

Aims & Scope

Osong Public Health and Research Perspectives (PHRP) is the international bimonthly (published at the end of February, April, June, August, October, and December) journal founded in 2010 by the Korea Disease Control and Prevention Agency (KDCA). With the mission of the KDCA, to create a disease-free world, PHRP encourages sharing medical information and knowledge in the areas of public health.

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The neglected issues of global health security that we should prepare for in our society

Jong-Koo Lee 

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According to the World Health Organization (WHO), the prevalence of the Omicron variant of coronavirus disease 2019 (COVID-19) is decreasing worldwide after its peak in January 2022, but the Omicron mutants, BA.4 and BA.5, have been reported to be present in 58 countries and 62 countries, respectively, and the numbers of patients are increasing in Portugal and the United States. Fortunately, there seems to be no change in the fatality rate, but the transmissibility, immune escape, and hospitalization rate are increasing [1]. The inflow of BA.4 and BA.5 into the Republic of Korea is also expected to increase. The number of patients in the Republic of Korea has recently been about 7,000 per week (132 per 1 million), which is 98% lower than in the third week of March (7,887 per 1 million), which was the peak of the pandemic. As a sero-epidemiological survey [2] showed that the antibody positivity rate was 94.9%, temporary herd immunity might have been reached; however, the proportion of natural infections rose from 0.6% in January to 36.1% in April, and many breakthrough infections have occurred despite a very high tertiary vaccination rate. COVID-19 infections continue to occur due to viral circulation in the community in the school-age population and among young people with low vaccination rates; this means that the outbreak of COVID-19 will continue for the time being. Furthermore, although the elderly (aged 60 or older) account for a decreasing proportion of COVID-19 patients, the fourth vaccination rate among the elderly is only 30.1%, and the number of deaths among the elderly is expected to increase in the near-term future. In particular, with the lifting of the social distancing measures and the waning of immunity acquired by vaccination and natural infection, we will need to prepare for the possibility of an increase in COVID-19 patients among school-age children and young adults during the vacation season. Worldwide, 6.3 million official deaths due to COVID-19 have been recorded; however, there have been approximately about 14.91 million more deaths than reported, corresponding to 9.49 million more deaths than have been globally reported as directly attributable to COVID-19. The estimates of excess deaths—with 7.89 million in lower- to middle-income countries, and 640,000 in low-income countries [3]—indicate inequality in access to public health goods, including vaccines and therapeutics, which must be addressed by global health alliances and solidarity. In the midst of the issue of excess mortality, the Democratic Republic of Korea (North Korea) announced that COVID-19 cases have officially occurred in that country. According to the KCNA Watch, a fever whose cause could not be identified explosively spread across the country starting in late April, and more than 350,000 people contracted this fever in a short span of time, of whom at least 162,200 had healed completely as of early to mid-

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May. On May 12, approximately 18,000 people caught this fever nationwide and, at that time, up to 187,800 people were isolated and receiving medical treatment. Six people had died [4]. The number of cases then spiked, and as of June 24, there were 4,657,190 cases of fever, 73 deaths, and 17,250 fever cases reported per day [5]. Therefore, it seems that the worst has passed. Nevertheless, the WHO said that the situation is “getting worse, not better,” and we therefore need more detailed information to make an accurate judgment. However, questions are being raised about the unexpectedly low mortality rate. It seems that accurate numbers of patients could not be officially reported to the WHO due to the lack of capacity for polymerase chain reaction confirmation tests. As a lack of therapeutic drugs has made it difficult to manage symptomatic patients, and severe cases have been reported, the Republic of Korea (South Korea) is also preparing to help North Korea with the donation of basic essential drugs, COVID-19 therapeutics, and vaccines from a humanitarian point of view. Despite the refusal of the COVAX vaccine, international aid for control of the outbreak is expected to be essential, as closure of the border is unlikely to be feasible for long without essential medicine and vaccination.

The 75th WHO World Assembly was held in the last week of May 2022. There were many intense discussions regarding the limitations of WHO leadership and how to prepare countries to respond to the current unprecedented pandemic. Broadly speaking, the discussions dealt with the possibilities of a pandemic treaty, revised international health regulations (IHR), or both simultaneously. Reasons in favor of a pandemic treaty are that 61 out of 194 countries have already recognized the need for a treaty, the management of zoonotic diseases is difficult to resolve through the current IHR governance system without cooperation with the World Organization for Animal Health, and a new treaty is needed for the One Health Framework. Some countries argued that the United States, China, and Brazil are negative about a new treaty, that the World Trade Organization’s TRIPS Article 27 (2) (Exceptional Drug Patents if Public Health Needs) and Article 31 (Enforcement of Compulsory Drug Enforcement) are likely to be revised without a new treaty, and that it is easier to revise IHR than to make treaties (as exemplified by the Framework Convention for Tobacco Control, which took 12 years to enter into effect). Both sides raised the problem of a persistent budgetary shortage and the need for a new secretariat.

As scholars in favor of the new treaty, Haik Nikogosian and Ilona Kickbusch [6] argued that a treaty under Article 19 of the WHO Constitution could resolve issues beyond the scope of IHR (2005). They categorized these issues into

5 groups that cannot be covered by IHR: Politically, a treaty would attract the much-needed attention and commitment from the highest levels of state and government. Legally, treaties are gradually translated into national laws in most legal systems after ratification. From an institutional perspective, a treaty would allow a dedicated governing body—a Conference of the Parties—to regularly review and resolve evolving matters. From a multisectoral perspective, the ratification and subsequent introduction of a treaty into a country’s national laws creates a binding framework for all relevant sectors and the government as a whole. The last set of issues that a treaty could resolve would be those that do not reasonably fall under the scope of Article 21 of the WHO Constitution for Regulations, which is the only other type of binding instrument that the WHO can use. This treaty on pandemics would be an expression of true political will to act collectively in response to unprecedented pandemics.

The other group of scholars in favor of the treaty is exemplified by the Panel for a Global Public Health Convention. These scholars—Barbara M. Stocking and Lawrence Costin et al.—usually discuss the possibility of a Global Health Treaty, but at this panel, they discussed a Framework Convention limited to the field of infectious diseases [7]. I talked about the possibility of a treaty with them. They argued that the most important reasons for needing a treaty are as follows: first, the lack of compliance during COVID-19; second, the fact that a treaty must be signed at the head-of-state level; and third, the possibility that a treaty could prevent outbreaks from developing into pandemics. One of the key measures required in the treaty would be country preparedness, which would require significant external financing for low- and some middle-income countries. The other key measures would be transparency and external verification. Another advantage of a Framework Convention is that it can also have a number of protocols covering different issues. These protocols could be revised as our understanding of pandemics continues to grow, and new protocols for specific areas could be developed at the request of the Conference of Parties. First of all, the most important mechanism is verification and compliance, which will make us safer than we are.

However, the 75th WHO World Health Assembly focused on revising IHR, not on forming a new treaty, and the zero draft report of the Working Group on Strengthening WHO Preparedness and Response to Health Emergencies to the 75th World Health Assembly was adopted. The recommendations were as follows [8]: (1) WHO’s political leadership; (2) cooperation and collaboration; (3) WHO at the center; (4) financing; (5) sustainability of COVID-19 innovative mechanisms; (6) global surveillance; (7) strengthening IHR implementation, compliance, and potential amendments;

and (8) equity. There is no doubt that revision of IHR is an important current issue, but I am not sure that our government and related non-state actors continue to pay attention to and express their opinions both regarding IHR revision and the possibility of a new treaty, which will become an important topic in global health diplomacy. Active involvement of the government and academia of the Republic of Korea in this project will make our nation one of the leading countries in the field of global health.

Notes

Ethics Approval

Not applicable.

Conflicts of Interest

The author has no conflicts of interest to declare.

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Effect of clofibrate on reducing neonatal jaundice: a systematic review and meta-analysis

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ABSTRACT

In neonates, bilirubin tends to be deposited in body tissues, especially the skin and mucous membranes. Jaundice is an early symptom of bilirubin excretion disorders. Therefore, the aim of this study was to investigate the effect of clofibrate on reducing neonatal jaundice. In this systematic review, international databases, including PubMed, Scopus, Web of Science, Embase, Cochrane, and Google Scholar, were searched without time and language restrictions. The reference lists of all studies ultimately included were manually searched. In the 17 articles reviewed, with a sample size of 665 people published between 2005 and 2019, the average weight of the neonates varied from 2,186 g to 4,000 g. Furthermore, the average age of neonates varied from 2 days to 9 days. Four doses of clofibrate (25, 30, 50, 100 mg/kg of neonatal body weight) were used. The bilirubin level of neonates significantly decreased in the intervention group 24, 36, 48, and 72 hours after the start of treatment. Clofibrate administration decreased total serum bilirubin, especially from the second day onwards, and also reduced hospitalization time, hospital costs, and side effects from hospitalization.

Keywords: Clofibrate; Hyperbilirubinemia; Jaundice; Neonatal jaundice

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Introduction

Bilirubin is a compound produced by the catabolism of hemoglobin that tends to be deposited in the body tissues of neonates, especially the skin and mucous membranes. Jaundice is an early symptom of bilirubin excretion disorders. If bilirubin is not excreted from the body in time, it will reside in the brain tissue and cause temporary and permanent neurological disorders by damaging the brainstem, in a condition known as kernicterus [1]. Elevated bilirubin levels (hyperbilirubinemia) are among the most common disorders in infancy,

observed in 60% of infants, of whom 10% have the severe form for which treatment is needed [2]. The rate of hyperbilirubinemia in premature neonates is 80% [3], and neonatal jaundice is observed in up to 85% of all live births. If there is no hemolysis, sepsis, trauma at birth, or prematurity, it usually resolves within 3 to 5 days without significant complications. However, evidence suggests that severe neonatal jaundice (SNJ) leads to substantial morbidity and mortality. SNJ is also an important cause of neurological disorders and other long-term consequences, including cerebral palsy, non-syndromic auditory neuropathy, deafness, and learning difficulties. A recent report by Slusher et al. [4] noted that at least 481,000 term/near-term neonates are affected by SNJ/hyperbilirubinemia each year, of whom 114,000 die and more than 63,000 survive with kernicterus. In the USA, jaundice is seen in 15.6% of hospitalized neonates. The incidence of SNJ is 667.8 per 10,000 live births in Africa and 3.7 per 10,000 live births in Europe [5]. Although this disorder generally resolves, an appropriate intervention to avoid bilirubin neurotoxicity should be seriously considered [6]. There are 3 ways to treat hyperbilirubinemia: phototherapy, blood transfusion, and medication. The most common of these methods is phototherapy, and transfusion of the baby's blood in conditions of excessive bilirubin [7–10]. Although blood transfusion is one of the main treatments for hyperbilirubinemia, it has some side effects [11,12]. These detrimental side effects suggest that an alternative drug treatment strategy should be developed to address this disorder. Drug interventions include D-penicillamine, phenobarbital, clofibrate, bile salts, metalloporphyrins, laxatives, and bilirubin oxidases [6,13–15]. Clofibrate is a glucuronosyltransferase inducer suggested to reduce bilirubin levels in neonates with hyperbilirubinemia [16–21]. Clofibrate is an activator of peroxisome proliferator-activated receptors (PPARs) that effectively lowers cholesterol and triglyceride levels in adults. It also induces glucuronyl transferase and causes the accumulation and excretion of bilirubin. Some studies have also suggested reducing neonates' need for phototherapy and shortening their hospitalization course [11,17–21]. Clofibrate is a practical drug recommended for the treatment of neonatal hyperbilirubinemia. Research results have shown that clofibrate effectively reduces neonatal jaundice, with an effect appearing 24 hours after treatment [16,19–21]. A single dose of 50 mg/kg of clofibrate to treat neonatal hyperbilirubinemia shortens the hospitalization course, which is also economically advantageous [6]. Clofibrate may have short-term benefits for neonates with hyperbilirubinemia, especially for term neonates and

neonates without hemolytic diseases [19–22]. Clofibrate results in a faster reduction of total serum bilirubin (TSB) and a shorter hospitalization course, and no side effects have been observed in full-term neonates with jaundice [7,16,19–21].

A recent Cochrane review on clofibrate administration as an adjunct to phototherapy for neonatal unconjugated hyperbilirubinemia was limited due to a high degree of heterogeneity among the trials, a lack of trials from different geographical regions, and a lack of data on mortality from kernicterus and long-term safety [23]. Therefore, the present study aimed to evaluate the effect of clofibrate on the reduction of TSB and neonatal jaundice.

Materials and Methods

Study Protocol

This systematic review and meta-analysis investigated the effect of clofibrate on reducing neonatal jaundice. This study was written based on the PRISMA protocol for systematic review and meta-analysis studies.

Statistical Population

Studies in which neonates were treated with clofibrate to reduce their blood bilirubin levels in addition to phototherapy were evaluated. In selecting these people, no restrictions were imposed on sex, age, race, and weight at birth.

Study Outcome

The main outcome considered was a reduction in bilirubin levels.

Search Strategy

In this systematic review, the international databases, including PubMed, Scopus, Web of Science, Embase, Cochrane, and Google Scholar, were searched without time and language restrictions. If an article was published in a language other than English, the full text of the article was translated into Persian to extract the relevant information. The search was performed using the standard keywords "jaundice," "icterus," "hyperbilirubinemia," "neonatal," "infant," "clofibrate," "meta-analysis," and "systematic review," as well as their equivalent MeSH terms (updated through May 15, 2021). Their compounds were also searched in the abovementioned databases using the (AND, OR) operators. The reference lists of all studies that were ultimately included were also manually searched. Table 1 shows the search strategy in some databases and Table 2 presents the results for the evaluation of quality of studies [1,2,6–8,11,12,16–18,23–29].

Table 1. Search strategy in selected databases

Database	Search strategy
Scopus	(TITLE-ABS-KEY (Clofibrate) AND TITLE-ABS-KEY (<i>hyperbilirubinemia</i> OR <i>jaundice</i>) AND TITLE-ABS-KEY (<i>infant</i> OR <i>neonatal</i>))
PubMed	((((Clofibrate [Title/Abstract]) AND (Hyperbilirubinemia [Title/Abstract] OR Jaundice [Title/Abstract])) AND (Infant [Title/Abstract] OR neonatal [Title/Abstract]))
Web of Science	You searched for: TOPIC: (Clofibrate) AND TOPIC: (Hyperbilirubinemia OR Jaundice) AND TOPIC: (Infant OR neonatal)
Cochrane	Clofibrate in Title Abstract Keyword AND Hyperbilirubinemia OR Jaundice in Title Abstract Keyword AND Infant OR neonatal in Title Abstract Keyword

Table 2. Quality evaluation of studies

Study	Q1	Q2	Q3	Q4	Q5	Q6	Q7
Ahadi et al. [2]	Low	Low	Low	Low	Low	High	Unclear
Gholami et al. [25]	Low	High	Low	Low	Low	Low	Low
Mahyar et al. [12]	Low	Low	Low	Low	Low	Low	High
Kumar et al. [23]	Low	Low	Low	Low	Unclear	Low	Low
NouriShadkam et al. [18]	Low	Low	Low	Low	Low	Low	Unclear
Fallah et al. [6]	Low	Low	Low	Unclear	Low	Low	Low
Habibi et al. [16]	Low	Low	Low	High	Low	Low	Low
Alosy [24]	High	Low	Low	Low	Low	Low	Low
Kandharkar [27]	High	Low	Low	Low	Low	Low	Low
Sakha et al. [26]	Low	Low	Low	Low	Low	Low	High
Zahedpasha et al. [7]	Low	Low	Unclear	High	Low	Low	Low
Moslehi and Pishva [17]	Low	High	Low	Low	Low	Low	Low
Badeli et al. [1]	Low	Low	Low	Unclear	Low	Low	Low
Zahedpasha et al. [28]	Low	Unclear	Low	Low	High	Low	Low
Sharafi et al. [8]	Low	Low	Low	Unclear	Low	Low	Low
Mohammadzadeh et al. [29]	Low	Unclear	Low	Low	Low	High	Low
Mohammadzadeh et al. [11]	Low	High	Low	Low	Low	Low	High

Q1, random sequence generation; Q2, allocation concealment; Q3, blinding of participants; Q4, Blinding of outcome assessment; Q5, incomplete outcome data; Q6, selective reporting; Q7, anything else, ideally prespecified.

Inclusion and Exclusion Criteria

PICO (patient, intervention, comparison, outcome) components

The study population was all neonates who received clofibrate to reduce bilirubin levels in addition to phototherapy. The intervention was clofibrate administration. The comparison was neonates who used placebo in addition to phototherapy or received no treatment other than phototherapy. The study outcome was bilirubin.

Inclusion criteria for preliminary studies

In this meta-analysis, the preliminary studies included randomized clinical trials with or without blinding. The intervention groups in the included trials were neonates who had received clofibrate in addition to phototherapy, and the control groups received no intervention or placebo.

