and 50.0% of untreated survivors did not survive after 16 and 26 days, respectively. About 57.0% of treated and 33.0% of untreated patients survived after 50 days. The treatment group had a significantly higher survival rate ($p < 0.001$, Figure S1), as reflected by an HR for mortality of 2.09 (95% CI, 1.77–2.46) in the untreated group compared to the treatment group (Table 2).

Cox Proportional-Hazard Regression Model

The Cox proportional-hazard regression model is a method developed by David Roxbee Cox. To identify significant differences in COVID-19 mortality based on remdesivir treatment, each factor was serially introduced to a regression model. No noticeable difference in mortality risk was found between the treatment and untreated groups after controlling only for age (HR, 1.11; 95% CI, 0.99–1.26). However, the HR for mortality was 1.74 (95% CI, 1.54–1.97) in the untreated group compared to the treatment group after controlling for age and severity, and the HR was 1.76 (95% CI, 1.56–1.98) in the untreated group after controlling for age, severity, and comorbidities, similar to the results observed from the previous model (Table 3).

Discussion

Significant differences were found in all demographic characteristics, including sex, age, severity, and isolation status, between the treatment and untreated groups. These differences were inevitable because this study was not designed as a clinical trial and the 2 groups could not be fully controlled. Confirmed COVID-19 patients during the study period could receive remdesivir treatment if they were eligible, but the decision was still made by the treating physician and it could have been affected by many other uncontrollable factors.

A limitation is that KDCA's COVID-19 clinical information collection systems do not provide details regarding

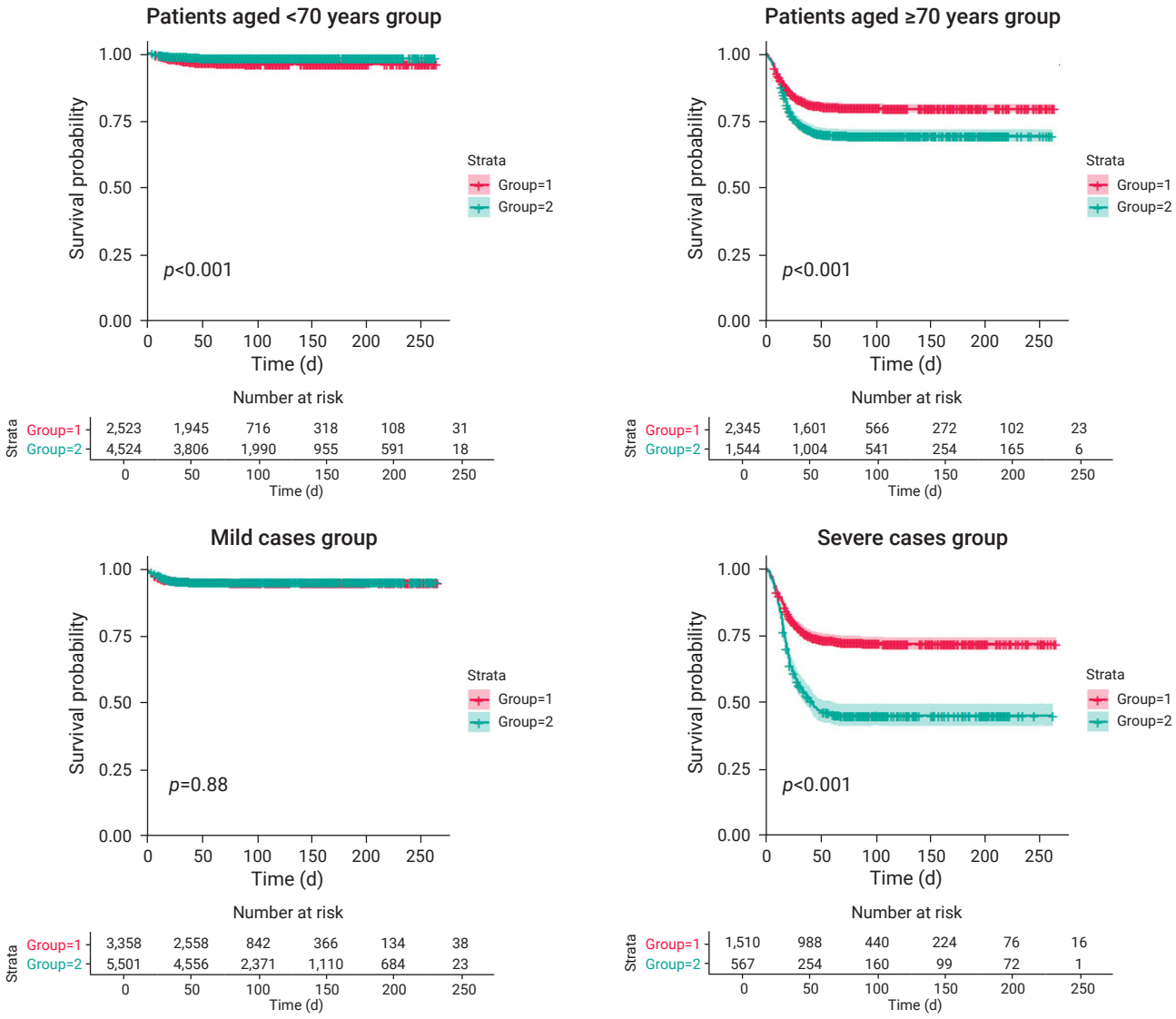

Figure 1. The treatment group had a higher survival rate than the untreated group for patients aged <70 years ($p < 0.001$). The treatment group had a higher survival rate than the untreated group for patients aged ≥70 years ($p < 0.001$). In mild cases, the difference in survival time between the 2 groups was not statistically significant ($p = 0.88$). In severe cases, the treatment group had a higher survival rate than the untreated group ($p < 0.001$). Group1 is a treated group and Group 2 is a untreated group.

comorbidities and only show the presence of comorbidities. For this reason, differences in comorbidities in the study population could not be further estimated. However, no noticeable differences in the distribution of comorbidities were found among deceased patients aside from neurological disorders, which were more frequent in the untreated group than in the treatment group.

In the survival analysis considering different age groups, the untreated group showed a lower mortality risk (HR, 0.46) than the treatment group among patients aged <70 years. The lower risk in the untreated group may be attributed to the higher proportion of mild cases and the lower proportion of patients with comorbidities aged <70 years in the untreated group.

For patients aged ≥70 years, the HR for mortality in the untreated group was 1.59 compared to the treatment group, showing better outcomes in the treatment group. A high proportion of patients aged ≥70 years had severe COVID-19. A recent study on patients admitted to a hospital for COVID-19 in South Korea reported that early remdesivir administration prevented symptoms from worsening in patients with severe COVID-19 [10], and this study also showed that the early use of remdesivir reduced the risk of COVID-19 mortality by reducing symptom exacerbation in

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severe cases.

In the survival analysis considering different severity groups, no differences in the time to death and HR for mortality were found between the treatment and untreated groups in mild cases, possibly because mild cases often recover regardless of remdesivir treatment. However, the HR for mortality was 2.32 times among severe cases in the untreated group, and the time to death (in 25.0% of patients) was 40 days in the treatment group and 18 days in the untreated group. Considering that the untreated group had a higher HR and shorter time to death than the treatment group despite the treated group having a higher proportion of severe cases, remdesivir showed positive results in preventing death. Although the results of the study are similar in that they showed a therapeutic effect in severely ill patients, there are some differences from other studies conducted by the National Institutes of Health of the United States on the effectiveness of remdesivir (ACTT-1). That study found that patients requiring low-flow nasal oxygen therapy (that is, a nasal cannula or face mask oxygenation, 15 L per minute or less) had the greatest benefit from remdesivir. This benefit was attenuated in patients requiring high-flow nasal oxygenation and noninvasive ventilation and largely absent in those requiring invasive ventilation or extracorporeal membrane oxygenation [7].

Differences in survival rate were identified in severe cases aged ≥70 years. The time to death (in 25.0% of patients) was 21 days in the treatment group and 16 days in the untreated group, and the HR for mortality was 2.09 in the untreated group. These results show that the therapeutic effect of remdesivir was consistently observed after considering patients' age and severity.

In the Cox proportional-hazard regression analysis, the HR for mortality was 1.76 in the untreated group. This result is consistent with the final report of the NIAID, in which remdesivir lowered mortality compared to the placebo group [7]. However, in the definition of mild and severe cases, the NIAID in the United States defined a condition that did not require hospitalization as mild, and all COVID-19 patients with pneumonia and hypoxemia were defined as severe cases. This difference may be relevant for the interpretation of the results.

Table 2. Hazard ratios for mortality in untreated and treated patients by group

Type	HR (95% CI)
Patients aged <70 y	
Treated (*n*=2,523)	1
Untreated (*n*=4,524)	0.46 (0.34–0.62)
Patients aged ≥70 y	
Treated (*n*=2,345)	1
Untreated (*n*=1,544)	1.59 (1.40–1.80)
Mild case[a]	
Treated (*n*=3,358)	1
Untreated (*n*=5,501)	0.98 (0.80–1.21)
Severe case[b]	
Treated (*n*=1,510)	1
Untreated (*n*=567)	2.32 (2.00–2.69)
Severe cases and aged ≥70 y	
Treated (*n*=874)	1
Untreated (*n*=387)	2.09 (1.77–2.46)

HR, hazard ratio; CI, confidence interval.
[a]Mild case: patient requiring oxygen therapy (nasal cannula or mask). [b]Severe case: patient requiring high-flow oxygen therapy, mechanical ventilator, or extracorporeal membrane oxygenation/continuous renal replacement therapy.

Table 3. Factors affecting mortality among coronavirus disease 2,019 patients treated or not treated with remdesivir

Variable	Model 1[a]	Model 2[b]	Model 3[c]
Remdesivir administered (*n*=10,936)			
Yes	1	1	1
No	1.11 (0.99–1.26)	1.74 (1.54–1.97)	1.76 (1.56–1.98)
Age (*n*=10,936)			
<70 y	1	1	1
≥70 y	3.95 (3.47–4.49)	2.67 (2.35–3.04)	2.27 (2.00–2.58)
Severity (*n*=10,936)			
Mild		1	1
Severe		8.51 (7.46–9.72)	7.61 (6.68–8.67)
Comorbidities (*n*=10,936)			
No			1
Yes			2.75 (2.33–3.24)

Data are presented as hazard ratio (95% confidence interval).
[a]Controlled for age. [b]Controlled for age and severity. [c]Controlled for age, severity, and comorbidities.

Conclusion

This study showed similar results as previous studies on the therapeutic effect of remdesivir. However, the results of this study should be interpreted with caution as this study was not designed as a clinical trial. Nevertheless, this study has meaningful findings, as it included all patients with remdesivir treatment since the approval and supply of the medication in South Korea. A further analysis of the effect of comorbidities on remdesivir treatment outcomes and the effects of other COVID-19 variants must be conducted to achieve a better understanding of the effect of remdesivir on COVID-19.

Supplementary Material

Figure S1. Survival curves of severe cases aged ≥70 years with or without remdesivir treatment. The treatment group had a higher survival rate ($p < 0.001$). Supplementary data are available at https://doi.org/10.24171/j.phrp.2022.0138.

Notes

Ethics Approval

This study was exempted from review by the Institutional Review Board of the Korea Disease Control and Prevention Agency (IRB No: 2021-11-01-PE-A). The requirement for informed consent was waived because of the retrospective nature of this study.

Conflicts of Interest

The authors have no conflicts of interest to declare.

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None.

Availability of Data

Detailed data used in this study cannot be disclosed to the outside because it contains personal information in accordance with Article 2 Paragraph 1 of the Personal Information Protection Act. If you have additional questions about the study, please contact the corresponding author, Dr. Jin Gwack, gwackjin@korea.kr.

Authors' Contributions

Conceptualization: BIK; Formal analysis: MY; Project administration: JK; Supervision: JK, BIK, JG; Writing–original draft: MY; Writing–review & editing: all authors.

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Brief Report

Presumed population immunity to SARS-CoV-2 in South Korea, April 2022

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ABSTRACT

Objectives: We estimated the overall and age-specific percentages of the Korean population with presumed immunity against severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) as of April 2022 using the national registry.
Methods: We used the national coronavirus disease 2019 (COVID-19) infection and vaccination registry from South Korea, as described to define individuals with a previous history of COVID-19 infection, vaccination, or both, as persons with presumed immunity.
Results: Of a total of 53,304,627 observed persons, 24.4% had vaccination and infection, 58.1% had vaccination and no infection, 7.6% had infection and no vaccination, and 9.9% had no immunity. The SARS-CoV-2 Omicron variant emerged at a time when the presumed population immunity ranged from 80% to 85%; however, nearly half of the children were presumed to have no immunity.
Conclusion: We report a gap in population immunity, with lower presumed protection in children than in adults. The approach presented in this work can provide valuable informed tools to assist vaccine policy-making at a national level.

Keywords: COVID-19; Immunity; Population; SARS-CoV-2; Vaccines

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Introduction

The level of population immunity is essential to guide the public health response against coronavirus disease 2019 (COVID-19) [1]. While most studies have estimated the level of population immunity primarily using sampled data or simulation models [2,3], these methods have intrinsic limitations in terms of the generalizability of the data. In this study, we attempted to use real-world numbers to calculate the population immunity level in a robust manner using a centralized, standardized dataset in South Korea. We estimated the overall

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and age-specific percentage of the Korean population with presumed immunity against severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) due to natural infection, vaccination, or both.

Materials and Methods

In South Korea, as of May 2022, more than 17 million COVID-19 confirmed cases had been reported (33% of total population), while 85% of its population had received at least 2 doses of COVID-19 vaccines [4]. We used the national COVID-19 infection and vaccination registry from South Korea, as described in a previous study, to define individuals with a previous history of COVID-19 infection, vaccination, or both, as persons with presumed immunity [5]. We excluded 141,690 persons who had more than 2 reports of infection, errors in vaccination records, and those who received vaccines outside of the country. We classified age groups as 0 to 4 years, 5 to 11 years, 12 to 17 years, 18 to 59 years, 60 to 74 years, and ≥75 years to perform descriptive analyses investigating the percentage of the population that could be presumed immune because of vaccination and/or infection. From the COVID-19 infection and vaccination registry spanning from February 26, 2021 to April 30, 2022, 4 mutually exclusive composites were constructed: (1) no immunity (i.e., uninfected, unvaccinated, or 1 dose of vaccination for the Pfizer-BioNTech, Moderna, and AstraZeneca vaccines); (2) infection and no vaccination (including 1 dose of vaccination); (3) vaccination (1 dose for the Janssen vaccine and 2 or more doses for other vaccines) and no infection, and; (4) vaccination (1 dose for the Janssen vaccine and 2 or more doses for other vaccines) and infection.