Exclusion criteria

Exclusion criteria included failure to report the required information, case reports, low-quality studies based on the Cochrane Institute’s clinical quality assessment checklist, lack of access to the full texts of studies, studies examining the effect of clofibrate on neonatal jaundice based on measurements of bilirubin levels in the umbilical cord of neonates, and those investigating the effect of clofibrate combined with another drug on neonatal jaundice.

Quality evaluation of studies

After identifying the initial studies, 2 authors independently evaluated all the initial studies using the Cochrane Institute’s clinical quality assessment checklist. This checklist includes 7 items, each evaluating 1 of the dimensions or types of essential biases in clinical trials. Each item in this checklist has 3 options: a high risk of bias, a low risk of bias, and unclear. After completing the bias risk assessment in all

studies, disagreements about the item options in each study were evaluated and resolved through consensus. Table 2 shows the quality evaluation of studies.

Data Extraction

Two researchers independently extracted data from studies to minimize reporting bias and data collection errors. The researchers entered the extracted data onto a checklist, including the first author's name, the year of study publication, study title, the number of samples, the mean and standard deviation of neonatal bilirubin levels before and after the intervention, age, sex, and neonatal weight, clofibrate dosage, and follow-up duration. A third researcher reviewed the data extracted by the 2 previous researchers to correct any discrepancies. If the required data were not reported in an article, a request for the data was sent through correspondence with the article's author.

Statistical Analysis

Due to the quantitative nature of the outcome of interest, the effect size of the intervention was calculated based on the mean difference in serum bilirubin levels before and after the intervention compared to the mean difference outside the experimental group.

Data from studies were combined for the meta-analysis according to the number of samples, mean, and standard deviation. In order to evaluate the heterogeneity of the studies, the Cochrane Q test and the I^2 index were used. Since a fixed-effects model is used when heterogeneity is low and a stochastic-effects model is used when a high degree of heterogeneity is present, the present study used a stochastic-effects model. Data analysis was performed using Stata ver. 14.0 (StataCorp., College Station, TX, USA). A p -value <0.05 was considered to indicate statistical significance.

Results

Initially, 980 articles were found in the above databases. After reviewing the titles, 385 duplicate studies were excluded. The remaining 595 abstracts were reviewed, and 487 articles were eliminated according to the exclusion criteria. Ninety-one of the remaining 108 articles were removed due to incomplete information or the lack of a full text. Finally, the remaining 17 articles entered the quality evaluation stage; all of these articles were deemed to be of good quality and included in the meta-analysis. Figure 1 presents a flow chart of the inclusion of studies in the systematic review and meta-analysis.

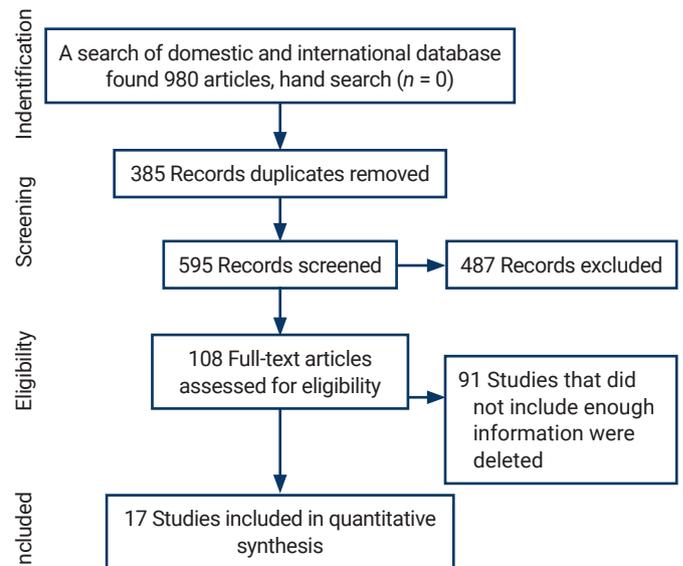


Figure 1. Flow chart of the inclusion of studies in the systematic review and meta-analysis.

Characteristics of Studies Included in the Systematic Review

Table 3 presents information on the articles entered into the systematic review and meta-analysis. In the 17 articles reviewed, with a sample size of 665 people published between 2005 and 2019, the average weight of the neonates varied from 2,186 g to 4,000 g. The average age of the neonates ranged from 2.09 days to 9.8 days. Four doses of clofibrate (25, 30, 50, 100 mg/kg of neonatal body weight) were used in the studies. All studies were conducted in Iraq, Iran, and India. Table 3 shows the characteristics of studies included in this systematic review [1,2,6–8,11,12,16–18,23–29].

Since the study phases were different (6, 12, 16, 24, 36, 48, and 72 hours after the intervention), we could not conduct a subgroup analysis based on clofibrate dose, age, weight, or the countries studied.

Figure 2 shows a comparison of neonatal bilirubin levels between the control and case groups before the intervention. There was no statistically significant difference between the control and case groups with respect to the mean scores of neonatal bilirubin levels. No statistically significant difference was observed between both groups in terms of neonatal bilirubin levels 6 hours after the intervention.

Figure 3 shows a comparison of neonatal bilirubin levels between both groups 12 hours after the intervention. Neonatal bilirubin levels in the intervention group were 0.71 mg/dL lower than those in controls, but the difference was not statistically significant. Figure 4 shows a comparison of neonatal bilirubin levels between both groups 24 hours after the intervention. Clofibrate use significantly decreased the

Table 3. Characteristics of the studies included in the systematic review

Study	Year of publication	Type of study	Country	Sample size	No. of girls	No. of boys	Age (d)	Weight (kg)	Dosage of clofibrate (mg/kg)
Ahadi et al. [2]	2013	Double-blind clinical trial	Iran	30	16	14	2.09	2.5-4	100
Gholami et al. [25]	2019	Randomized controlled clinical trial	Iran	30			4.45	3.193-3.460	50
Gholami et al. [25]	2019	Randomized controlled clinical trial	Iran	30			4.45	3.193-3.460	100
Mahyar et al. [12]	2019	Randomized clinical trial	Iran	20	11	9	5	3.196	30
Kumar et al. [23]	2017	Randomized controlled trial	India	45	24	21	4	2.760	50
NouriShadkam et al. [18]	2016	Double-blind randomized clinical trial	Iran	41	21	20	6.41	3.490	100
Fallah et al. [6]	2012	Parallel single-blind randomized clinical trial	Iran	30	14	16	4.73	3.202	50
Habibi et al. [16]	2012	Single-blind clinical trial	Iran	26	11	15	3.31	3.057	100
Alosy [24]	2017	Case-control study	Iraq	100					100
Kandharkar [27]	2019	Randomized controlled trial	India	32	16	16	3.1	2.845	100
Sakha et al. [26]	2009	Double-blind, placebo-controlled, randomized trial	Iran	35	15	20	6.2	2.330	100
Zahedpasha et al. [7]	2007	Randomized clinical trial	Iran	30	16	14	5.67	3.083-3.300	100
Moslehi and Pishva [17]	2007	Clinical randomized controlled trial	Iran	30	13	17	5.25	2.564	25
Moslehi and Pishva [17]	2007	Clinical randomized controlled trial	Iran	30	16	14	5.18	2.525	50
Badeli et al. [1]	2008	Clinical trial	Iran	45	19	26	5	3.190	100
Zahedpasha et al. [28]	2008	Randomized clinical trial	Iran	21			5.81	3.195-5.200	100
Sharafi et al. [8]	2010	Clinical trial	Iran	30	18	12	6.8	3.107	50
Mohammadzadeh et al. [29]	2009	Randomized double-blind placebo-controlled trial	Iran	30	18	12	8.7	2.186	100
Mohammadzadeh et al. [11]	2005	Clinical controlled study	Iran	30	10	20	9.8	3.257	100

neonatal bilirubin levels in the intervention group by 1.20 mg/dL compared to the control group. A significant difference was observed between the control and intervention groups with respect to the mean neonatal bilirubin levels. The neonatal bilirubin levels in the intervention group were 2.39 mg/dL lower than those in the control group.

Figure 5 shows a comparison of neonatal bilirubin levels between both groups 48 hours after the intervention. Neonatal bilirubin levels in the intervention group were 1.52 mg/dL lower than those of the control group, and this difference was statistically significant. At 72 hours after the intervention, neonatal bilirubin levels in the intervention group were 0.75 mg/dL lower than those in the control group, but this difference was not statistically significant.

Neonatal bilirubin levels in the intervention group significantly decreased by 1.64 at 6 hours after the intervention, by 2.79 at 12 hours after the intervention, and by 1.81 at 16 hours after intervention. Two days after treatment, the neonatal bilirubin levels in the intervention group significantly decreased by 3.88 compared to the beginning of the study, and by 36 hours after the intervention, a significant decrease (by 4.01) in neonatal bilirubin levels was observed in the intervention group. By 48 hours, the neonatal bilirubin levels in the intervention group significantly decreased by 4.86 compared to before clofibrate consumption, and a 3.87 decrease was observed at 72 hours. In all phases, neonatal bilirubin levels decreased significantly in the intervention group compared to before the intervention

Discussion

No statistically significant difference was observed between the control and intervention groups with respect to the mean neonatal TSB values before the intervention. Until 6 and 12 hours after the intervention, neonatal TSB levels decreased in both groups, without statistically significant between-group differences.

Twelve hours after the intervention, neonatal TSB levels in the intervention group were 0.71 lower than those in the control group, which was not a statistically significant difference. The neonatal TSB levels in the intervention group were 0.54, 1.20, 2.39, 1.52, and 0.71 lower than those in the control group at 16, 18, 24, 36, 48, and 72 hours after the intervention, respectively, and these differences were statistically significant.

The mean TSB level was significantly decreased by 1.64 at 12 hours after the intervention, 2.79 at 16 hours after the intervention, 1.81 at 24 hours after the intervention, 3.88 at 36 hours after the intervention, 4.01 at 48 hours after the intervention and 4.86 at 72 hours after the intervention in

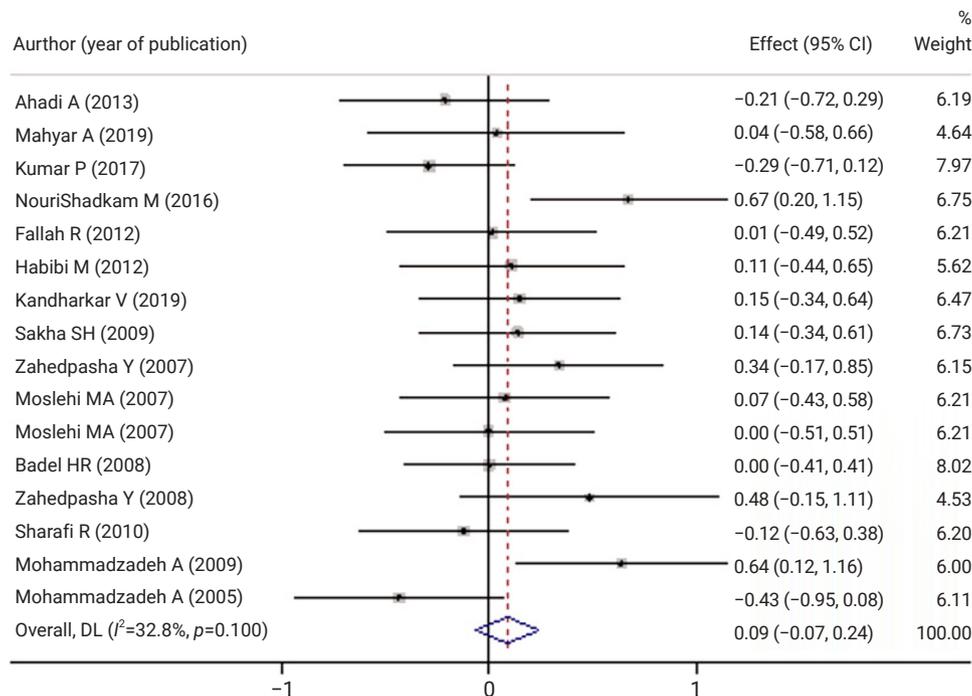


Figure 2. Comparison of neonatal bilirubin levels between the control and case groups before the intervention. Weights are from random-effects model. CI, confidence interval; DL, DerSimonian-Laird.

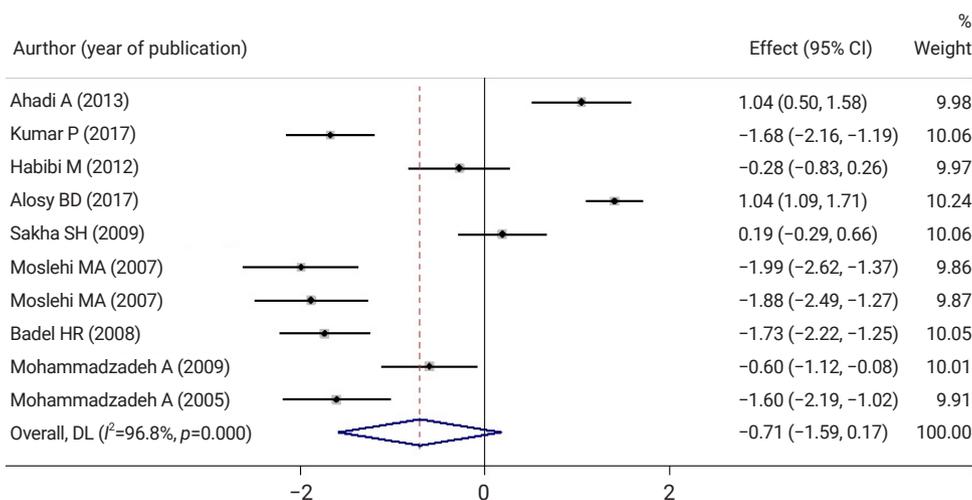


Figure 3. Comparison of neonatal bilirubin levels between both groups 12 hours after the intervention. Weights are from random-effects model. CI, confidence interval; DL, DerSimonian-Laird.

the intervention group. The neonatal TSB levels significantly decreased in the intervention group in all phases compared to before the intervention.

The results reported by Caballero-Noguez et al. [30] regarding changes in total and indirect bilirubin levels in 2 groups (phenobarbital and clofibrate) compared to the control group showed that TSB levels significantly decreased 24 and 72 hours after the intervention. Alosy [24] showed

that 12 hours, 24 hours, and 4 days after the intervention, TSB levels decreased in the clofibrate group and the control group, but this drop was more significant in the clofibrate group, which is consistent with our study. This may be due to the effect of clofibrate on enhancing glucuronyl transferase activity, as a result of which clofibrate raises hepatic bilirubin clearance in 6 hours. Unlike sodium phenobarbital, clofibrate does not cause sleepiness or respiratory depression. It also

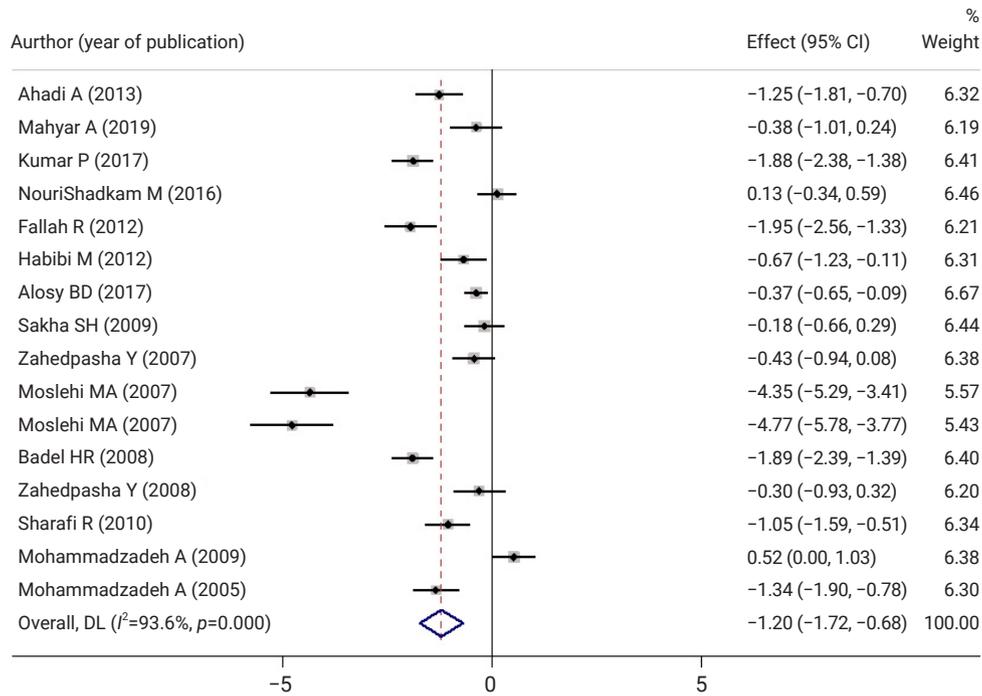


Figure 4. Comparison of neonatal bilirubin levels between both groups 24 hours after the intervention. Weights are from random-effects model. CI, confidence interval; DL, DerSimonian-Laird.