In addition, we calculated age-specific proportions with each composite by surveillance weeks from January 1, 2022, to April 30, 2022. The proportion of vaccination in each age group for 2 weeks previously was assigned to the cumulative vaccination coverage of a given week. The group with no immunity was defined as the sum of those without a history of vaccination and/or infection with COVID-19. We calculated the cumulative density of no immunity by week and age group. To assess the association of the age-specific weekly incidence of COVID-19 with the cumulative density of no immunity and vaccination coverage, we used Poisson regression models.

The statistical analysis was performed using R package (ver. 4.0.2; R Foundation for Statistical Computing, Vienna, Austria). This study was conducted as a legally mandated public health investigation under the authority of the Infectious Diseases Control and Prevention Act (No. 12444 and No. 13392) and was reviewed by the Institutional Board Review of Korea Disease Control and Prevention Agency (IRB No: 2021-12-03-PE-A).

Results

Of a total of 53,304,627 observed persons, 13,014,902 (24.4%) had vaccination and infection, 30,955,551 (58.1%) had vaccination and no infection, 4,068,131 (7.6%) had infection and no vaccination, and 5,266,043 (9.9%) had no immunity as of April 2022 (Figure 1). The percentages of adults aged 18 to 59 years, 60 to 74 years, and ≥75 years with no immunity were 6.6%, 4.4%, and 6.7%, respectively, whereas the percentages of children and adolescents aged 0 to 4 years, 5 to 11 years, and 12 to 17 years with no immunity were 54.0%, 40.5%, and 16.9%, respectively. The proportion of infection and no vaccination was highest in children aged 5 to 11 years (59.5%), followed by those aged 0 to 4 years (46.0%) and 12 to 17 years (19.7%).

Between January 1 and April 30, 2022, the percentage of people with no immunity decreased from 20.5% to 9.9% in the entire population (Table 1). In all age groups, the incidence rate of COVID-19 peaked at surveillance week 11, when the percentage of no immunity reached 13.1% (Table 1; Figure S1). The proportion of no immunity decreased in the adult population from 11.8% to 6.6% (18–59 years), from 6.6% to 4.4% (60–74 years), and from 10.0% to 6.7% (≥75 years); whereas in children and adolescents, the decrease was from 91.6% to 54.0% (0–4 years), from 98.3% to 40.5% (5–11 years), and from 65.0% to 16.9% (12–17 years).

Adults aged 18 to 59 years, 60 to 74 years, and ≥75 years, in whom less than 25% of the population had no immunity, displayed a smaller peak and shorter duration of COVID-19 incidence per 100,000 than children aged 12 to 17 years, 5 to 11 years, and 0 to 4 years (Figure S2). Table S1 shows the association of age-specific COVID-19 incidence with the proportion of children with no immunity in the age groups of 0 to 4 years, 5 to 11 years, and 12 to 17 years, as relative risk (RR) and 95% confidence intervals. A higher RR was found in children aged 12 to 17 years than in children aged 0 to 4 years and 5 to 11 years.

Discussion

In South Korea, the SARS-CoV-2 Omicron variant emerged and spread at a time when the presumed population immunity ranged from 80% to 85%; however, there were significant discrepancies between age groups. Following the surge in cases due to the spread of the Omicron variant in early 2022, the number of new incident cases has decreased dramatically since April 2022 [6]. During week 1 of 2022, the percentages of adults presumed to have no immunity were

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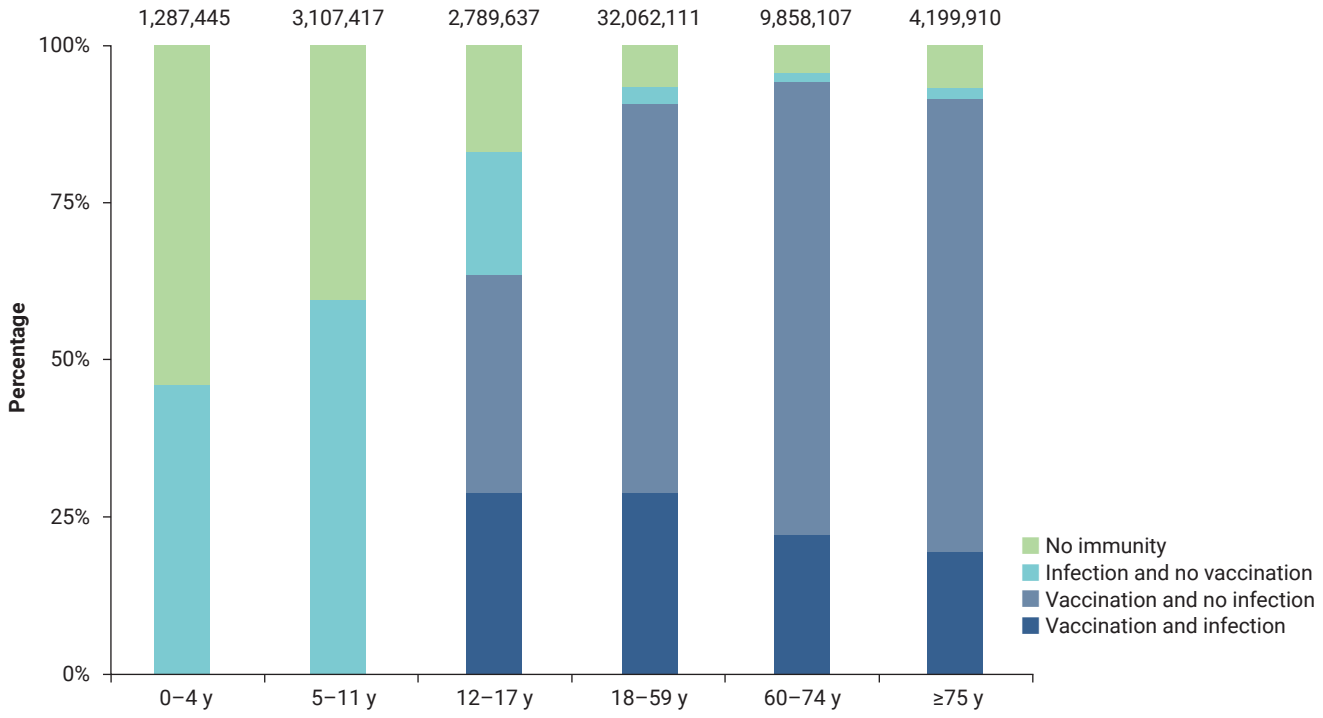

Figure 1. Percentage of the population in each category of presumed immunity due to natural infection, vaccination, both, or neither, by age group as of April 30, 2022.

11.8% (18–59 years), 6.6% (60–74 years), and 10.0% (≥75 years), while these percentages were higher in children, at 91.6% (0–4 years), 98.2% (5– 11 years), and 65.0% (12–17 years). Vaccination in the adult population started in February 2021, whereas the vaccines have been offered to the age groups of 12 to 17 years and 5 to 11 years since October 2021 and March 2022, respectively, which partly explains the population susceptibility in children [5]. The disproportionate distribution of COVID-19 vaccination between age groups likely resulted in the observed discrepancy in population immunity, as demonstrated in a previous study [7]. Nevertheless, our findings showed widespread population immunity among persons aged 60 years and above, largely obtained through vaccination. The high population immunity among this at-risk age group, primarily induced by vaccination, may have resulted in relatively low death rates among this population [8]. It is imperative to recognize that SARS-CoV-2 infection-induced immunity and vaccine-induced immunity may offer different levels of protection. Previous studies indicate that immunity from natural infection is not as predictable as vaccine-induced immunity, and booster vaccination significantly enhances protection from severe illness.