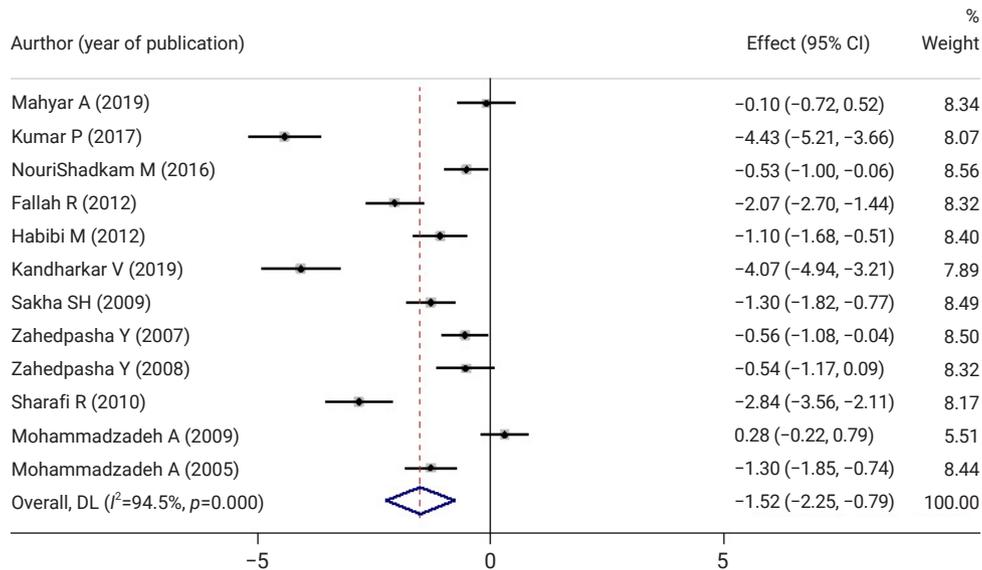


Figure 5. Comparison of neonatal bilirubin levels between both groups 48 hours after the intervention. Weights are from random-effects model. CI, confidence interval; DL, DerSimonian-Laird.

results in liver bilirubin clearance [16]. Fallah et al. [6] showed that 12 and 48 hours after the intervention, 27 neonates in the clofibrate group (90%) and 15 neonates in the control group (56.7%) had TSB levels less than 14 mg/dL ($p=0.02$). The mean length of hospitalization (mean \pm standard deviation: 1.7 ± 0.7 days vs. 1.2 ± 3.2 days; $p=0.03$) and the duration of

phototherapy (mean \pm standard deviation: 30.2 ± 13.99 hours vs. 46.2 ± 58.5 hours; $p=0.001$) were significantly lower in the clofibrate group. Loose stool was only observed in 2 clofibrate patients. There was no significant difference in the safety of the treatments, and they showed that a dose of 50 mg/kg of clofibrate was effective in treating neonatal

hyperbilirubinemia and reducing hospitalization duration and cost.

TSB levels in the clofibrate group and phototherapy at 12, 24, 36, and 48 hours after the intervention were significantly lower than those in the phototherapy group. Significantly less phototherapy was needed in the clofibrate group than in the phototherapy-only group [1,19].

Long-term administration of clofibrate in adults has several side effects, such as nausea and vomiting, loose stool, muscle cramps, and pruritus; however, no such effects have been reported in neonates who receive high doses of clofibrate [1,11,25].

Studies have shown that both clofibrate and phenobarbital reduce TSB levels in a single dose, but phenobarbital is more effective; therefore, phenobarbital reduces TSB levels more rapidly than clofibrate, thereby reducing hospitalization time and costs [24].

Studies have shown that in addition to reducing TSB levels, clofibrate also shortens the duration of phototherapy. Clofibrate may have short-term benefits in full-term infants who do not have a hemolytic disease; however, long-term follow-up is required to evaluate its safety and long-term effects. At present, there is no evidence suggesting that clofibrate can alter the likelihood of death and kernicterus [25].

Habibi et al. [16] showed that clofibrate reduced TSB 24 hours after administration, while in other studies, it was effective 12 and 16 hours after clofibrate administration. Clofibrate activates PPARs and regulates plasma lipid levels by lowering very-low-density lipoproteins. The drug is absorbed from the gastrointestinal tract and rapidly hydrolyzed to an active metabolite (clofibric acid). This active metabolite is ultimately excreted through urine as conjugated glucuronide. Sakha et al. [26] also showed that clofibrate is an effective supplementary drug in neonatal hyperbilirubinemia, leading to a decrease in TSB levels and a reduction in the phototherapy duration in full-term and premature neonate. Kumar et al. [23] and Kandharkar [27] observed that clofibrate administration significantly reduced serum TSB levels at 48 hours after the intervention. Mahyar et al. [12] showed that purgative manna and clofibrate did not reduce TSB levels in unconjugated hyperbilirubinemia neonates, which is inconsistent with our study and previous studies.

Eghbalian et al. [31] showed that the prescription of 25 mg/kg clofibrate as a single dose, just as the dose of 50 mg/kg as a single dose, could significantly reduce serum bilirubin levels. These researchers recommended using a low dose of clofibrate to treat neonatal unconjugated hyperbilirubinemia.

Gholitabar et al. [32] argued that the existing data have

been insufficient to absolutely confirm the effect of clofibrate on neonatal jaundice, and more studies are needed to be conducted on this issue. Clofibrate is an available drug that can effectively treat neonatal hyperbilirubinemia without any side effects. However, the general administration of this drug in high-risk neonates, such as premature infants and those with hemolytic jaundice should be further investigated [11].

Moslehi and Pishva [17] showed no statistically significant difference between a low dose (25 mg/kg) and a moderate dose (50 mg/kg) of clofibrate. Six hours after clofibrate administration, indirect TSB levels decreased compared with the control group. Clofibrate also reduces the need for phototherapy in healthy individuals. NouriShadkam et al. [18] showed that clofibrate was ineffective on TSB on the first day, but on the second day, it was effective in decreasing TSB. Eghbalian et al. [21] reported that clofibrate was an effective supplementary drug in neonatal hyperbilirubinemia, leading to decreased TSB levels and a shortened phototherapy duration in premature neonates. Sharafi et al. [8] showed that clofibrate was effective for outpatients with neonatal hyperbilirubinemia undergoing phototherapy at home.

Conclusion

According to the results of this study, administration of clofibrate decreased TSB, especially from the second day onwards, and also reduced hospitalization time, hospital costs, and hospitalization-associated complications.

Larger randomized controlled trials (complying with all principles of study design) along with longer follow-up and consideration of hemolytic diseases and blood transfusion are needed to further elucidate this issue.

The reviewed studies showed that doses of 25–100 mg/kg and short-term administration of clofibrate did not lead to any complications during the treatment and follow-up periods. Lipids and unconjugated bilirubin can conjoin with each other and bind to albumin. Therefore, changes in bilirubin levels must be adjusted with consideration of alterations in the lipid profile. In this regard, lipids are among the most important macronutrients, playing necessary roles in cell growth and development in newborns; therefore, the long-term administration of clofibrate could impair organ development and growth.

In the reviewed studies, complications were mostly evaluated by clinical observations, which could be considered as a limitation of clinical studies. Thus, it is recommended to perform laboratory tests and biochemistry examinations (according to the side effects) in future studies to obtain more useful results.

Limitations of the Study

The full text of some studies was not available, and some information required for data analysis was incomplete.

Notes

Ethics Approval

This study was approved by the Institutional Review Board of Hamadan University of Medical Sciences (IR.UMSHA.REC.1400.364) and performed in accordance with the principles of the Declaration of Helsinki. 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.

Funding

None.

Availability of Data

All data generated or analyzed during this study are included in this published article. Other data may be requested through the corresponding author.

Authors' Contributions

Conceptualization: RR; Data curation: FE; Formal analysis: RR; Investigation: AHD; Methodology: RR; Project administration: RR; Resources: FE; Software: LK; Supervision: RR; Validation: LK; Visualization: HB; Writing-original draft: RR; Writing-review & editing: all authors.

Additional Contributions

Lotfollah Karimi (Hamedan University of Technology, Hamedan, Iran) provided statistical support.

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Seroprevalence of immunoglobulin G antibodies against SARS-CoV-2 in children and adolescents in Delhi, India, from January to October 2021: a repeated cross-sectional analysis

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ABSTRACT

Objectives: The aim of this study was to assess changes in the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) immunoglobulin G (IgG) seroprevalence among children and adolescents in Delhi, India from January 2021 to October 2021.

Methods: This was a repeated cross-sectional analysis of participants aged 5 to 17 years from 2 SARS-CoV-2 seroprevalence surveys conducted in Delhi, India during January 2021 and September to October 2021. Anti-SARS-CoV-2 IgG antibodies were detected by using the VITROS assay (90% sensitivity, 100% specificity).

Results: The seroprevalence among 5- to 17-year-old school-age children and adolescents increased from 52.8% (95% confidence interval [CI], 51.3%–54.3%) in January 2021 to 81.8% (95% CI, 80.9%–82.6%) in September to October 2021. The assay-adjusted seroprevalence was 90.8% (95% CI, 89.8%–91.7%). Seropositivity positively correlated with participants' age ($p < 0.001$), but not sex ($p = 0.388$). A signal to cut-off ratio ≥ 4.00 , correlating with the presence of neutralization antibodies, was observed in 4,814 (57.9%) participants.

Conclusion: The high percentage of seroconversion among children and adolescents indicates the presence of natural infection-induced immunity from past exposure to the SARS-CoV-2 virus. However, the lack of hybrid immunity and the concomitant likelihood of lower levels of neutralization antibodies than in adults due to the absence of vaccination warrants careful monitoring and surveillance of infection risk and disease severity from newer and emergent variants.

Keywords: COVID-19; India; Infection; SARS-CoV-2

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Introduction

People below 18 years of age comprise nearly 34% of the Indian population [1], but prior to the emergence of newer variants of concern accounted for <5% of the total burden of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infections [2]. Global evidence is indicative of children and adolescents having less susceptibility to SARS-CoV-2 infection than adults, with much lower rates of severe coronavirus disease 2019 (COVID-19) [3,4]. A retrospective analysis of mortality data from the state of Odisha in India with a population of approximately 43 million reported only 36 COVID-19-related child deaths through August 2021 [5]. Furthermore, a small fraction of the pediatric population experiences the persistence of symptoms beyond several weeks post-recovery, signifying the need to contain transmission [6].

Worldwide seroprevalence studies in the general population have reported comparable infection rates between children and adults despite the lower incidence of confirmed cases in the former, signifying the asymptomatic or mild course of illness in children that may frequently go undetected [7,8]. However, the transmission dynamics of the virus in children are unclear, for which reason repeated cross-sectional serosurveys in the same geographic area may provide crucial insights into the spread of infection in this group [3,9]. Furthermore, COVID-19 vaccination coverage in the under-18 age group in most lower-middle-income countries is low, rendering them more vulnerable to infection and disease [10]. The objective of this study was to assess changes in SARS-CoV-2 immunoglobulin G (IgG) seroprevalence among children and adolescents from January 2021 to October 2021.

Materials and Methods

This was a repeated cross-sectional analysis of 5- to 17-year-old participants from 2 SARS-CoV-2 seroprevalence surveys conducted in Delhi, India during January 2021 and September to October 2021. Both serosurveys were conducted in the general population aged ≥ 5 years and had an identical sample size (approximately 28,000), sampling methodology and laboratory procedures [11]. The time intervals represent the period before and after the second wave of the COVID-19 pandemic in Delhi, India, which was predominantly caused by the SARS-CoV-2 Delta (B.1.617.2) variant.

Delhi is a city and union territory of India with a population of roughly 19 million distributed across 11 districts and 280 wards with 5 major types of residential settlements, comprising planned colonies, urban slums, resettlement colonies, unauthorized colonies, and rural areas [12]. Each ward has a median population of approximately 70,000.

A total of 4,286 participants aged between 5 to 17 years were included in the September to October serosurvey round. This sample size was adequate considering an expected seroprevalence of 53%, as in the January 2021 round [11], with 95% confidence levels, 2% absolute precision, a design effect of 1.5, and a 20% non-response rate. Two-stage sampling was used. Within each ward, a line-list of settlements was made, and each settlement was classified as 1 of the 5 types: (1) planned colonies, (2) resettlement colonies, (3) urban slums/JJ clusters, (4) unauthorized colonies, and (5) villages. Next, the proportion of population belonging to each settlement type for every ward was tentatively estimated. One hundred participants were then selected from each ward, stratified according to the settlement type, with the probability proportional to the (settlement type) population size estimated in the previous step. The sampling areas within each ward were then selected from the line-list of available settlement types, with a preference for selecting 2 areas per settlement type using the simple random sampling method. Within each selected sampling area, households were selected through systematic random sampling. Finally, from each household, a single participant was selected using the age-order procedure, wherein all the eligible members were listed in ascending order of their ages, with subsequent application of the lottery method.

Data in the January 2021 round were collected on paper, while in the September to October 2021 round, data were collected electronically using a customized Android tablet application. The data collection for each of these rapid serosurveys lasted 12 to 15 days. The field volunteers were trained in several batches through virtual (online) training sessions on the sampling strategy, selection of participants, data entry, labeling of vials, and validation rules for the generation and assignment of a unique identification number to each participant.

From each participant, 3 to 4 mL of venous blood was collected under aseptic precautions by a trained phlebotomist and transported for processing to a single designated laboratory. The VITROS assay on VITROS 3600 (Ortho Clinical Diagnostics, Raritan, NJ, USA), which is based on chemiluminescence technology, was used for the screening and detection of anti-SARS-CoV-2 IgG antibodies [13]. This assay was reported as having a specificity of 100% and a sensitivity of 90%, which meets the World Health Organization's prescribed guidelines for conducting SARS-CoV-2 serosurveys [14]. A signal to cut-off (S/CO) ratio of ≥ 1 was considered as reactive and < 1 as non-reactive. Using the current assay, the presence of SARS-CoV-2 neutralizing antibodies is strongly correlated with an S/CO ratio ≥ 4.0 [15].

Statistical Analysis

The data were analyzed using IBM SPSS ver. 25.0 (IBM Corp., Armonk, NY, USA). The seroprevalence estimates were reported as proportions with 95% confidence intervals (CIs). The adjusted seroprevalence was estimated after application of the Rogien-Gladen estimator, which allows a statistical correction based on the test assay's sensitivity and specificity using the formula, true prevalence = apparent prevalence + (specificity - 1) / (specificity + sensitivity - 1) [16].

The results were expressed as frequency and proportions for categorical variables. Continuous variables were reported as mean and standard deviation for those with a normal distribution, and as median and interquartile range for those with a non-normal distribution. The chi-square test was used to assess associations between categorical variables. A *p*-value of <0.05 was considered to indicate statistical significance.

Ethics

The study was approved by the Institutional Ethics Committee of Maulana Azad Medical College & Associated Hospitals, New Delhi (vide F.1/IEC/MAMC/85/03/2021/No428, dated 21.08.2021). We enrolled children aged <7 years after electronically obtaining parental consent, while for those aged from 7 to 17 years, both participant assent and parental consent were obtained electronically.

Results

Participant Characteristics (September to October 2021 Round)

A total of 4,286 participants were initially recruited of which blood samples were successfully processed in 4,211 cases including 2,165 males (51.4%) and 2,046 (48.6 %) females. The mean ± standard deviation age of the participants was

12.7 ± 3.4 years. The participants were enrolled from the following housing settlement types: planned colonies, 896 (23.2%); urban slums, 1,780 (46.0%); resettlement colonies, 454 (11.7%); unauthorized colonies, 211 (5.4%); and villages, 527 (13.6%) (*n* = 3,868, missing = 343).

Anti-SARS-CoV-2 IgG antibodies were detected in 3,445 participants. The crude SARS-CoV-2 IgG seroprevalence was 81.8% (95% CI, 80.9%–82.6%), and after further adjustment for assay characteristics, the seroprevalence was estimated as 90.8% (95% CI, 89.8%–91.7%).

Change in SARS-CoV-2 IgG Seroprevalence and the Predictors of Seropositivity (January to October 2021)

The seroprevalence of SARS-CoV-2 infection in the 5 to 17 years age-group increased from 52.8% in January 2021 to 81.8% in September to October 2021. The IgG seroprevalence increased from 48.4% to 75.9% in the 5 to 9 years age group, from 54.5% to 82.8% in the 10 to 14 age group, and from 52.0% to 83.8% in the 15 to 17 years age group (Table 1). In the adjusted analysis, older (15–17 years) adolescents had significantly higher odds of infection (adjusted odds ratio, 1.6; 95% CI, 1.4–1.9) than younger children (5–9 years), but no statistically significant association was observed with participants' sex (Table 2). Residence in slums and resettlement colonies was independently associated with higher seropositivity in January 2021, but not during the September to October 2021 round (Table 3).