We found that with a higher population immunity level in a given age group, a lower peak of COVID-19 incidence can be expected, as seen in Figures S1 and S2. The contact mixing pattern between different age groups widely varies across countries and settings [1]. In Korea, the contact number in school-aged children was found to be this age group had the highest contact number of all [9], suggesting that the improved population immunity in this age group may have substantially reduced the community transmission of SARS-CoV-2.

This study has a number of limitations. First, we did not take into account primary and secondary vaccine failures, or the waning of immunity, in estimating the level of population immunity. Second, differences in the types of vaccines, the interval since the last vaccination, and the number of doses may have confounded the results of this study. Second, the observed period spans before and after school opening, which limits the generalizability of our results. Third, following the cases of reinfections after the introduction of the Omicron variant, the assumption of "presumed immunity" from previous infection may not be applicable. Despite these limitations, our results present a rapid assessment of population immunity, which was quickly translated into policy-making in the national vaccination campaign. The results support continual recommendations to vaccinate children and adolescents, who could be the main source of transmission in the next

Table 1. Number and percentage of the population in each category, by surveillance week between January 1, 2022 and April 30, 2022

Surveillance week	No immunity	Infection and no vaccination	Vaccination and no infection	Vaccination and infection
1	10,905,513 (20.5)	374,645 (0.7)	41,680,379 (78.2)	207,676 (0.4)
2	10,635,974 (20.0)	385,279 (0.7)	41,924,075 (78.6)	224,239 (0.4)
3	10,155,681 (19.1)	397,744 (0.7)	42,364,812 (79.5)	252,807 (0.5)
4	9,674,052 (18.1)	421,461 (0.8)	42,753,499 (80.2)	322,827 (0.6)
5	9,350,688 (17.5)	463,118 (0.9)	42,897,727 (80.5)	460,981 (0.9)
6	9,104,593 (17.1)	541,346 (1.0)	42,813,001 (80.3)	721,637 (1.4)
7	8,854,503 (16.6)	694,472 (1.3)	42,462,836 (79.7)	1,177,594 (2.2)
8	8,516,735 (16.0)	946,857 (1.8)	41,782,045 (78.4)	1,952,045 (3.7)
9	8,280,203 (15.5)	1,288,935 (2.4)	40,581,153 (76.1)	3,064,374 (5.7)
10	7,636,354 (14.3)	1,751,893 (3.3)	39,385,520 (73.9)	4,702,319 (8.8)
11	6,992,694 (13.1)	2,386,982 (4.5)	37,245,703 (69.9)	6,872,281 (12.9)
12	6,406,646 (12.0)	2,953,122 (5.5)	35,194,383 (66.0)	8,710,922 (16.3)
13	5,950,033 (11.2)	3,389,758 (6.4)	33,617,782 (63.1)	10,304,739 (19.3)
14	5,652,728 (10.6)	3,700,644 (6.9)	32,475,772 (60.9)	11,456,348 (21.5)
15	5,454,046 (10.2)	3,888,444 (7.3)	31,718,183 (59.5)	12,233,027 (22.9)
16	5,337,503 (10.0)	3,999,925 (7.5)	31,256,300 (58.6)	12,706,071 (23.8)
17	5,266,043 (9.9)	4,068,131 (7.6)	30,955,551 (58.1)	13,014,902 (24.4)

Data are presented as *n* (%).

COVID-19 outbreak.

Herein, we report a gap in population immunity, with lower presumed protection in children than in adults. The approach presented in this work can provide valuable informed tools to assist vaccine policy-making at a national level.

Supplementary Material

Figure S1. Age-specific percentage of the population in each category of presumed immunity due to natural infection, vaccination, both, or neither, by surveillance week between January 1, 2022 and April 30, 2022; **Figure S2.** Proportion of no immunity and COVID-19 incidence by age group; **Table S1.** Association of age-specific COVID-19 incidence with the proportion of children with no immunity. Supplementary data are available at https://doi.org/10.24171/j.phrp.2022.0209.

Notes

Ethics Approval

This study was approved by the Institutional Review Board of Korea Disease Control and Prevention Agency (No: 2021-12-03-PE-A) and performed in accordance with the principles of the Declaration of Helsinki. The informed consent was waived because of the retrospective nature of this study.

Conflicts of Interest

The authors have no conflicts of interest to declare.

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None.

Availability of Data

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

Authors' Contributions

Conceptualization: EJJ, YJC, YJP; Data curation: EJJ, YYK, RKK; Formal analysis: EJJ, JK, DSL, JHL, SY; Investigation: EJJ, YJC, JHL, SY, SL; Methodology: EJJ, JK, SY; Project administration: RKK, DSL, JHL; Resources: SL, YJP; Software: EJJ, SAC; Supervision: SL, YJP; Validation: EJJ, YJC, SAC; Visualization: EJJ, SAC; Writing–original draft: EJJ, YJC; Writing–review & editing: all authors.

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Brief Report

Adverse events of the Pfizer-BioNTech COVID-19 vaccine in Korean children and adolescents aged 5 to 17 years

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ABSTRACT

Objectives: This study aimed to identify potential safety signals and adverse events following the primary Pfizer-BioNTech coronavirus disease 2019 (COVID-19) vaccination series among children and adolescents aged 5 to 17 years in the Republic of Korea.
Methods: Adverse events reported through the COVID-19 vaccination management system (CVMS, a web-based passive vaccine safety surveillance system) and adverse events and health conditions collected from a text message-based survey were analyzed.
Results: A total of 14,786 adverse events among 5 to 17-year-old children and adolescents were reported in the CVMS; 14,334 (96.9%) were non-serious and 452 (3.1%) were serious, including 125 suspected cases of acute cardiovascular injury and 101 suspected cases of anaphylaxis. The overall reporting rate was lower in 5 to 11-year-old children (64.5 per 100,000 doses) than in 12 to 17-year-old adolescents (300.5 per 100,000 doses). The text message survey identified that local and systemic adverse events after either dose were reported less frequently in 5 to 11-year-old children than in 12 to 17-year-old adolescents ($p < 0.001$). The most commonly reported adverse events were pain at the injection site, myalgia, headache, and fatigue/tiredness.
Conclusion: The overall results are consistent with the results of controlled trials; serious adverse events were extremely rare among 5 to 17-year-old children and adolescents following Pfizer-BioNTech COVID-19 vaccination. Adverse events were less frequent in children aged 5 to 11 years than in adolescents aged 12 to 17 years.

Keywords: Adolescent; Child; COVID-19; Safety; Vaccination; Vaccines

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Introduction

In the Republic of Korea (ROK), only the Pfizer-BioNTech (BNT-162b2) messenger RNA (mRNA) coronavirus disease 2019 (COVID-19) vaccine has been authorized for use in persons

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aged ≥5 years based on safety and efficacy data from controlled trials organized in the United States (US) by the Korea Ministry of Food and Drug Safety [1–3]. The Pfizer-BioNTech COVID-19 vaccine (30 μg, 0.3 mL each) was initially authorized for use in persons aged ≥16 years on March 5, 2021 [4], and expanded to include adolescents aged ≥12 years on July 16, 2021 [5]. The use of the Pfizer-BioNTech COVID-19 vaccine (10 μg, 0.2 mL each) for children aged 5 to 11 years was authorized on February 23, 2022 [6].