Distribution of the Signal to Cut-Off Ratio in the Seropositive Participants (September to October 2021)

The median (interquartile range) S/CO ratio in the SARS-CoV-2 seropositive (IgG) subgroup was 6.7 (3.5–10.8). A S/CO ≥ 4.00 was observed in 58% (*n* = 4,211) participants and in 70.8% of the seropositive (IgG) subgroup (*n* = 3,445). Among

Table 1. Trends of IgG SARS-CoV-2 seroprevalence among children in Delhi (January to October 2021)

Variable	Sample size	Crude seroprevalence (%) (95% CI)	After assay adjustment (%) (95% CI) ^{a)}
5–9 y			
January 2021	701	48.4 (44.6–52.1)	53.7 (49.6–57.8)
October 2021	823	75.9 (72.9–78.7)	84.3 (81.0–87.5)
10–14 y			
January 2021	1,757	54.5 (52.2–56.9)	60.6 (58.0–63.2)
October 2021	1,836	82.8 (81.0–84.4)	92.0 (90.0–93.8)
15–17 y			
January 2021	1,879	52.0 (49.7–54.3)	57.8 (55.2–60.3)
October 2021	1,552	83.8 (81.8–85.5)	93.1 (90.9–95.0)

IgG, immunoglobulin G; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; CI, confidence interval.

^{a)}On crude seroprevalence.

Table 2. Factors associated with SARS-CoV-2 seropositivity (September to October 2021)

Variable	n (%)	IgG seropositive (%)	Adjusted odds ratio (95% CI)	p-value
Age (y) (n = 4,211)				< 0.001
5–11	1,493 (35.5)	1,164 (78.0)	1	
12–17	2,718 (64.5)	2,281 (83.9)	1.5 (1.2–1.7)	
Sex (n = 4,211)				0.18
Male	2,165 (51.4)	1,765 (81.5)	1	
Female	2,046 (48.6)	1,680 (82.1)	1.1 (0.9–1.3)	
Settlement type (n = 3,868)				0.33
Slum/resettlement	2,234 (57.8)	1,814 (81.2)	0.92 (0.9–1.1)	
Planned/unauthorized/village	1,634 (42.2)	1,345 (82.3)	1	
Diagnosed with COVID-19 (n = 3,865)				0.90
Yes	822 (21.3)	674 (82.0)	1 (0.8–1.2)	
No	3,043 (78.7)	2,482 (81.6)	1	

SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; IgG, immunoglobulin G; CI, confidence interval; COVID-19, coronavirus disease 2019.

Table 3. Factors associated with SARS-CoV-2 seropositivity (January 2021)

Variable	n (%) (n = 4,338)	IgG seropositive (%)	Adjusted odds ratio (95% CI)	p-value
Age (y)				0.03
5–11	1,312 (30.2)	656 (50.0)	1	
12–17	3,026 (69.8)	1,618 (53.5)	1.1 (1.0–1.3)	
Sex				0.049
Male	2,091 (48.2)	1,064 (50.9)	1	
Female	2,247 (51.8)	1,210 (53.9)	1.1 (1.0–1.3)	
Settlement type				0.08
Slum/resettlement	1,736 (40.0)	938 (54.0)	1.1 (1.0–1.3)	
Planned/authorized/village	2,602 (60.0)	1,336 (51.3)	1	
Diagnosed with COVID-19				< 0.001
Yes	102 (2.4)	77 (75.5)	-	
No (n = 4,301) ^{a)}	4,199 (97.6)	2,175 (51.8)		

SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; IgG, immunoglobulin G; CI, confidence interval; COVID-19, coronavirus disease 2019; -, not included in the regression (adjusted model).

^{a)}37 Values were missing.

the SARS-CoV-2 seropositive (IgG) participants, there was a statistically significant difference in the S/CO ratio between school going adolescents (12–17 years) and younger children (5–11 years; $p < 0.001$), but not between male and female participants ($p = 0.114$) (Table 4).

Discussion

The present study shows that approximately 4 out of 5 children and adolescents aged below 18 years had evidence of past exposure to SARS-CoV-2 infection, which, after adjustment for the tests' imperfections, was estimated to correspond to a true seroprevalence of over 90% [11]. The high percentage of seroconversion among unvaccinated children and adolescents in this study indicates the

presence of natural infection-induced immunity from past exposure to SARS-CoV-2. In comparison, the SARS-CoV-2 IgG seroprevalence in the adult population in Delhi increased from 50.3% (95% CI, 49.7%–51.0%) in January 2021 to 91% (95% CI, 90.6%–91.4%) in September to October 2021 (Figure 1) due to natural infection, COVID-19 vaccination, or hybrid immunity [11,17].

The nationwide serosurveys conducted by the Indian Council of Medical Research also reported the SARS-CoV-2 seroprevalence to have increased from 27.2% (95% CI, 24.9%–29.4%) in December 2020 to 60.1% (95% CI, 59%–61.1%) in July 2021 in the 10–17 and 6–17 age groups, respectively [7,18]. The increased seroprevalence in Delhi was probably due to the severe impact of the second wave of the COVID-19 pandemic in Delhi; this wave caused over 0.73 million cases,

Table 4. IgG SARS-CoV-2 seroprevalence and S/CO ratio in children, September to October 2021

Age group (y)	Male (n = 1,765)		Female (n = 1,680)		Total (n = 3,445) ^{a)}	
	S/CO ≥4	S/CO	S/CO ≥4	S/CO	S/CO ≥4	S/CO
5–11	383 (66.0)	6.4 ± 3.9	410 (70.2)	6.8 ± 3.9	793 (68.1)	6.6 ± 3.9
12–17	843 (71.1)	7.7 ± 4.7	807 (73.6)	7.9 ± 4.7	1,650 (72.3)	7.8 ± 4.7

Data are presented as n (%) or mean ± standard deviation.

IgG, immunoglobulin G; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; S/CO, signal to cut-off.

^{a)}IgG seropositive only.

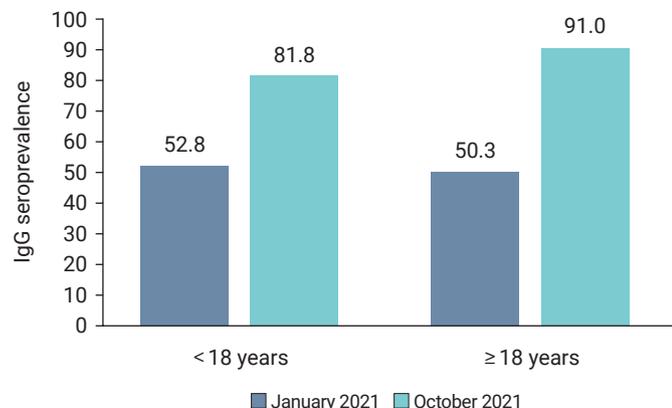


Figure 1. Comparison of immunoglobulin G (IgG) seroprevalence in under-18 and adult participants.

including 11,075 deaths [19]. A similar large increase in SARS-CoV-2 seropositivity was reported in the aftermath of the Delta wave among children in England [20].

In this study, higher seroprevalence in those with a history of laboratory-confirmed COVID-19 was not observed. However, only 2.4% of the participants had a known history of COVID-19, a finding which agrees with previous studies suggestive of a significantly higher frequency of asymptomatic infections and undertesting in children than in adults [21,22]. A population-based study in Geneva also observed lower seroprevalence rates among younger (6–9 years old) children [23]. Moreover, in this study, high rates of seroconversion were observed in multiple pediatric age groups, a finding also reported in German and Danish studies [4,24]. However, a large cohort study in Canada observed that younger children were more likely than older children to transmit SARS-CoV-2 infection to other household members, suggestive of divergent dynamics of disease transmission [25].

The present study has the following key implications. The high percentage of seroconversion among children and adolescents indicates the presence of natural infection-induced immunity from past exposure to SARS-CoV-2. Although variants of concern, especially Omicron, can

potentially bypass this immune response and cause reinfection and incident disease, the possibility of severe disease needing hospitalization is likely to remain low [26]. Careful monitoring and surveillance are needed to detect any possible effect of the absence of hybrid immunity because of a lack of vaccination in children compared to adults on their overall risk of infection and disease severity from newer and emergent variants. Nevertheless, evidence for prioritizing the vaccination of children at the expense of unvaccinated adult populations nationally and globally is lacking, since seroprevalence in children is comparable to that in adults.

Certain limitations of this study should be noted. First, the field volunteers did not adhere to the guideline for recording details of non-responding households in the data collection application, for which reason there was no audit trail for non-response estimates. We tentatively estimated the non-response rate to be <20% based on the feedback provided by the field volunteers and experiences from the previous rounds of the serosurveys. Most population-based seroprevalence studies in India have also reported high non-response rates, especially in the pediatric age group [17,27]. In this study, major reasons for non-response were parental concerns, fear of pain during blood sample collection, and the perceived lack of individual benefit. Nevertheless, considering the high seroprevalence, the non-response bias is unlikely to have significantly impacted the results of this study.

Second, the sex distribution of the 5 to 17 years age-group population according to the 2011 census estimates for Delhi is approximately 54% males and 46% females, compared to 51.4% and 48.6% in the study sample. Considering the observation of slightly higher seroprevalence in females than in males, the absence of adjustment for sex weights would have slightly underestimated the true seroprevalence of SARS-CoV-2 in the pediatric population. Third, SARS-CoV-2 neutralizing antibodies were screened in only a subset (approximately 10%) of the participants, and the correlation observed with the S/CO ratio was then generalized to the complete sample as an indirect predictor of immunological

protection [15]. Fourth, there is growing recognition of the waning of anti-SARS-CoV-2 IgG antibodies, which may reduce the seroprevalence levels but may not necessarily have a detrimental impact on immune protection against reinfection because of existing cell media immunity and immunological memory [28,29]. Fifth, we were unable to estimate the durability of antibody levels because of the lack of prospective follow-up of the study participants.

In conclusion, nearly 9 in 10 children and adolescents in Delhi had IgG antibodies against SARS-CoV-2, with high proportions of seroconversion observed across multiple age-group groups and both sexes. Future studies should assess the real-world effectiveness of COVID-19 vaccines authorized for pediatric groups in preventing symptomatic infection, inhibiting disease transmission, protecting against severe disease, and avoiding long-COVID symptoms.

Notes

Ethics Approval

The study was approved by the Institutional Ethics Committee, Maulana Azad Medical College & Associated Hospitals, New Delhi (vide F.1/IEC/MAMC/85/03/2021/No428 dated 21.08.2021).

Conflicts of Interest

The authors have no conflicts of interest to declare.

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Availability of Data

The data that support the findings of this study are available from the corresponding author upon reasonable request.

Authors' Contributions

Conceptualization: all authors; Data curation: SM; Formal analysis: SB; Investigation: PS; Methodology: all authors; Project administration: PS, SM; Resources: MMS; Supervision: PS, MMS; Validation: PS, MMS; Writing-original draft: SB; Writing-review & editing: all authors.

Additional Contributions

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Transmission parameters of coronavirus disease 2019 in South Asian countries

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ABSTRACT

Objectives: This study aimed to estimate the transmission parameters, effective reproduction number, epidemic peak, and future exposure of coronavirus disease 2019 (COVID-19) in South Asian countries.

Methods: A susceptible-exposed-infected-recovered-death (SEIRD) model programmed with MATLAB was developed for this purpose. Data were collected (till June 28, 2021) from the official webpage of World Health Organization, along with the Center for Systems Science and Engineering at Johns Hopkins University. The model was simulated to measure the primary transmission parameters. The reproduction number was measured using the next-generating matrix method.

Results: The primary transmission rate followed an exponential Gaussian process regression. India showed the highest transmission rate (0.037) and Bhutan the lowest (0.023). The simulated epidemic peaks matched the reported peaks, thereby validating the SEIRD model. The simulation was carried out up to December 31, 2020 using the reported data till June 9, 2020.

Conclusion: The information gathered in this research will be helpful for authorities to prevent the transmission of COVID-19 in the subsequent wave or in the future.

Keywords: Compartmental model; COVID-19; Epidemic peak; Next generating matrix; Reproduction number; South Asia

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Introduction

South Asia consists of 8 countries: India, Bangladesh, Pakistan, Afghanistan, Nepal, Bhutan, Maldives, and Sri Lanka. This is the world most densely populated geographical region, where almost one-fourth of the world's population lives. Since its emergence in Wuhan in December 2019, coronavirus disease 2019 (COVID-19) has spread to 219 countries and territories in the world [1]. As of June 28, 2021, the world had 180,817,269 confirmed cases and 3,923,238 deaths. Similar to Europe and America, South Asian countries are also experiencing a continued

COVID-19 outbreak, especially in India, Pakistan, and Bangladesh. Hence, COVID-19 has become a significant health concern for the region. Among the South Asian countries, the first COVID-19 confirmed case was found in Nepal on January 23, 2020 [1]. Afghanistan detected the first confirmed case on March 24, 2020. By June 28, 2021, the highest number of cumulative confirmed cases (30,316,897) had been recorded in India and the lowest number of cases (2,062) in Bhutan. The highest recovery rate from COVID-19 cases was found in Bhutan (99.94%), with 1 death, whereas in Afghanistan, 62,288 patients had recovered out of 115,751 confirmed COVID-19 cases [2]. The recovery rate of all countries has been above 95%, with the exception of Afghanistan (93%). On March 13, 2020, India reported the first death from COVID-19 among all South Asian Association for Regional Cooperation (SAARC) countries. In total, 7,750 deaths were recorded in India as of June 9, 2020, corresponding to the highest rate of all SAARC countries. The highest case fatality rate was found in Afghanistan (6.5%), followed by Pakistan (2.4%) and Bangladesh (1.7%).

The above statistics indicate that India was at high risk for COVID-19, in terms of the total number of confirmed cases, followed by Pakistan, Bangladesh, and Afghanistan, whereas the other 4 countries might be considered safe from COVID-19. A detailed study on the transmission rate and early reproduction number is necessary to understand the situation better. Estimating the transmission parameter is required to predict future transmission, the peak of the epidemic, and the impact of the government's action. Researchers have focused on the transmissibility of COVID-19 in China, Japan, Europe, and America, while less attention has been given to South Asian countries. However, the poor health facilities, high population density, and poor literacy rate of developing countries underscore the importance of studying disease transmission in these areas. Hence, detailed research on the transmissibility and probable future of the disease in this region is necessary to investigate the current scenario and potential danger.

Mathematical modeling [3–7] plays a crucial role in estimating the transmission, reproduction number, and prediction of infectious diseases. A few studies have focused on the interactions of individual behavior [5] and social distancing [6] with disease spread, while others have concentrated on disease control by manipulating the numerical values of social distancing parameters [7]. The effective reproduction number (R_e), which is a crucial parameter to measure the transmissibility of the disease, defines the number of secondary cases produced by 1 infected individual from the total population of the region [8]. When $R_e > 1$, the number of active infected cases will increase; hence, there will be an

epidemic. The disease will be endemic when $R_e = 1$, while $R_e < 1$ indicates a decline in the number of cases, meaning that there is no possibility of an epidemic.

On January 23, 2020, the WHO estimated the reproduction rate of COVID-19 as between 1.4 and 2.5. Later Liu et al. [9] reported the mean and median estimates of R_0 to be 3.29 and 2.79 in their review of 12 published papers. A review of 50 published articles by Rahman et al. [10] found that the mean basic reproduction number was 2.71 and the median was 2.73, with an interquartile range (IQR) of 1.73 and a range of 0.32 to 6.47, in countries including Italy, Iran, South Korea, Singapore, Japan, Israel, Algeria, Brazil, and China. In the Middle East, the estimated R_0 was found to be 2.60 to 7.41, with a mean of 3.76, a median value of 3.51, and an IQR of 1.16 from a susceptible-infected-recovered model [11]. Using an exponential growth rate and a time-dependent method, the real-time effective reproduction number of COVID-19 in Italy (3.27), France (6.32), Spain (5.08), and Germany (6.07) were estimated by Yuan et al. [12]. Zhuang et al. [13] assessed the basic reproduction number in Italy (2.6 or 3.3) and South Korea (2.6 or 3.2) using a stochastic model for different starting date. Epidemiological modeling was used to estimate the basic reproduction number in China [14] as 6.47, Japan [15] as 2.50 (before voluntary event cancellation) or 1.88 (after voluntary event cancellation), and Italy [16]. The variation in previous research is not surprising as the transmission of COVID-19 depends upon environmental factors, countries' control measures, people's behavior, hospital facilities, social distancing [17], and preventive measures [18]. The impact of social distancing on COVID-19 transmission in South Korea has been studied [17]. Preventive measures are crucial to prevent and control the rapid spread of COVID-19 [18].