Since then, the Pfizer-BioNTech vaccine has been nationally distributed to adolescents aged 16 to 17 years starting on October 18, 2021, and to adolescents aged 12 to 15 years starting on November 1, 2021, following a decision by the Korea Advisory Committee on Immunization Practices (KACIP) in 2021 [7,8]. Following the KACIP in 2022, the Pfizer-BioNTech vaccine was offered to children aged 5 to 11 years starting on March 31, 2022, with the recommendation of an 8-week interval between the 2 doses based on findings that showed increased safety and efficacy with the extended interval [9–12].

To monitor adverse events following immunization (AEFIs) and identify potential safety signals for further evaluation, the Korea Disease Control and Prevention Agency (KDCA) manages the COVID-19 vaccination management system (CVMS, a web-based passive vaccine safety surveillance system), in which doctors and forensic pathologists can report AEFIs regardless of a causal association between events and vaccines as per the Infectious Disease Control and Prevention Act [13]. The KDCA also operates a text message-based vaccine safety surveillance system that surveys adverse events and health conditions following COVID-19 vaccination for particular populations who consent to receive text message surveys through smartphones on the day of their first vaccination [13].

This study aimed to identify potential safety signals and adverse events following the primary series of Pfizer-BioNTech vaccination, including dose 1 and dose 2, for children and adolescents aged 5 to 17 years in the ROK. This study analyzed data on adverse events reported in the CVMS and the text message-based vaccine safety surveillance system.

Materials and Methods

COVID-19 Vaccination Management System

From March 5, 2021 to July 2, 2022, in total, 4,995,280 primary doses of the Pfizer-BioNTech vaccination series were administered to children and adolescents aged 5 to 17 years in the ROK, and 14,786 adverse events after vaccination were reported to the CVMS. Data on an additional dose (dose 3), vaccines other than the Pfizer-BioNTech vaccine for children aged 5 to 11 years (10 μg) and adolescents aged 12 to 17 years (30 μg), and vaccination that occurred abroad and before authorization for use in children and adolescents in the ROK were excluded. Adverse events reported in the CVMS were divided into non-serious and serious events in accordance with the Guidelines for Adverse Events Following COVID-19 Immunization [13]. Non-serious events included common symptoms such as redness, pain, and swelling at the injection site, myalgia, fever, headache, chills, and others. The following adverse events were classified as serious: death, anaphylaxis, adverse events of special interest (AESIs), intensive care unit admission, life-threatening events, permanent disability or sequelae, and others. The characteristics of adverse events reported in the CVMS among 5 to 17-year-old children and adolescents were analyzed by sex, age group, and vaccine dose. The types of symptoms and signs were presented in descending order of the number of cases reported as adverse events. The events do not indicate medically confirmed diagnoses, as adverse events reported to the CVMS are suspected cases.

Text Message-Based Vaccine Safety Surveillance System

Text messages were sent to parents or guardians of children and adolescents aged 5 to 17 years in the ROK who received the primary series of the Pfizer-BioNTech vaccine, on a daily basis until day 7 post-vaccination to investigate adverse events and health conditions. A total of 10,398 adolescents aged 12 to 17 years from December 13, 2021 to January 26, 2022, and 1,025 children aged 5 to 11 years from March 31 to June 20, 2022, were enrolled in the text message-based surveillance system. The surveys asked questions about experiences of local and systemic adverse events, limits to normal daily activities, and visits to medical facilities following vaccination. The respondents were able to report multiple adverse events on each day. The characteristics of respondents were described by sex and age, and adverse events and health conditions reported at least once during days 0 to 7 following vaccination were assessed by vaccine doses and age groups. All variables were examined using the chi-square or Fisher exact test as appropriate to compare adverse events and health conditions between age groups and vaccine doses. A p-value <0.05 indicated statistical significance.

SAS ver. 9.4 (SAS Institute, Cary, NC, USA) was used to conduct all analyses. The passive surveillance activity was conducted and authorized by the KDCA; the study was not subject to institutional review board approval under government regulations. The study of the text message-based surveillance was exempted from review by the Public Institutional

Review Board designated by the Korea Ministry of Health and Welfare (No: P01-202206-01-033).

Results

Adverse Events Reported in the COVID-19 Vaccination Management System

From March 5, 2021 to July 2, 2022, the CVMS confirmed a total of 14,786 adverse events among children and adolescents aged 5 to 17 years after primary doses of the Pfizer-BioNTech vaccination series (Table 1); 14,334 (96.9%) were non-serious and 452 (3.1%) were serious. Serious adverse events included death (5, 0.0%), suspected anaphylaxis (101, 0.7%) and major adverse events including AESIs for COVID-19 vaccines (346, 2.3%). During the study period, 4,995,280 doses were administered to children and adolescents aged 5 to 17 years, and the overall reporting rate per 100,000 doses administered was 296.0 (dose 1, 270.0; dose 2, 323.3). The reporting rate per 100,000 doses after the primary vaccination series by sex was 283.6 in males and 309.2 in females. The reporting rate per 100,000 doses was lower in children aged 5 to 11 years (64.5/100,000 doses) than in adolescents aged 12 to 17 years (300.5/100,000 doses). Among non-serious adverse events, the most commonly reported symptoms based on the reporting rate per 100,000 doses were headache (75.4/100,000 doses), chest pain (68.4/100,000 doses), myalgia (43.1/100,000 doses), dizziness (41.3/100,000 doses), and nausea (36.9/100,000 doses) (Table 2). Among serious adverse events, acute cardiovascular injury including myocarditis/pericarditis (2.5/100,000 doses) had the highest reporting rate per 100,000 doses, followed by anaphylaxis, including anaphylactoid reactions (2.0/100,000 doses), convulsions or seizures (1.0/100,000 doses), acute paralysis (0.8/100,000 doses), and vaccine-associated enhanced disease (0.8/100,000 doses).

Adverse Events Collected in the Text Message-Based Vaccine Safety Surveillance System

From December 13, 2021 to June 20, 2022, the total number of children and adolescents aged 5 to 17 years enrolled in at least 1 text message survey on days 0 to 7 following Pfizer-BioNTech COVID-19 vaccination was 11,414 after dose 1

Table 1. Characteristics of adverse events reported to the CVMS among children and adolescents aged 5 to 17 years after Pfizer-BioNTech COVID-19 vaccination, Republic of Korea, March 5, 2021 to July 2, 2022