To the best of the authors' knowledge, there is limited research on the comparison of the transmissibility of COVID-19 in the South Asian region till date. In this situation, it is necessary to conduct a comparative analysis of the transmissibility of COVID-19 in this region. Towards that direction, this paper presents an analysis using a detailed compartmental modeling approach to investigate the transmissibility of COVID-19 in South Asia. A susceptible-exposed-infected-recovered-death (SEIRD) model was developed for this purpose. The effective reproduction number, infection rate, cure rate, and death rate of COVID-19 in all 8 countries of the South Asian region were evaluated using the developed model.

Although most of the papers found in the literature used a constant transmission rate, this study modeled transmissibility as a dynamic phenomenon. The model described in this paper considered most compartments

from susceptibility to recovery or death. Moreover, this model integrated a machine learning algorithm with the compartmental model, enabling the simulation results to closely mirror the reported data.

Materials and Methods

Data Collection

The WHO [19] and Center for Systems Science and Engineering at Johns Hopkins University [1] were the main sources of data used in this study. We collected data from those sources and used them in our model after matching them with each other. The data collection period was from the date of the first infection to June 28, 2021. Data on confirmed (infected), cured, and death cases of the first wave were used for the simulation.

Development of the SEIRD Model

According to our model, we divided the population (N) of a particular country into 5 compartments: susceptible (S , vulnerable to COVID-19 infection), exposed (E , latent individual or asymptomatic infectious), infected (I , symptomatic infected), recovered (R , immune to COVID-19), and death (D , death due to COVID-19). The details of the SEIRD model are described below.

$$(1) \quad \frac{dS}{dt} = -\frac{1}{N}(\beta_1 IS) - \frac{1}{N}(\beta_2 ES)$$

$$(2) \quad \frac{dE}{dt} = \frac{1}{N}(\beta_1 IS) + \frac{1}{N}(\beta_2 ES) - \alpha E$$

$$(3) \quad \frac{dI}{dt} = \alpha E - \gamma I - \lambda I$$

$$(4) \quad \frac{dR}{dt} = \gamma I$$

$$(5) \quad \frac{dD}{dt} = \lambda I.$$

During the pandemic, we considered the total population of each particular region as constant, leading to the equation $N=S+E+I+R+D$ at each time t . The infectivity parameters, β_1 and β_2 , control the rate of transmission. In this model, β_1 represents the probability of infection per exposure when a susceptible individual (S) has contact with an infected person (I) and becomes a latent exposed individual (E), while β_2 represents the potential rate per exposure when a susceptible individual (S) has mutual contact with an exposed individual (E) and transmits it to another exposed individual (E). A detailed diagram is shown in Figure 1. Since the probability of contact between susceptible and exposed individuals is higher than that between susceptible and infected individuals, we assume that $\beta_2 = 5\beta_1$ [15]. The incubation rate, α , is the rate of latent individuals becoming infectious (the average duration of incubation is $1/\alpha$).

In the development of the model, a number of assumptions were considered, as summarized below.

- Births and natural deaths (excluding deaths due to COVID-19) during the epidemic were not considered.
- This paper did not consider external influences, such as weather, herd immunity, or vaccination, on the outbreak.
- During the forecast period, mobility, behavior, and social distancing are considered to evolve in the same manner as from the first date of infection to June 9, 2020.

Numerical Model

Once the transmission parameters were estimated, we calculated the infection, cure, and death rate using the iterative technique explained below.

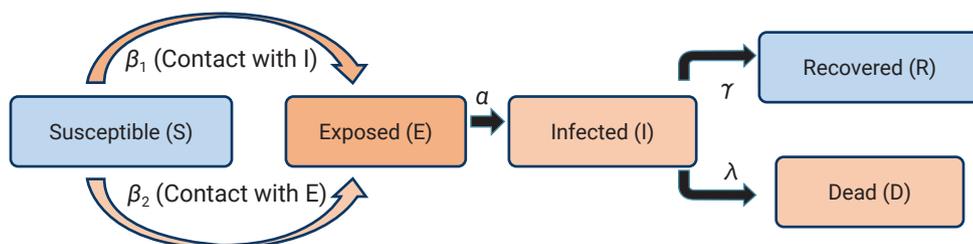


Figure 1. Schematic of the susceptible-exposed-infected-recovered-death model.

Considering $\dot{x}(t) = \frac{dx(t)}{dt}$, equation (1 to 5) can be rewritten in a matrix form as follows:

$$(6) \quad \begin{bmatrix} \dot{E} \\ \dot{I} \end{bmatrix} = \begin{bmatrix} -\frac{1}{N}IS & -\frac{1}{N}ES & 0 & 0 & 0 \\ \frac{1}{N}IS & \frac{1}{N}ES & -E & 0 & 0 \\ 0 & 0 & E & -I & -I \\ 0 & 0 & 0 & I & 0 \\ 0 & 0 & 0 & 0 & I \end{bmatrix} \begin{bmatrix} \beta_1 \\ \beta_2 \\ \alpha \\ \gamma \\ \lambda \end{bmatrix},$$

which can be further written in a simple form

$$(7) \quad \dot{x}(t) = A(t) \times \Theta(t)$$

where, $x = [E \ I]^T, \Theta = [\beta_1(t) \ \beta_2(t) \ \alpha \ \gamma \ \lambda]^T$.

Discretizing the time variable as $t = n \Delta t$, we derived the following form of $\dot{x}(t)$ using Euler's forward difference scheme.

$$(8) \quad X(t+1) = \Delta t \dot{x}(t) + X(t)$$

where, $X(t) = [S(t) \ E(t) \ I(t) \ C(t) \ D(t)]^T, \Delta t$ is the time step, and n is a natural number. Combining equation (7) and equation (8), we obtained

$$(9) \quad X(t+1) = \Delta t [A(t) \times \Theta(t)] + X(t)$$

The infection, cure, and death rates were calculated using equation (9).

Effective Reproduction Number

We used the next-generating matrix method to calculate the effective reproduction number [20], as explained below:

Consider $X_1(E, I)$ to be the group of exposed and infected individuals and $X_2(S, R, D)$ to be the group of susceptible, recovered, and dead individuals.

Let $f(X_1, X_2)$ and $v(X_1, X_2)$ be the vectors for new infection parameters and other parameters, respectively. Assuming $N \approx S$, then,

$$f(X, Y) = \begin{bmatrix} \beta_1 I + \beta_2 E \\ 0 \end{bmatrix} \text{ and } v(X, Y) = \begin{bmatrix} \alpha E \\ -\alpha E + \gamma + \lambda \end{bmatrix}$$

$$F = \frac{df}{dx} = \begin{bmatrix} \beta_2 & \beta_1 \\ 0 & 0 \end{bmatrix} \text{ and } V = \frac{dv}{dx} = \begin{bmatrix} \alpha & 0 \\ -\alpha & \gamma + \lambda \end{bmatrix}$$

$$FV^{-1} = \begin{bmatrix} \beta_2 & \beta_1 \\ 0 & 0 \end{bmatrix} \begin{bmatrix} \frac{1}{\alpha} & 0 \\ \frac{1}{\gamma + \lambda} & \frac{1}{\gamma + \lambda} \end{bmatrix} = \begin{bmatrix} \frac{\beta_2}{\alpha} + \frac{\beta_1}{\gamma + \lambda} & \frac{\beta_1}{\gamma + \lambda} \\ 0 & 0 \end{bmatrix}$$

The maximum eigenvalue of FV^{-1} is $R_0 = \frac{\beta_2}{\alpha} + \frac{\beta_1}{\gamma + \lambda}$. Hence, the expression of R_0 is $\frac{\beta_2}{\alpha} + \frac{\beta_1}{\gamma + \lambda}$.

Parameter Estimation and Model Calibration

Parameter estimation is the most crucial part of the SEIRD model. To estimate the parameters, we used publicly available reported data from the first day of infection for a particular country up to June 9, 2020 during the first phase. The transmission rate parameters β_1 and β_2 depend on government actions such as lockdown, shutdown, social distancing, and migration, which change considerably during the pandemic. Considering β_1 and β_2 as constant, thus, would call into question the accuracy of the model. The death and recovery rates γ and λ are considered constant as they depend on the population's immunity, health facilities, and management of the country, which do not change substantially within a certain time. We used the reported values of $I(t), E(t), R(t), \text{ and } D(t)$ in the SEIRD model and carried out a regression analysis to determine the value of $\beta_1(t)$.

The regression analysis was carried out using linear regression [21], different support vector machine (SVM) models, and Gaussian process regression (GPR). The root mean square error, R-squared (R^2), and plot residual (Figure 2) indicated that the exponential GPR was best fitted for the primary transmission rate in Bangladesh. Figure 2 illustrates the primary transmission rate (SEIRD model) fit results with regression through the robust linear, fine Gaussian SVM, quadratic Gaussian SVM, and exponential GPR methods. The blue dotted line represents the result of the SEIRD model, while the red line shows the result of the regression methods. The regression results for South Asian countries obtained using the exponential GPR are shown in Figure 3. The blue dotted line represents the result of the SEIRD model, while the red line shows the result of the regression methods. Figures 4 and 5, which present the probability distribution and boxplot of the primary transmission rate. Figure 5 implies that India had the highest disease transmission rate among the South Asian countries, followed by Nepal, Bangladesh, and Afghanistan. The transmission rate of Pakistan and Maldives were almost the same. The lowest transmission rate was found in Bhutan and Sri Lanka. The mean (from a normal probability distribution) and median (from a boxplot) of the primary transmission rate are summarized in Table 1.

Results and Discussion

Figure 6 shows the time evolution of the effective reproduction number in the 8 countries of the South Asian region. In each

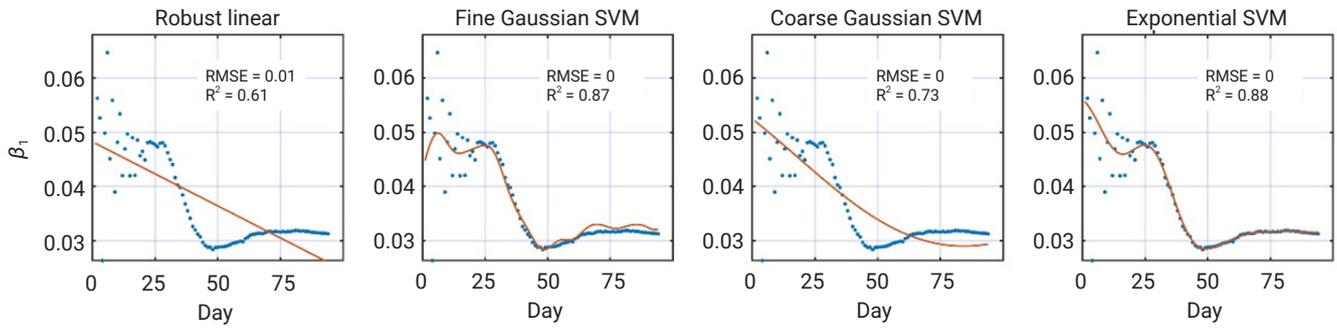


Figure 2. Primary transmission rate through regression models (red line) and susceptible-exposed-infected-recovered-death data (blue dots). The date when the first coronavirus disease 2019 case is diagnosed is considered day one for the respective country. SVM, support vector machine; RMSE, root mean squared error; R^2 , R-squared.

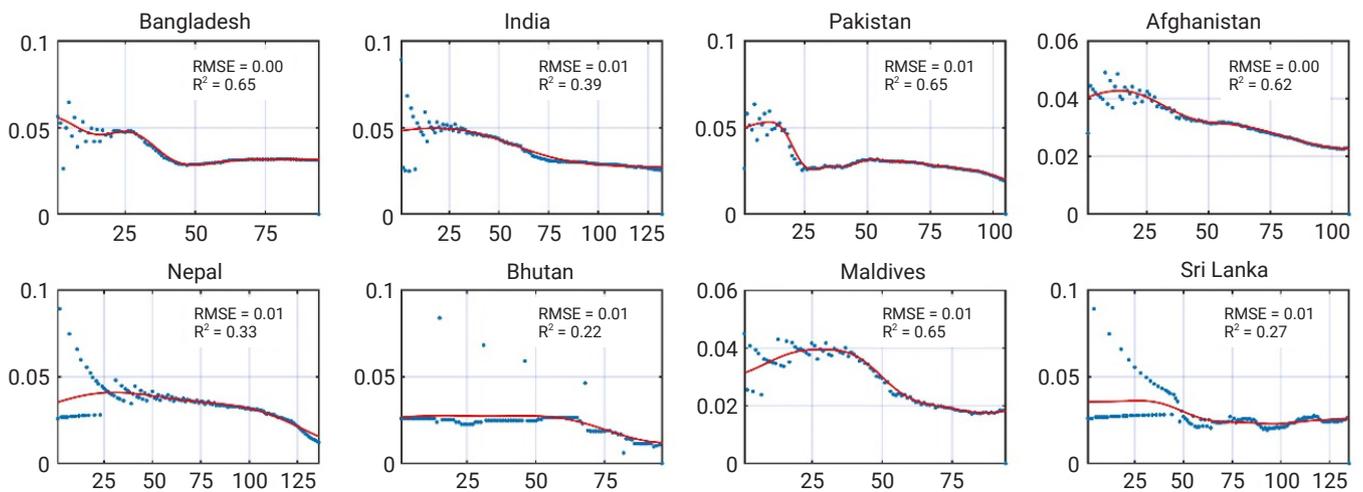


Figure 3. Regression analysis of the primary transmission rate. RSME, root squared mean error; R^2 , R-squared. X: day of the epidemic (considering the first detected case as day 1 for respective countries), Y: primary transmission rate.

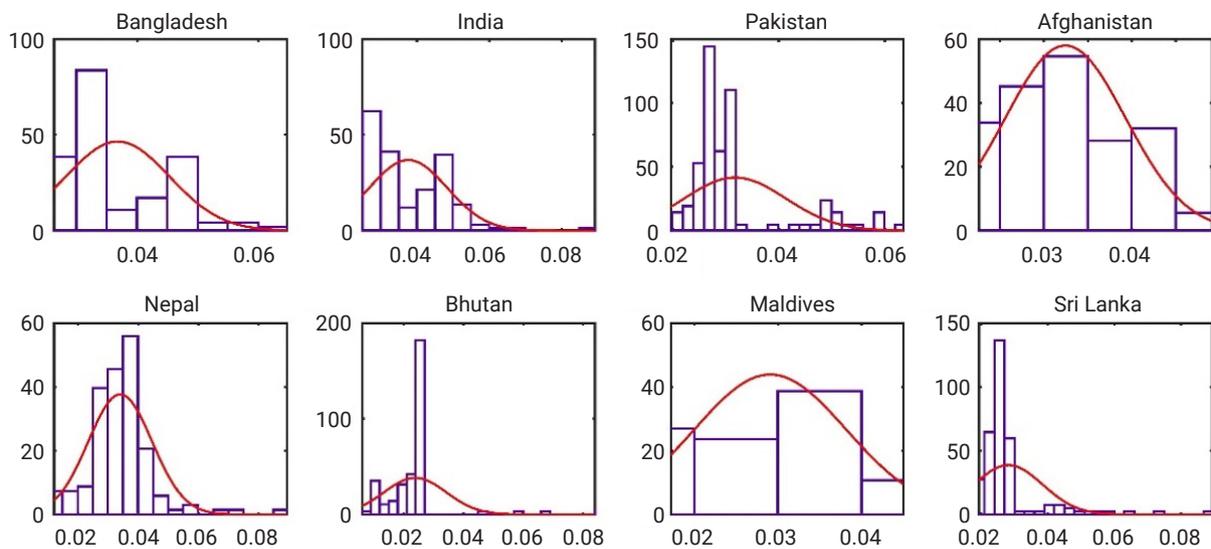


Figure 4. Probability distribution of the primary transmission rate (from the susceptible-exposed-infected-recovered-death model). X: primary transmission rate, Y: frequency.

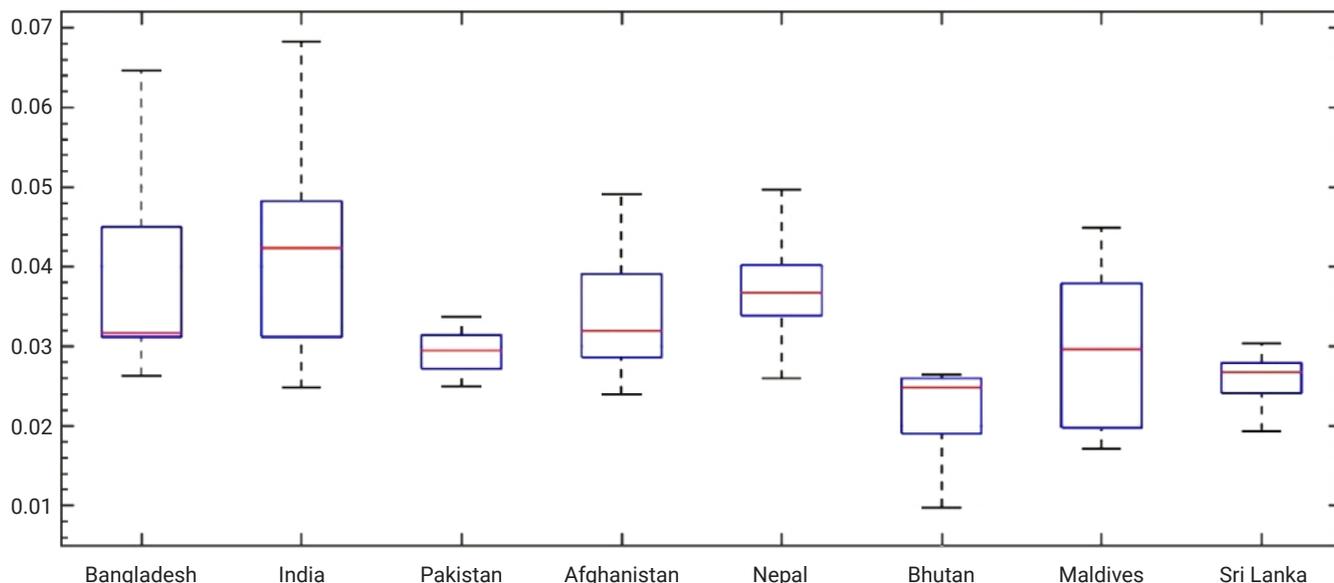


Figure 5. Boxplot of the primary transmission rate in different South Asian countries (from the susceptible-exposed-infected-recovered-death model).

Table 1. Transmission, death, and cure rates and the basic reproduction number (until June 9, 2020)

Country	β_1 (mean)	β_1 (median)	Γ	λ ($\times 10^{-3}$)	R_0 (mean with 95% confidence interval) ^{a)}
Bangladesh	0.036	0.032	0.018	1.15	3.14 ± 0.09
India	0.037	0.033	0.046	2.65	2.08 ± 0.13
Pakistan	0.032	0.029	0.031	1.95	2.08 ± 0.16
Afghanistan	0.033	0.032	0.007	1	5.28 ± 0.16
Nepal	0.029	0.034	0.006	0.16	5.63 ± 0.62
Bhutan	0.023	0.025	0.009	0	3.51 ± 0.31
Maldives	0.029	0.030	0.030	0.25	1.97 ± 0.14
Sri Lanka	0.028	0.026	0.033	0.55	1.83 ± 0.26

^{a)}Mean \pm standard deviation.

graph, the reproduction number is plotted along Y-axis and the day along the X-axis. The estimated reproduction numbers (mean values) with 95% confidence intervals are shown in Table 1. The boxplot of the effective reproduction number of different countries is shown in Figure 7. Figures 8–15 show the simulation results (with 95% confidence intervals) and reported data, respectively. Reported data are plotted with the red dotted line while, the blue line represents the simulation results, and the shaded region indicates the 95% confidence interval of the simulation data. From Figures 8–15, almost all the reported data lie within the 95% confidence interval of the simulation data. This clearly demonstrates our SEIRD model's potential to accurately estimate the disease parameters and severity of the outbreak.

Among the South Asian countries, Sri Lanka showed

the lowest reproduction number (1.83 ± 0.26), followed by Maldives (1.97 ± 0.14). In contrast, the highest reproduction number was found in Nepal (5.63 ± 0.62), followed by Afghanistan (5.28 ± 0.16). The reproduction number of Bangladesh was (3.14 ± 0.09), which was slightly higher than that of India (2.08 ± 0.13) and Pakistan (2.08 ± 0.16). Surprisingly, despite having the lowest number of infected cases, Bhutan showed a higher reproduction number (3.51 ± 0.3) than that of other countries, except for Nepal and Afghanistan. The reason for this inconsistency is the low cure rate of the country (0.009). Similarly, although the cumulative number of infected cases was lower in Nepal than in Bangladesh, India, Pakistan, and Afghanistan, Nepal had the highest reproduction number. This is also due to the low cure rate of the country (0.006).

As shown in Figure 6, at the earlier stage of the epidemic,

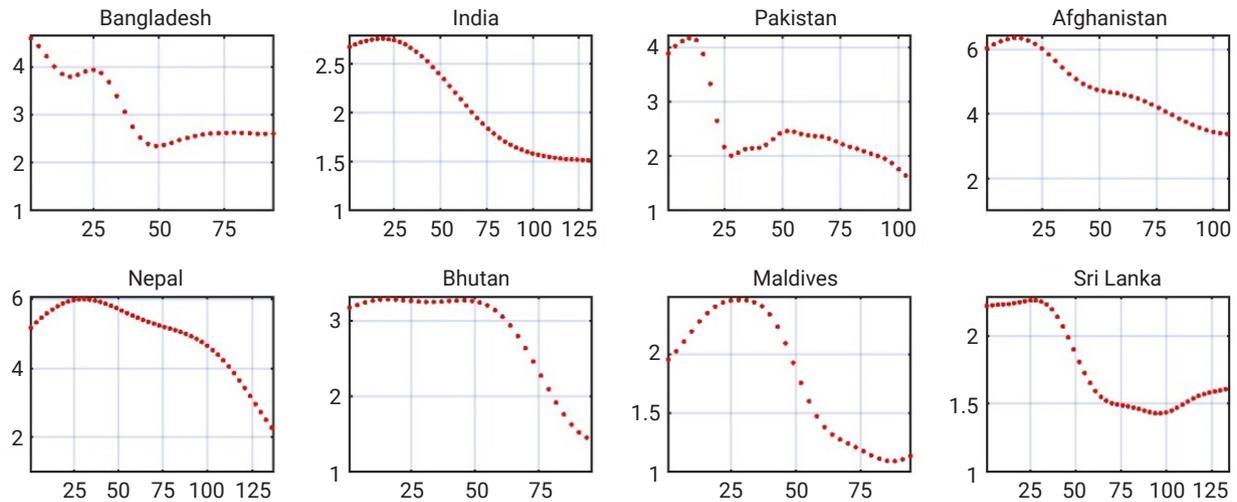


Figure 6. Coronavirus disease 2019 effective reproduction rates in different South Asian countries (susceptible-exposed-infected-recovered-death model). X: day of the epidemic (considering the first detected case as day 1 for respective countries), Y: R_e .

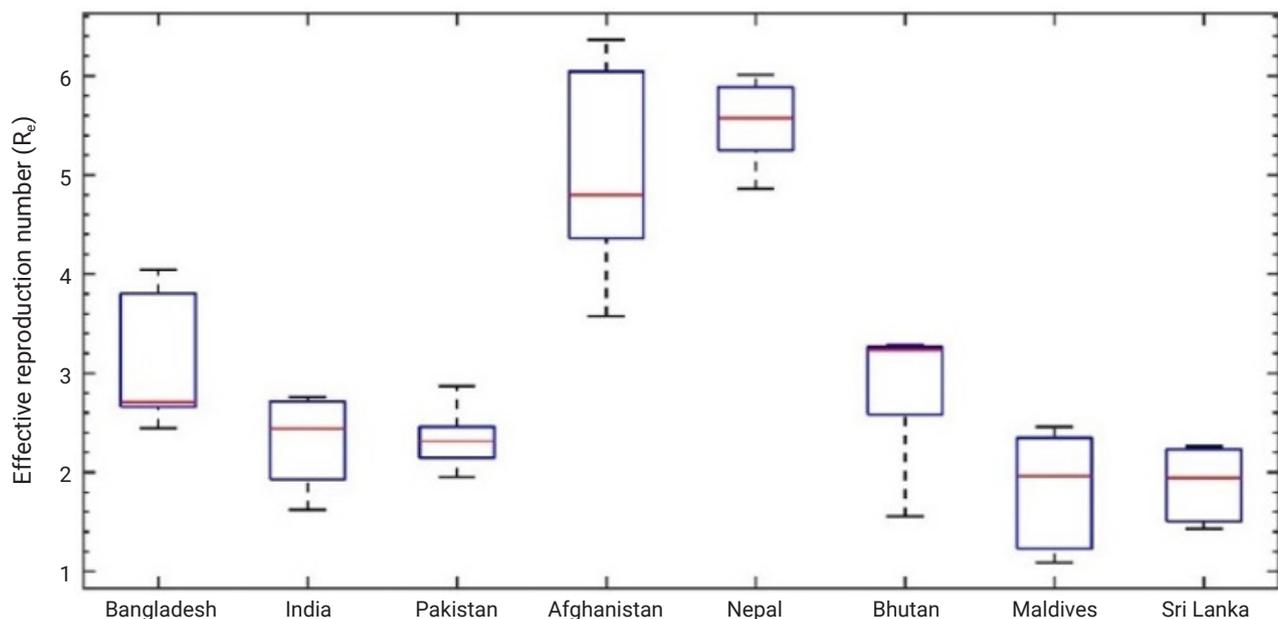


Figure 7. Boxplot of the effective reproduction number in different South Asian countries (from the susceptible-exposed-infected-recovered-death model).

all countries experienced a higher reproduction number; however, a significant decline was noticed later. Government actions to control the outbreak, reduction of population mobility, and public awareness were primarily responsible for this decline. Bangladesh showed a gradual increase during 50 days after the first infection and a stable reproduction number later. Starting 125 days after the first infection, India experienced a decreasing pattern of the reproduction number. The effective reproduction number of Pakistan was above 4 in the first few days of the outbreak, which declined

to 2 by 25 days. The number again increased after 25 days, plateaued, and then decreased again. Afghanistan started with a reproduction number above 6, which then steadily decreased. Similarly, Nepal started with a high value of the reproduction number, and then showed a decreasing curve from approximately day 25 to 125. Initially, the reproduction number of Bhutan was fairly stable. However, it started declining after roughly 50 days of the outbreak. Maldives experienced an early increase and a significant decay after almost 30 days. A stable reproduction number was shown

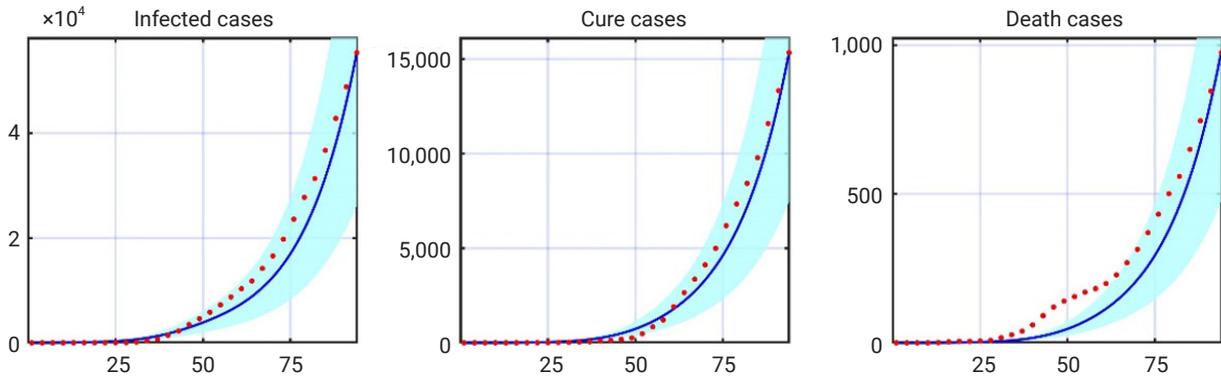


Figure 8. Comparison of reported data with simulation results for Bangladesh. Blue solid line: simulation, red dotted line: reported data, shaded area: 95% confidence interval of the simulation data. X: day of the epidemic (considering the first detected case as day 1), Y: number of cases.

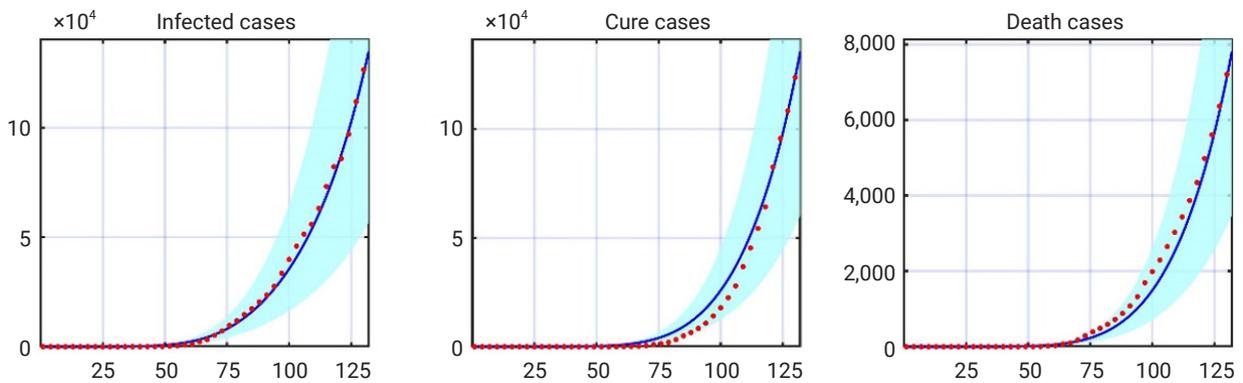


Figure 9. Comparison of reported data with simulation results for India. Blue solid line: simulation, red dotted line: reported data, shaded area: 95% confidence interval of the simulation data. X: day of the epidemic (considering the first detected case as day 1), Y: number of cases.

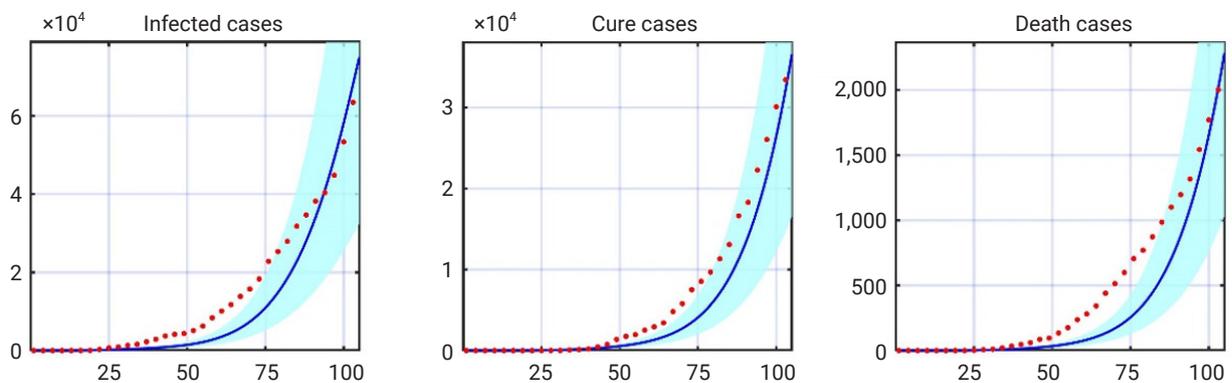


Figure 10. Comparison of reported data with simulation results for Pakistan. Blue solid line: simulation, red dotted line: reported data, shaded area: 95% confidence interval of the simulation data. X: day of the epidemic (considering the first detected case as day 1), Y: number of cases.

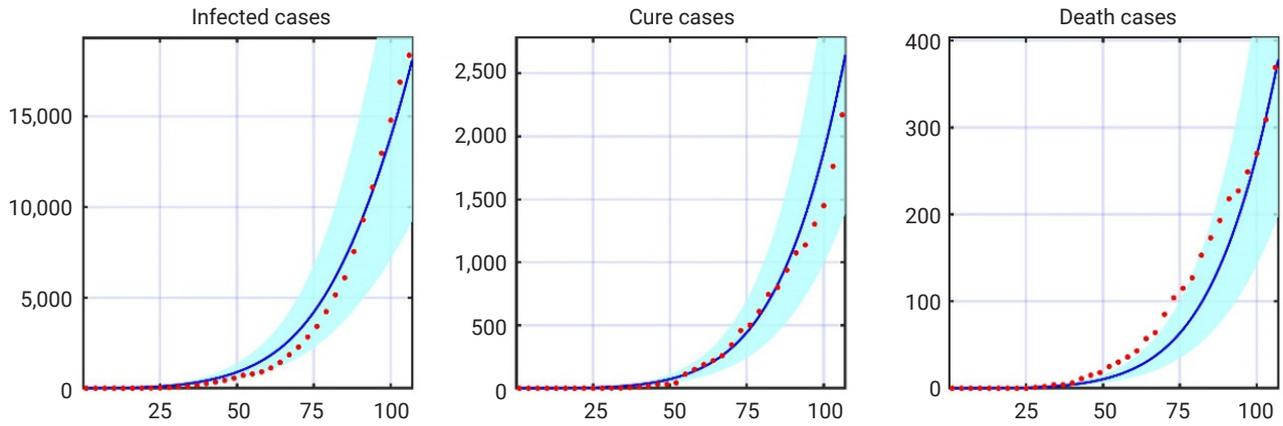


Figure 11. Comparison of reported data with simulation results for Afghanistan. Blue solid line: simulation, red dotted line: reported data, shaded area: 95% confidence interval of the simulation data. X: day of the epidemic (considering the first detected case as day 1), Y: number of cases.