Variable	No. of doses administered	Adverse events (n = 14,786)[a]					
		Total	Non-serious adverse events[b]	Serious adverse events[c]			
				Sub-total	Death	Anaphylaxis	Others[d]
Total	4,995,280	14,786 (296.0)	14,334 (287.0)	452 (9.0)	5 (0.1)	101 (2.0)	346 (6.9)
Dose 1	2,555,595	6,899 (270.0)	6,659 (260.6)	240 (9.4)	0	82 (3.2)	158 (6.2)
Dose 2	2,439,685	7,887 (323.3)	7,675 (314.6)	212 (8.7)	5 (0.2)	19 (0.8)	188 (7.7)
Sex							
Male	2,568,739	7,284 (283.6)	7,028 (273.6)	256 (10.0)	3 (0.1)	46 (1.8)	207 (8.1)
Dose 1	1,314,670	3,329 (253.2)	3,199 (243.3)	130 (9.9)	0	36 (2.7)	94 (7.2)
Dose 2	1,254,069	3,955 (315.4)	3,829 (305.3)	126 (10.0)	3 (0.2)	10 (0.8)	113 (9.0)
Female	2,426,541	7,502 (309.2)	7,306 (301.1)	196 (8.1)	2 (0.1)	55 (2.3)	139 (5.7)
Dose 1	1,240,925	3,570 (287.7)	3,460 (278.8)	110 (8.9)	0	46 (3.7)	64 (5.2)
Dose 2	1,185,616	3,932 (331.6)	3,846 (324.4)	86 (7.3)	2 (0.2)	9 (0.8)	75 (6.3)
Age (y)							
5–11	94,518	61 (64.5)	59 (62.4)	2 (2.1)	0	1 (1.1)	1 (1.1)
Dose 1	58,636	47 (80.2)	45 (76.7)	2 (3.4)	0	1 (1.7)	1 (1.7)
Dose 2	35,882	14 (39.0)	14 (39.0)	0	0	0	0
12–17	4,900,762	14,725 (300.5)	14,275 (291.3)	450 (9.2)	5 (0.1)	100 (2.0)	345 (7.0)
Dose 1	2,496,959	6,852 (274.4)	6,614 (264.9)	238 (9.5)	0	81 (3.2)	157 (6.3)
Dose 2	2,403,803	7,873 (327.5)	7,661 (318.7)	212 (8.8)	5 (0.2)	19 (0.8)	188 (7.8)

Data are presented as n (per 100,000): the reporting rate of adverse events per 100,000 doses administered.
CVMS, COVID-19 vaccination management system; COVID-19, coronavirus disease 2019.
[a]Data were based on suspected adverse events following COVID-19 vaccination reported by medical institutions or doctors. The results do not indicate medically confirmed diagnoses or causality between the events and the vaccines. [b]Non-serious adverse events include common symptoms such as redness at the injection site, pain, swelling, myalgia, fever, headache, chills, and others. [c]Serious adverse events include the following: death, suspected anaphylaxis, and others. [d]Others include major adverse events including adverse events of special interest, intensive care unit admission, life-threatening events, permanent disability or sequelae, and others.

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Table 2. Types of symptoms and signs reported to the CVMS among children and adolescents aged 5 to 17 years after Pfizer-BioNTech COVID-19 vaccination, Republic of Korea, March 5, 2021 to July 2, 2022

Symptoms and signs (n = 14,786)[a]	Case (per 100,000)
Non-serious adverse events (n = 14,334)	
Headache	3,765 (75.4)
Chest pain	3,417 (68.4)
Myalgia	2,152 (43.1)
Dizziness	2,065 (41.3)
Nausea	1,843 (36.9)
Fever	1,550 (31.0)
Allergic reactions	918 (18.4)
Vomiting	889 (17.8)
Abdominal pain	872 (17.5)
Chills	848 (17.0)
Pain, redness, or swelling at the injection site within 3 days after	541 (10.8)
Diarrhea	526 (10.5)
Lymphadenitis	447 (8.9)
Abnormal uterine bleeding	140 (2.8)
Cellulitis	71 (1.4)
Arthritis	59 (1.2)
Dyspnea[b]	46 (0.9)
Severe local adverse events	33 (0.7)
Itching[b]	13 (0.3)
Abscess at the injection site	2 (< 0.1)
Systemic disseminated Bacillus Calmette-Guerin infection	1 (< 0.1)
Severe adverse events (n = 452) including reports of death	
Acute cardiovascular injury[c]	125 (2.5)
Anaphylaxis[d]	101 (2.0)
Convulsions or seizures	49 (1.0)
Acute paralysis	42 (0.8)
Vaccine-associated enhanced disease	42 (0.8)
Acute respiratory distress syndrome	18 (0.4)
Encephalopathy or encephalitis	17 (0.3)
Thrombocytopenia	7 (0.1)
Thrombocytopenic purpura	6 (0.1)
Osteitis or osteomyelitis	5 (0.1)
Anosmia or ageusia	5 (0.1)
Erythema multiforme	5 (0.1)
Coagulation disorder	4 (0.1)
Acute kidney injury	4 (0.1)
Single organ cutaneous vasculitis	3 (0.1)
Multisystem inflammatory syndrome	3 (0.1)
Acute liver injury	3 (0.1)
Thrombosis	3 (0.1)
Meningitis	2 (< 0.1)
Guillain-Barre syndrome	2 (< 0.1)
Myelitis	1 (< 0.1)
Capillary leak syndrome	1 (< 0.1)
Chilblains	1 (< 0.1)

Data are presented as n (per 100,000): the reporting rate of adverse events per 100,000 doses administered.
CVMS, COVID-19 vaccination management system; COVID-19, coronavirus disease 2019.
[a]Data were based on suspected adverse events following COVID-19 vaccination reported by medical institutions or doctors. The results do not indicate medically confirmed diagnoses or causality between the events and the vaccines. [b]These were reported from March 10, 2022. [c]Acute cardiovascular injury includes myocarditis, pericarditis, and others. [d]Anaphylaxis includes anaphylactoid reactions.

(male, 47.0%; female, 53.0%), and 3,688 after dose 2 (male, 46.8%; female, 53.2%) (Table 3). The number of respondents by age group was 1,025 (9.0%) after dose 1 and 541 (14.7%) after dose 2 among 5 to 11-year-old children, and 10,389 (91.0%) after dose 1 and 3,147 (85.3%) after dose 2 among 12 to 17-year-old adolescents respectively. During the week after either dose, local adverse events were reported more frequently than systemic adverse events in both age groups. The reporting rate of local adverse events after dose 1 was 32.8% in 5 to 11-year-old children and 48.2% in 12 to 17-year-old adolescents ($p < 0.001$) (Figure 1; Table 4). After dose 2, the reporting rate of local adverse events was 27.4% in 5 to 11-year-old children and 53.1% in 12 to 17-year-old adolescents ($p < 0.001$). For systemic adverse events after dose 1, 26.8% of 5 to 11-year-old children and 41.9% of 12 to 17-year-old adolescents responded ($p < 0.001$), and the reporting rate after dose 2 was 22.4% for 5 to 11-year-old children and 52.5% for 12 to 17-year-old adolescents ($p < 0.001$). The most frequently reported local adverse events were pain at the injection site and swelling, and the most commonly reported systemic adverse events were myalgia, headache, and fatigue or tiredness among both age groups after either dose (Table 4). Symptoms were most frequently reported during days 0 to 1, but were least frequently reported or disappeared during days 6 to 7 post-

Table 3. Characteristics of children and adolescents aged 5 to 17 years who completed at least 1 text message-based survey on days 0 to 7 following Pfizer-BioNTech COVID-19 vaccination, Republic of Korea, December 13, 2021 to June 20, 2022

Characteristic	Dose 1 (n = 11,414)	Dose 2 (n = 3,688)
Sex		
Male	5,367 (47.0)	1,727 (46.8)
Female	6,047 (53.0)	1,961 (53.2)
Age (y)		
5–11	1,025 (9.0)	541 (14.7)
5	66 (0.6)	38 (1.0)
6	90 (0.8)	47 (1.3)
7	122 (1.1)	52 (1.4)
8	125 (1.1)	71 (1.9)
9	160 (1.4)	86 (2.3)
10	197 (1.7)	115 (3.1)
11	265 (2.3)	132 (3.6)
12–17	10,389 (91.0)	3,147 (85.3)
12	1,948 (17.1)	639 (17.3)
13	2,432 (21.3)	766 (20.8)
14	1,857 (16.3)	584 (15.8)
15	2,672 (23.4)	755 (20.5)
16	864 (7.6)	247 (6.7)
17	616 (5.4)	156 (4.2)

Data are presented as n (%).
COVID-19, coronavirus disease 2019.