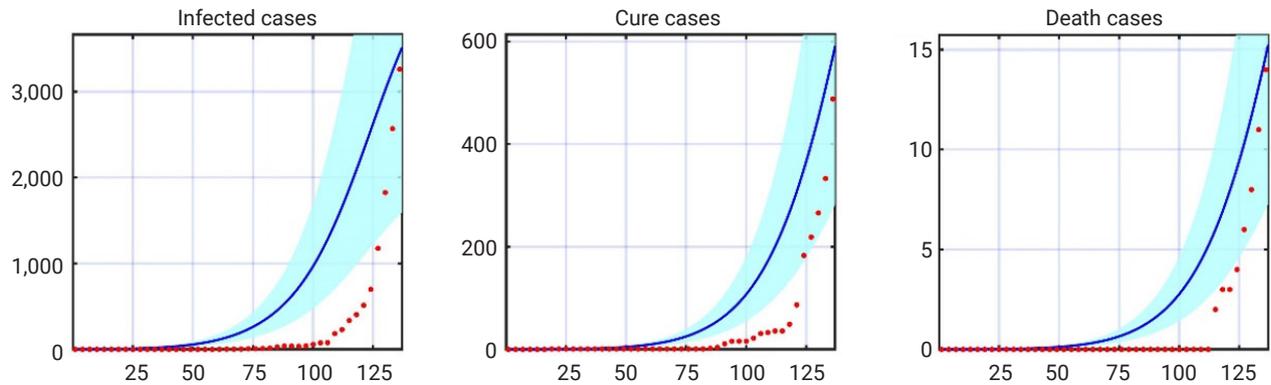


Figure 12. Comparison of reported data with simulation results for Nepal. Blue solid line: simulation, red dotted line: reported data, shaded area: 95% confidence interval of the simulation data. X: day of the epidemic (considering the first detected case as day 1), Y: number of cases.

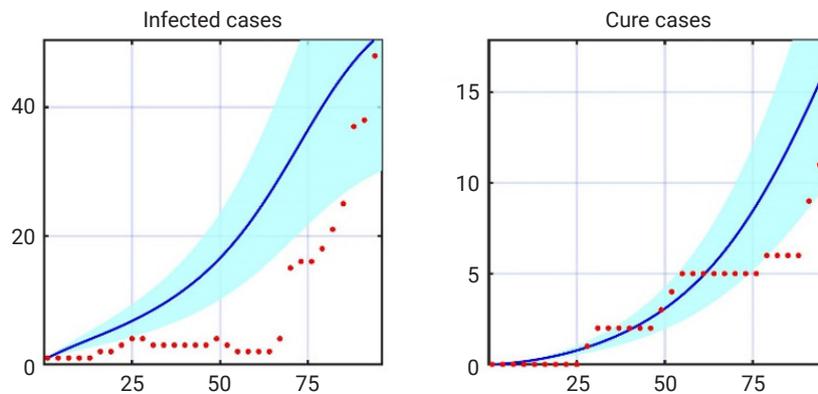


Figure 13. Comparison of reported data with simulation results for Bhutan. Blue solid line: simulation, red dotted line: reported data, shaded area: 95% confidence interval of the simulation data. X: day of the epidemic (considering the first detected case as day 1), Y: number of cases.

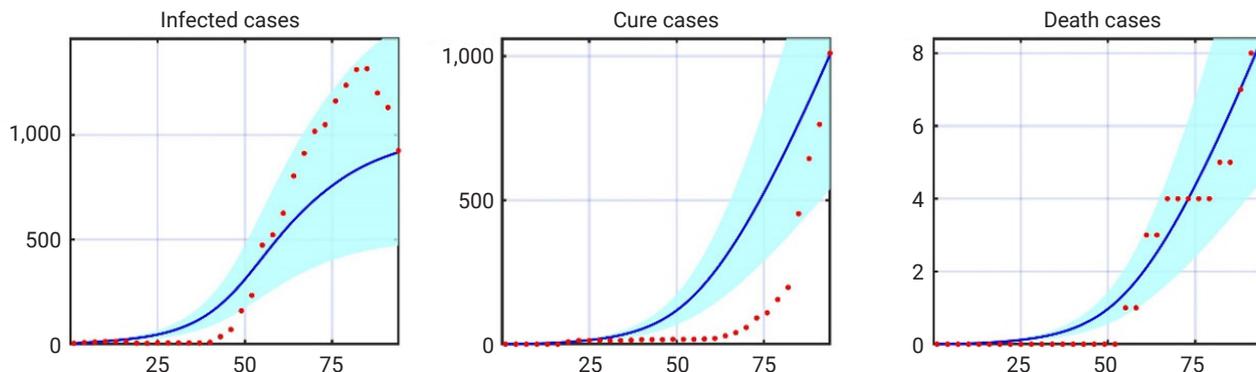


Figure 14. Comparison of reported data with simulation results for Maldives. Blue solid line: simulation, red dotted line: reported data, shaded area: 95% confidence interval of the simulation data X: day of the epidemic (considering the first detected case as day 1), Y: number of cases.

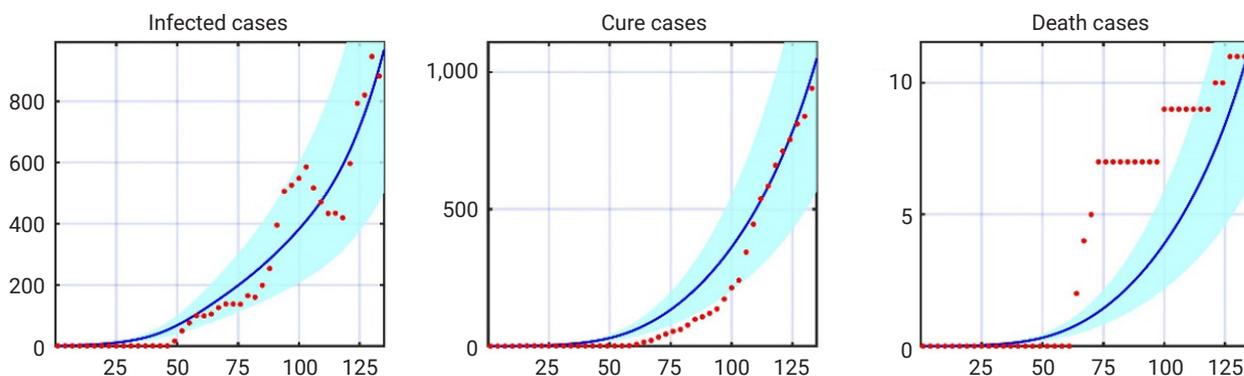


Figure 15. Comparison of reported data with simulation results for Sri Lanka. Blue solid line: simulation, red dotted line: reported data, shaded area: 95% confidence interval of the simulation data. X: day of the epidemic (considering the first detected case as day 1), Y: number of cases.

for Sri Lanka up to the first 30 days of the outbreak. Later, a notable descent was shown for up to almost 100 days, followed by a gradual increase.

Prediction of Epidemic Size and Peak Analysis

In this section, we made a forecast with early data of COVID-19 (up to December, 2020) and compared the scenario with reported data. Two main factors, the epidemic peak time (EPT) and epidemic size (ES), were considered for a comparison. The EPT was considered to be the time needed to reach the highest number of active infected cases, and the number of active infected cases at the EPT was considered the ES. The forecast for COVID-19 in South Asian countries is shown in Figure 16. The EPT and the active number of infection cases obtained from the SEIRD model and reported data are summarized in Table 2. This forecast assumed that the transmission rate would follow the same trend from the date (June 9, 2020) as in the early days of infection (of a particular country). According to the simulation, Pakistan

reached the epidemic peak after at 132 days after the first infection. For India, Bangladesh, and Afghanistan, the epidemic peaked after 164, 159, and 227 days, respectively. Bangladesh showed an epidemic peak at 163 days after the first infection in the reported data. For India, the epidemic reached its peak after 233 days, and the active number of infections started to fall since then. In Pakistan, the epidemic peak was reached at 141 days after the first infection. A gradual decline in the number of the active infected cases then occurred until early October. A probable second wave of the virus started afterward. Afghanistan showed an early epidemic peak, just 84 days after the first infection, which was much earlier than our numerical result. The country showed a significant reduction of active infected cases up to September 2020 and a minor increase in October 2020.

Conclusion

This paper presents a compartmental model for analyzing

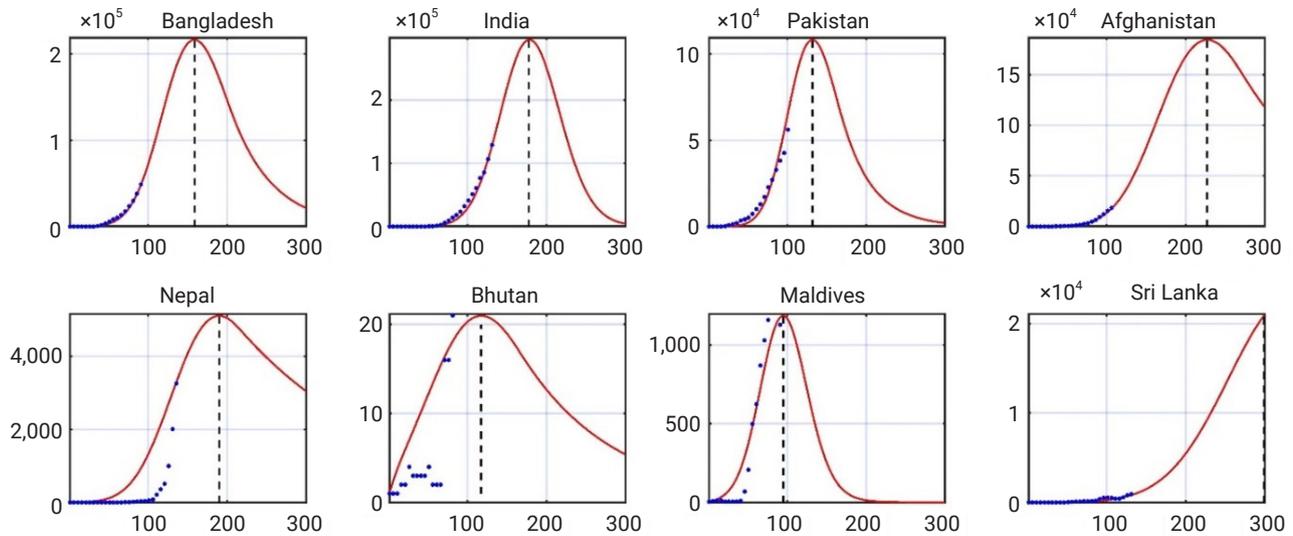


Figure 16. Infected population of different South Asian countries. Red line: simulated result, blue dotted line: reported data, black dot line: epidemic peak. X: day of the epidemic (considering the first detected case as day 1 for respective countries), Y: number of cases.

Table 2. Epidemic peak analysis (first wave)

Country	EPT (SEIRD)	EPT (reported)	ES (simulation)	ES (reported)
Bangladesh	159	165	216,886	115,572
India	178	233	296,301	1,018,454
Pakistan	132	129	108,459	108,466
Afghanistan	114	84	184,780	20,311
Nepal	191	158	5,113	10,341
Bhutan	117	102	20	45
Maldives	95	86	1,187	1,389
Sri Lanka	335	325	23,598	7,247

EPT, epidemic peak time; SEIRD, susceptible-exposed-infected-recovered-death; ES, epidemic size.

the current trend and predicting the epidemic peak and ES for South Asian countries. The results from the simulation showed a good fit with the reported data. Though the predictions of stochastic models are critical for practical purposes, the predictions of the EPT were quite close to the reported peaks. The highest transmission rate was found in India, while the second-highest was in Bangladesh. From the simulation results, countries like India, Bangladesh, Pakistan, and Afghanistan were at serious risk of COVID-19 during the first phase of the pandemic. While disease transmission was relatively low in Maldives and Sri Lanka, however, it is apparent that the cure rate in that region was much lower than elsewhere in the world.

Limitations and Future Recommendations

The current model used in this research considered 5 compartments: susceptibility, exposure, infection, recovery,

and death. Including other compartments, such as quarantine, hospitalization, and intensive care, might enhance the model and research outcomes. Initially, some countries lacked test facilities, COVID-19 dedicated hospitals, and COVID-19 specialists. These factors were not considered in the study. Furthermore, including government actions might also improve the model. This study only considered data from the first wave, and there is scope for further research using data from the second and third waves for some countries.

Notes

Ethics Approval

We did not collect or publish any data relevant to human or animal bodies. We used data from the World Health Organization. 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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Availability of Data

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

Authors' Contributions

Mridul Sannyal who was a student of Shahjalal University of Science and Technology, developed the detail model and MATLAB code, performed the analysis, and prepared the final manuscript. Abul Mukid Mohammad Mukadess who is a Professor of Shahjalal University of Science and Technology, designed the study, developed the conceptual and mathematical model, and prepared the manuscript's first draft.

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Changes in the pattern and disease burden of acute respiratory viral infections before and during the COVID-19 pandemic

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ABSTRACT

Objectives: We conducted a comparative analysis of the differences in the incidence of 8 acute respiratory viruses and the changes in their patterns before and during the coronavirus disease 2019 (COVID-19) pandemic.

Methods: Three sentinel surveillance systems of the Korea Disease Control and Prevention Agency and data from the Health Insurance Review and Assessment Service were analyzed. The average numbers of reported cases and the related hospital admissions and outpatient data were compared between April 2018–2019 and 2020–2021. Changes in the disease burden and medical expenditures between these 2 time periods were evaluated.

Results: During the COVID-19 pandemic, the number of reported cases of all acute respiratory viral infections, except for human bocavirus, decreased significantly. Data from the Health Insurance Review and Assessment Service also showed decreases in the actual amount of medical service usage and a marked reduction in medical expenditures.

Conclusion: Non-pharmacological interventions in response to COVID-19 showed preventive effects on the transmission of other respiratory viruses, as well as COVID-19. Although COVID-19 had a tremendous impact on society as a whole, with high social costs, there were also positive effects, such as a reduction in the incidence of acute respiratory viral infections.

Keywords: Cost of illness; COVID-19; Population surveillance; Respiratory infections

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Introduction

Since the first coronavirus disease 2019 (COVID-19) case was reported on January 20, 2020, Korea sequentially extended the crisis response level in its response against the spread of

COVID-19. It emphasized adherence to precautions for personal hygiene, including wearing a mask, and initiated society-wide measures such as social distancing. As part of these efforts, surface disinfection was also emphasized in healthcare facilities and all other areas [1]. The transmission of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2, the virus that causes COVID-19) and acute respiratory viruses occurs mainly through respiratory droplets via close contact, direct contact with infected people, or indirect contact with contaminated objects or surfaces [2]. Hence, the aforementioned preventive measures could affect the spread of both SARS-CoV-2 and other respiratory viruses, such as influenza. A major example of this effect is the early end of 2019–2020 seasonal influenza epidemic in Korea. The incidence of respiratory infections has markedly decreased compared with the pre-COVID-19 period [3–5]. In addition, the average positivity rate of the 8 acute respiratory viral infections (influenza and 7 acute respiratory infections) analyzed by the Korea Influenza and Respiratory Viruses Surveillance System (KINRESS) decreased from 54.7% and 62.0% between 2010 and 2019 to 39.1% and 38.7% in 2020, respectively [6,7]. The decrease in the direct disease burden of these 8 acute respiratory viral infections and the subsequent reduction in medical expenses were measured in this study. Although the sentinel surveillance system monitors the occurrence of these 8 acute respiratory viral infections, the reduction in the number of reported cases in the sentinel surveillance system cannot be used as a direct index of measuring medical expenditures or the disease burden due to differences between diseases in severity and the standards of medical expenses. This study aimed to compare the incidence of acute respiratory viral infections and the associated disease burdens. We comprehensively analyzed sentinel surveillance data from 3 surveillance systems: the KINRESS, Acute Respiratory Infection Surveillance System (ARI), and the Severe Acute Respiratory Infection Surveillance System (SARI) established by the Korea Disease Control and Prevention Agency (KDCA; Cheongju, Korea), as well as data on medical service utilization and expenditures from the Health Insurance Review and Assessment Service (HIRA).