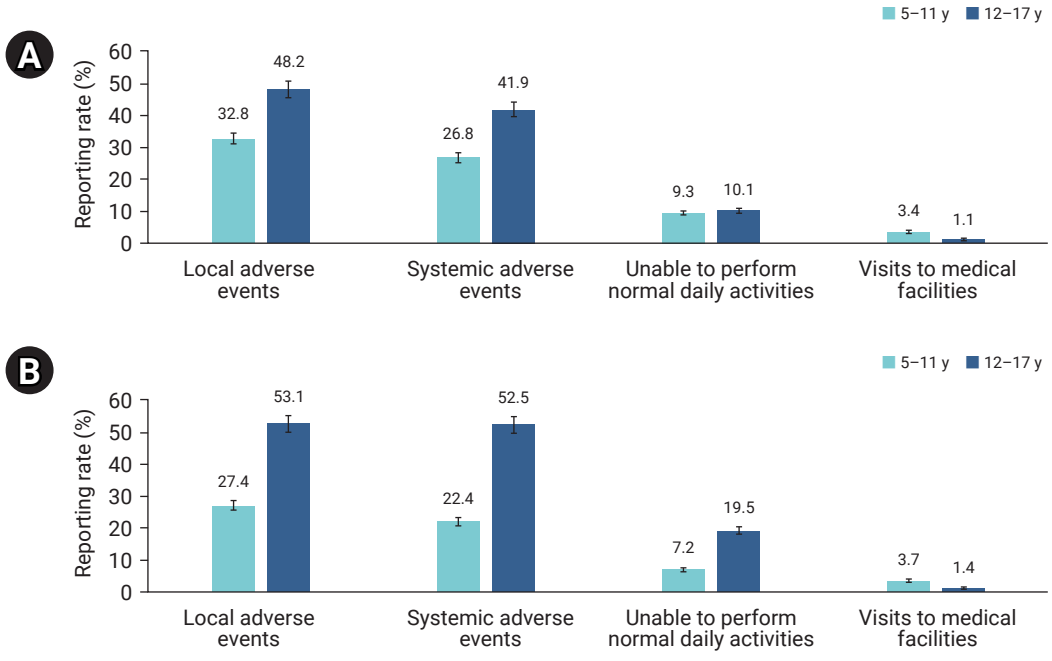

Figure 1. Adverse events and health conditions reported among children and adolescents aged 5 to 17 years following Pfizer-BioNTech coronavirus disease 2019 vaccination, Republic of Korea, December 13, 2021 to June 20, 2022. Values represent the percentage of respondents who reported adverse events and health conditions at least once during days 0 to 7 post-vaccination. (A) Dose 1. (B) Dose 2.
5–11 y, children aged 5–11 years; 12–17 y, adolescents aged 12–17 years.

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Table 4. Adverse events and health conditions reported among children and adolescents aged 5 to 17 years following Pfizer-BioNTech COVID-19 vaccination, Republic of Korea, December 13, 2021 to June 20, 2022

Events[a]	Dose 1 (n = 11,414)			Dose 2 (n = 3,688)		
	5–11 y (n = 1,025)	12–17 y (n = 10,389)	p-value[c]	5–11 y (n = 541)	12–17 y (n = 3,147)	p-value[c]
Local adverse events	336 (32.8)	5,009 (48.2)	< 0.001	148 (27.4)	1,672 (53.1)	< 0.001
Pain	309 (30.1)	4,612 (44.4)	< 0.001	133 (24.6)	1,546 (49.1)	< 0.001
Redness	17 (1.7)	234 (2.3)	0.216	11 (2.0)	108 (3.4)	0.089
Swelling	58 (5.7)	973 (9.4)	< 0.001	29 (5.4)	371 (11.8)	< 0.001
Itching	30 (2.9)	276 (2.7)	0.609	11 (2.0)	107 (3.4)	0.095
Urticaria	5 (0.5)	51 (0.5)	1	1 (0.2)	14 (0.4)	0.712
Others	42 (4.1)	592 (5.7)	0.033	25 (4.6)	195 (6.2)	0.153
Systemic adverse events	275 (26.8)	4,351 (41.9)	< 0.001	121 (22.4)	1,651 (52.5)	< 0.001
Fever	94 (9.2)	797 (7.7)	0.088	48 (8.9)	723 (23.0)	< 0.001
Chills	55 (5.4)	596 (5.7)	0.625	21 (3.9)	452 (14.4)	< 0.001
Headache	97 (9.5)	1,717 (16.5)	< 0.001	40 (7.4)	999 (31.7)	< 0.001
Joint pain	15 (1.5)	266 (2.6)	0.031	3 (0.6)	181 (5.8)	< 0.001
Myalgia	132 (12.9)	2,474 (23.8)	< 0.001	48 (8.9)	865 (27.5)	< 0.001
Fatigue or tiredness	95 (9.3)	2,091 (20.1)	< 0.001	45 (8.3)	892 (28.3)	< 0.001
Nausea	37 (3.6)	680 (6.5)	< 0.001	14 (2.6)	322 (10.2)	< 0.001
Vomiting	13 (1.3)	47 (0.5)	0.001	5 (0.9)	28 (0.9)	0.809
Diarrhea	16 (1.6)	224 (2.2)	0.205	6 (1.1)	81 (2.6)	0.038
Abdominal pain	20 (2.0)	379 (3.6)	0.005	10 (1.8)	171 (5.4)	< 0.001
Rash	3 (0.3)	35 (0.3)	1	0	16 (0.5)	0.151
Armpit tenderness	30 (2.9)	412 (4.0)	0.1	20 (3.7)	327 (10.4)	< 0.001
Chest pain[b]	8 (0.8)	-	-	6 (1.1)	-	-
Heart palpitations[b]	4 (0.4)	-	-	1 (0.2)	-	-
Others	42 (4.1)	523 (5.0)	0.187	19 (3.5)	180 (5.7)	0.036
Unable to perform normal daily activities	95 (9.3)	1,052 (10.1)	0.384	39 (7.2)	613 (19.5)	< 0.001
Visits to medical facilities	35 (3.4)	116 (1.1)	< 0.001	20 (3.7)	44 (1.4)	< 0.001
Emergency department visit	0	18 (0.2)	0.399	0	7 (0.2)	0.603
Hospitalization	0	2 (0)	1	1 (0.2)	0	0.147
Clinic visit	35 (3.4)	100 (1.0)	< 0.001	19 (3.5)	39 (1.2)	< 0.001

Data are presented as n (%): the percentage of respondents who reported adverse events and health conditions at least once during days 0 to 7 post-vaccination.

COVID-19, coronavirus disease 2019.

[a]Events reported by respondents who completed at least 1 text message-based survey on days 0 to 7. Respondents were able to report multiple adverse events on each day. [b]These were additionally investigated only for children aged 5 to 11 years. [c]Chi-square or Fisher exact test as appropriate.

vaccination. Almost one-tenth of 5 to 17-year-old children and adolescents responded that they were unable to perform their normal daily activities after dose 1 (p = 0.384), and this percentage after dose 2 was 7.2% in 5 to 11-year-old children and 19.5% in 12 to 17-year-old adolescents (p < 0.001) (Figure 1; Table 4). Approximately 1.1% to 3.7% of 5 to 17-year-old children and adolescents visited medical facilities during days 0 to 7 after either dose. In addition, in the 5 to 11-year-old group, none of the local and adverse events showed statistically significant differences between the 2 doses except for pain (p = 0.02) and myalgia (p = 0.018), while among 12 to 17-year-old group, all dose 1 and dose 2 comparisons were statistically significant except for urticaria, diarrhea, and rash (Table S1).

Discussion

Regarding the adverse events reported in the CVMS among children and adolescents aged 5 to 17 years after Pfizer-BioNTech COVID-19 vaccination, 96.9% were non-serious and 3.1% were serious. These proportions are similar to those in the safety data from the Vaccine Adverse Event Reporting System in the US; the great majority of adverse events were non-serious (5 to 11-year-old group, 97.4%; 12 to

17-year-old group, 90.7%), and serious adverse events were rare (5 to 11-year-old group, 2.6%; 12 to 17-year-old group, 9.3%) [14,15].

The serious adverse events reported in the CVMS included 125 suspected cases of acute cardiovascular injury, 101 suspected cases of anaphylaxis, and 5 deaths. Reviewing 101 suspected cases of anaphylaxis, the number of cases was 1 in 5 to 11-year-old children (1.0%) and 100 in 12 to 17-year-old adolescents (99.0%). The number of cases was greater after dose 1 (82, 81.2%) than after dose 2 (19, 18.8%), but similar between males (46, 45.5%) and females (55, 54.5%). Other studies also found that anaphylaxis cases were reported more frequently after dose 1 than after dose 2, highlighting the significance of closely monitoring people who receive a first dose of the COVID-19 vaccine [16–18]. Furthermore, among 125 suspected cases of acute cardiovascular injury, the number of suspected myocarditis/pericarditis reports was 103; 1 case (1.0%) was in a 5 to 11-year-old, and 102 cases (99.0%) were in 12 to 17-year-old adolescents. Similar to previous findings [19–22], these cases were more frequent after dose 2 (67, 65.0%) than after dose 1 (36, 35.0%), and in males (79, 76.7%) than in females (24, 23.3%). However, since all adverse events reported in the CVMS are suspected cases, these events do not indicate medically confirmed diagnoses; therefore, a follow-up study will be required to medically confirm major suspected cases of serious adverse events for further evaluation, such as causality assessment between events and vaccines. Until now, none of the death reports has been assessed to be associated with vaccination based on medical records and epidemiological investigation results through an initial review conducted by provincial rapid response teams.

The highest risk of myocarditis/pericarditis was observed in males aged 18 to 25 after dose 2 of the mRNA COVID-19 vaccine [19], and the reporting rate for mRNA-based COVID-19 vaccine-associated myocarditis appeared highest among males aged 12 to 29 years [20]. However, myocarditis/pericarditis cases following mRNA COVID-19 vaccination are rare among adolescents, and patients can recover quickly if treated well [23]. One study found no increased incidence of myocarditis/pericarditis after COVID-19 vaccination compared to other standard immunizations such as smallpox and influenza vaccines [22]. Furthermore, verified cases of myocarditis were rare among children aged 5 to 11 years after Pfizer-BioNTech vaccination in the US vaccine surveillance systems [24,25], and no cases of myocarditis were reported among 3,082 trial participants of the same age with 0 to 7 days of follow-up after dose 2 [26]. In this respect, the benefits of COVID-19 vaccination for children and adolescents aged 5 to 17 years are considered to outweigh the known and potential risks [27–30]; thus, this study does not support actions to exclude 5 to 17-year-old children and adolescents from vaccination and recommend that adverse events after COVID-19 vaccination should continue to be closely monitored to respond and provide additional information on COVID-19 vaccine safety, considering the limited information available in early safety monitoring [31].

The results of the text message survey on adverse events and health conditions for children and adolescents aged 5 to 17 years following the primary Pfizer-BioNTech COVID-19 vaccination series are similar to the safety data reported in the v-safe system [14,15,24] and controlled trials [1,2] among those in the US; local adverse events were more common than systemic adverse events following either dose, and the majority of symptoms were mild, without major safety issues, and disappeared within a few days after vaccination. Moreover, injection site pain was the most common local adverse event, and fatigue, headache, and myalgia were the most common systemic adverse events in v-safe and controlled trials.

According to the v-safe data [14,15], local (dose 1, 54.9%; dose 2, 56.8%) and systemic adverse events (dose 1, 35.3%; dose 2, 41.0%) among 5 to 11-year-old children were less frequently reported than local (dose 1, 62.7% to 63.9%; dose 2, 62.4% to 64.4%) and systemic adverse events (dose 1, 48.9% to 55.7%; dose 2, 63.4% to 69.9%) among 12 to 17-year-old adolescents. This trend is consistent with the results of the text message survey in this study; local and systemic adverse events were lower in children aged 5 to 11 years than in adolescents aged 12 to 17 years. However, this might be affected by the difference in the dose administered between children (10 μg) and adolescents (30 μg) [14] and the number of respondents enrolled in the surveys; thus, these figures should be compared with caution.

This study has some limitations. First, the data were based on suspected adverse events following COVID-19 vaccination, and the events were not medically confirmed for an accurate diagnosis; thus, the results do not indicate causality. Second, as adverse events reported to the CVMS are based on individuals who visit medical facilities, the reports are subject to underreporting. Third, since text message surveys merely relied on self-reported responses, the number of adverse events reported might have been overestimated due to the likelihood of responding by parents or guardians. Fourth, as the text messages were sent during a particular period, the findings cannot be generalized to the entire child and adolescent population in the ROK. Nevertheless, the key strength of this study, as far as we know, is that this is the first study on COVID-19 vaccine safety among children

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and adolescents aged 5 to 17 years in real-world settings in the ROK based on national vaccine safety surveillance data. This study found consistent safety information on the Pfizer-BioNTech COVID-19 vaccine with controlled trials; serious adverse events following vaccination were extremely rare, with no major safety issues among children and adolescents aged 5 to 17 years.

Supplementary Material

Table S1. Comparisons of adverse events and health conditions between vaccine doses among children and adolescents aged 5 to 17 years following Pfizer-BioNTech COVID-19 vaccination, Republic of Korea, December 13, 2021 to June 20, 2022. Supplementary data are available at https://doi.org/10.24171/j.phrp.2022.0233.

Notes

Ethics Approval

The passive surveillance activity was conducted and authorized by the public health authority; the study was not subject to the institutional review board approval under government regulations. The study of text message-based surveillance was exempted from review by the Public Institutional Review Board designated by the Korea Ministry of Health and Welfare (No: P01-202206-01-033).

Conflicts of Interest

The authors have no conflicts of interest to declare.

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None.

Availability of Data

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

Authors' Contributions

Conceptualization: SK, SYS, YKL, EC; Data curation: SK, YH, DSL; Formal analysis: SK, YH, DSL; Investigation: SK, YH; Methodology: all authors; Validation: SK, SYS, YKL; Visualization: SK, YH; Writing–original draft: SK, YKL; Writing–review & editing: all authors.

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OSONG PUBLIC HEALTH AND RESEARCH PERSPECTIVES

Instruction for authors

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