Materials and Methods

Definition

The KINRESS is a surveillance system that monitors acute respiratory viral infections in outpatients visiting over 52 primary clinics designated as sentinel sites. The national surveillance of ARI involves monitoring trends in the incidence of acute respiratory infections, including

influenza, in admitted patients and outpatients of 214 hospitals with over 200 beds. The national SARI surveillance system monitors patients with severe disease admitted to 42 medical institutions of the general hospital level who meet the SARI case definition (history of fever of 38.0°C or higher and cough with symptom onset within 10 days before hospitalization). The ARI and SARI have reports on viral respiratory infections confirmed by tests conducted in hospital laboratories. Meanwhile, in the KINRESS, the Public Health and Environment Research Institute, conducts polymerase chain reaction (PCR) tests on samples collected from sentinel sites. The results are reported to the KDCA for analysis at the national level. The SARI surveillance system was originally implemented at 13 hospitals for 8 months of the year. As COVID-19 spreads, the system was expanded to 42 hospitals and has been operated throughout the year. In this study, expenditures were converted from Korean won (KRW) to US dollars (USD) with the exchange rate of 1,200 KRW for 1 USD.

Data Source

In this study, the numbers of weekly cases of the 8 acute respiratory viruses reported via these 3 surveillance systems (KINRESS, ARI, and SARI) were collected for analysis: adenovirus (ADV), human bocavirus (HBoV), human coronavirus (HCoV), human metapneumovirus (HMPV), human rhinovirus (HRV), human parainfluenza virus (HPIV), respiratory syncytial virus (RSV), and influenza virus (IFV). The data filed as the main diagnoses in the HIRA between January 2018 and April 2021 according to the date of medical service covered by national mandatory health insurance were used to calculate the number of treatment cases per infection that corresponded to the disease codes for the main diagnoses: ADV (J120, B970), HBoV (J1280, J2080, J2180), HCoV (B972), HMPV (J123, J211), HRV (J206), HPIV (J122, J204), RSV (J121, J205J J210, B974), and IFV (J09, J10, J11). Claims by pharmacies and oriental medicine clinics were excluded. Data on 7 viruses (excluding HBoV) were downloaded from the healthcare big data hub website (<https://opendata.hira.or.kr/home.do>), which is managed by the HIRA, whereas data on HBoV were provided by the HIRA.

Study Design

A retrospective, ecological study design was used to analyze changes in the incidence of various respiratory infections before and during the COVID-19 pandemic. We comprehensively analyzed sentinel surveillance data from 3 surveillance systems: KINRESS, ARI, SARI established by the Korea Centers for Disease Control and Prevention (Cheongju, Korea). The surveillance systems analyzed in this study are

at the national level, covering all 17 metropolitan cities and provinces and offering national coverage. The number of cases was defined as the number of symptomatic patients who visited the sentinel sites and were confirmed with the viral respiratory infections through PCR. The data reported from week 1 of 2018 to week 16 of 2021 were aggregated by week and used for analysis. To compare trends in viral respiratory infections from each surveillance system (KINRESS, ARI, and SARI) before and during the COVID-19 pandemic (starting on January 20, 2020), the number of average weekly cases from 2018 to 2019 (24 months) and those from January 2020 to April 23, 2021 (16 months) was compared using the independent sample t-test. The reduction rate was determined from the means of the weekly averages between the 2 time periods. The disease burden of the 8 acute respiratory viral infections was measured using the monthly average number of patients during 2018–2019 (24 months) before the COVID-19 pandemic and January 2020–April 2021 (16 months) during the COVID-19 pandemic after organizing the data, which were previously categorized by disease codes of the main diagnosis and by type of infection. The reduction in disease burden was measured using the difference in the number of patients between the pre-COVID-19 period and during the COVID-19 pandemic. Direct medical expenditures were measured as the total medical care costs, defined as the sum of health insurance coverage and copays, from the 16-month periods of January 2018 to April 2019 (16 months) and January 2020 to April 2021 (16 months).

Statistical Analysis

Statistical analyzes were conducted using Excel 2013 (Microsoft Corp., Redmond, WA, USA) and IBM SPSS ver. 28.0 (IBM Corp., Armonk, NY, USA). The independent-samples t-test was used.

IRB Approval

The requirement for informed consent was exempted by the Institutional Review Board (IRB) of the KDCA (IRB-2021-06-03-PE-A) as there was no personal information in the study.

Results

The weekly incidence and the overall pattern of the 8 acute respiratory viruses based on each surveillance system before and during the COVID-19 pandemic were analyzed. In the KINRESS, HBoV showed no differences in the COVID-19 period (5.3 weekly cases on average) from the pre-COVID-19 period (5.3 weekly cases on average) (Table 1). However, the

reports of all the other viruses decreased significantly in all surveillance systems. In the KINRESS, HPIV showed the largest decrease (97.6%), whereas HRV showed the smallest decrease (44.0%). Likewise, in the ARI, HPIV showed the largest decrease (95.2%), and HCoV showed the smallest decrease (55.4%). In the SARI, HPIV and HMPV showed the largest decreases (94.9% and 94.5%), respectively, and HBoV showed the smallest decrease (41.6%). HPIV and HMPV showed the greatest reductions in all surveillance systems, and the remaining 6 viruses showed reduced reporting rates overall.

Among the 8 acute respiratory viruses in the surveillance systems (KINRESS, ARI, and SARI), 5 (HMPV, HCoV, RSV, HPIV, and IFV) showed almost no significant seasonal increase since week 13 of 2020, which is after the start of the COVID-19 pandemic (Figure 1). However, ADV, HBoV, and HRV continued to be reported, although the numbers in the COVID-19 period had decreased compared with the pre-COVID-19 period. Before the COVID-19 pandemic, ADV had no apparent seasonal trend, although its spread tended to somewhat decrease in later winter (February to March) in 2018 and 2019, whereas the other viral pathogens displayed clear seasonal trends. The number of HRV cases tended to increase in spring and fall and somewhat decrease in summer (August 2018 and 2019) and late winter (February 2018–March 2019). The number of HMPV infection cases started increasing in spring (March), peaked in May, and lasted until early summer (July). The number of HPIV infection cases started increasing in spring (March), peaked in June, and lasted until winter (January), with a somewhat low number of cases between February and March. RSV, HCoV, and IFV showed the highest incidence during the winter (November to February), and the number of IFV infection cases increased again in the spring of 2019 (March to May), which showed the second seasonal peak of IFV. The number of HBoV infection cases tended to increase between spring and early fall (April to September).

The monthly average number of cases of these 8 viruses in Korea during the same periods showed the following results: the number of HPIV infection cases decreased by 600.6 (93.9%) from 639.6 in 2018–2019 to 39.0 in January 2020 to April 2021, showing the largest reduction, followed by HMPV cases, with a decrease of 554.1 (91.7%) from 604.3 in 2018–2019 to 50.2 in January 2020 to April 2021. The number of ADV cases decreased by 286.9 (85.2%) from 336.9 in 2018–2019 to 49.9 in January 2020 to April 2021, and the number of RSV cases decreased by 1,627.0 (75.9%) from 2,143.9 in 2018–2019 to 516.9 in January 2020 to April 2021. The number of IFV cases decreased by 74.7% from 206,252.0 in 2018–2019 to 52,103.4 in January 2020 to April 2021. The

Table 1. Numbers of the weekly reports of acute respiratory virus infections compared between the pre-COVID-19 period and during the COVID-19 pandemic by the 3 different surveillance systems in the Republic of Korea

Virus	KINRESS			ARI			SARI		
	2018–2019 (n = 104)	2020– (n = 68)	Difference (%) ^{a)}	2018–2019 (n = 104)	2020– (n = 68)	Difference (%) ^{a)}	2018–2019 (n = 72)	2020– (n = 68)	Difference (%) ^{a)}
ADV	17.2 ± 8.0	6.7 ± 5.0	60.0***	276.8 ± 114.4	38.2 ± 46.5	86.2***	17.6 ± 9.2	2.4 ± 4.4	86.5***
HBoV	5.3 ± 6.5	5.3 ± 5.0	0.4	114.2 ± 95.1	29.7 ± 20.9	74.0***	4.9 ± 4.6	2.8 ± 2.8	41.6**
HRV	38.9 ± 17.7	21.8 ± 15.5	44.0***	534.1 ± 187.3	128.0 ± 89.0	76.0***	35.6 ± 18.5	9.5 ± 8.3	73.3***
HMPV	11.4 ± 14.7	1.2 ± 3.0	89.6***	134.6 ± 179.4	11.6 ± 27.7	91.4***	12.5 ± 20.4	0.7 ± 1.8	94.5***
RSV	9.7 ± 12.5	2.7 ± 7.0	44.0***	270.4 ± 354.1	65.1 ± 176.9	75.9***	26.5 ± 26.0	4.1 ± 13.0	84.4***
HCoV	10.0 ± 12.5	2.7 ± 7.0	72.2***	110.2 ± 114.8	49.2 ± 113.9	55.4***	8.5 ± 7.8	2.0 ± 5.4	77.0***
HPIV	14.5 ± 13.2	0.4 ± 1.0	97.6***	224.9 ± 175.8	10.8 ± 22.8	95.2***	10.1 ± 8.7	0.5 ± 1.1	94.9***
IFV	35.9 ± 49.7	10.3 ± 32.7	71.3***	361.4 ± 615.5	125.3 ± 392.7	65.3**	29.5 ± 41.2	4.9 ± 15.7	83.6***

Data are presented as mean ± standard deviation. 2018–2019: before COVID-19, 2020–: during COVID-19. KINRESS, ARI 2018–2019 (n = 104; 52 weeks in each year), 2020–April 24, 2021 (n = 68; 52 weeks in 2020+16 weeks in 2021), SARI 2018–2019 (n = 72; operated for about 8 months during the influenza epidemic before the COVID-19 outbreak, no data during weeks 19–35 of 2018 and weeks 22–36 of 2019).

COVID-19, coronavirus disease 2019; KINRESS, Korea Influenza and Respiratory Viruses Surveillance System; ARI, Acute Respiratory Infection Surveillance System; SARI, Severe Acute Respiratory Infection Surveillance System; ADV, adenovirus; HBoV, human bocavirus; HRV, human rhinovirus; HMPV, metapneumovirus; RSV, respiratory syncytial virus; HCoV, human coronavirus; HPIV, parainfluenza virus; IFV, influenza virus.

^{a)} $\frac{((2018-2019)-(2020-))}{(2018-2019)} \times 100$.

p < 0.01, *p < 0.001.

numbers of HRV cases decreased by 440.6 (56.0%) from 787.2 in 2018–2019 to 346.6 in January 2020 to April 2021, the number of HBoV cases decreased by 166.4 (38.3%) from 434.5 in 2018–2019 to 268.1 in January 2020 to April 2021, and the number of HCoV cases increased by 3.6 (450.0%) from 0.8 in 2018–2019 to 4.4 in January 2020 to April 2021.

The largest reduction in admission was found for HPIV (96.6%), followed in descending order by HMPV (92.4%), ADV (87.0%), RSV (81.6%), IFV (71.9%), HCoV (55.9%), HRV (33.9%), and HBoV (13.7%). For outpatient care, the largest reduction was found for HMPV (90.4%), followed by HPIV (89.7%), ADV (81.4%), IFV (75.0%), RSV (70.3%), HBoV (52.4%), and HCoV (55.0%) (Table 2). However, the number of HCoV infection cases increased from 0.1 in 2018–2019 to 4.1 in January 2020 to April 2021, showing a 1,675.0% increase.

The direct medical expenditures for the 8 acute respiratory virus infections were 335,191,696.4 USD in 2018 to April 2019 and 83,857,157.8 USD in January 2020 to April 2021, showing a 75.0% decrease (Figure 2). Among them, IFV accounted for 89.6% of the total medical expenditures (300,402,640.8 USD) in January 2018 to April 2019 and for 89.2% of the total medical expenditures (74,822,896.7 USD) in January 2020 to April 2021. The high incidence of IFV explains why it accounted for approximately 90% of the total medical expenditures for the 8 viruses.

Discussion

This study measured the reduction in the disease burden and medical expenditures observed after the implementation of social distancing, adherence to hygiene precautions, and surface disinfection during the response to the COVID-19 pandemic. We found that acute respiratory infections decreased significantly during the response to COVID-19, whereas most acute respiratory viruses displayed clear seasonal trends before the COVID-19 pandemic [6]. Significant reductions were also found for hospital visits and the observations made by the SARI, which is a system based on admitted patients. The direct medical costs of the 8 acute respiratory virus infections also decreased from 75% to 90% depending on the viral infections, reflecting the reduced number of cases of all 8 viral infections.

A study by Jang et al. [7] on the factors determining medical expenses and length of stay for admitted patients with COVID-19 in Korea reported that the average medical cost for COVID-19 cases was 1,193.7 USD based on HIRA data. The total number of COVID-19 cases in Korea between January 2020 and April 2021 was 122,634, and the direct medical costs for COVID-19 during this time were 146,388,205.8 USD. During this time, the medical expenditures for the 8 acute

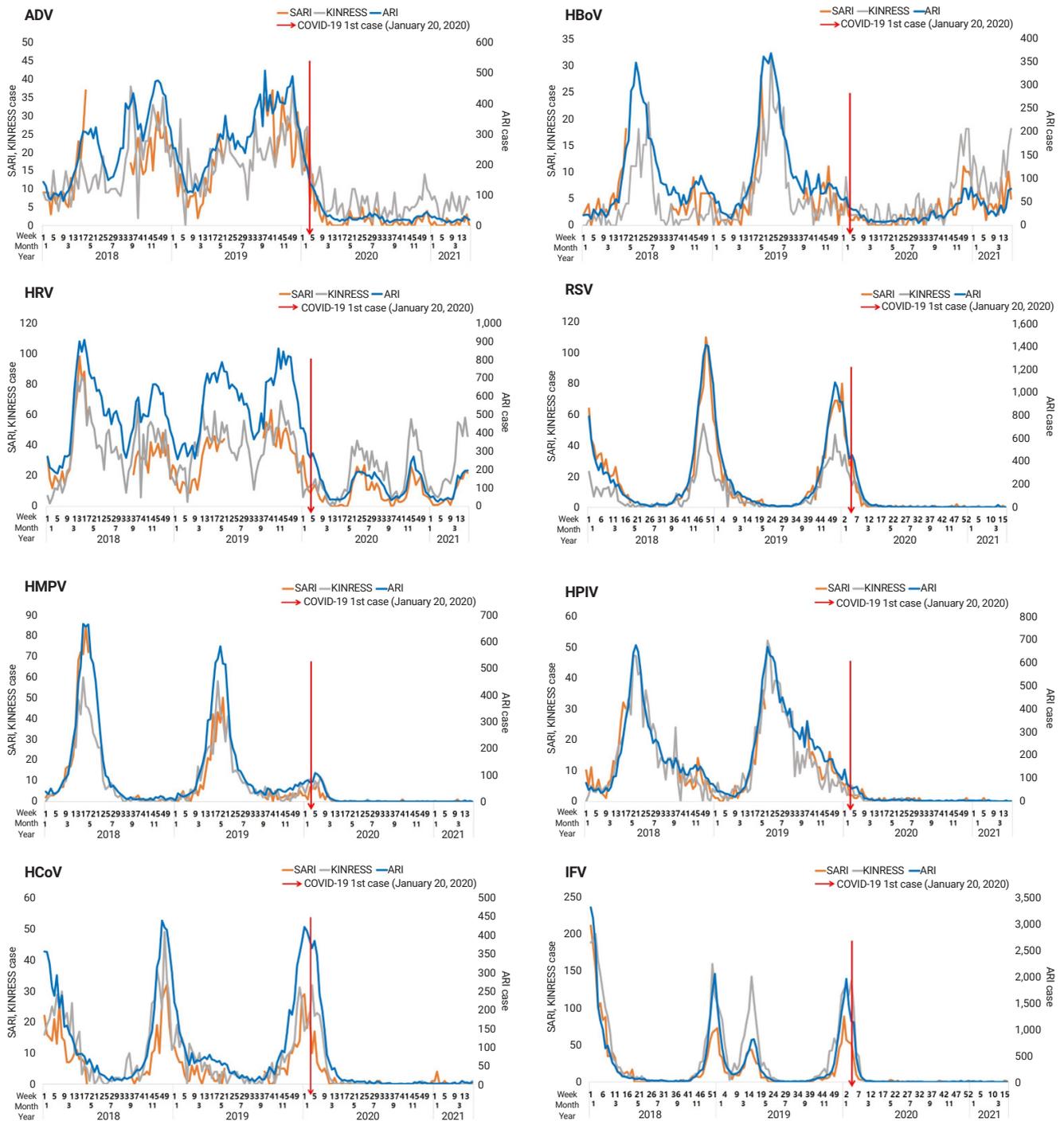


Figure 1. Weekly numbers of acute respiratory virus infections reported through 3 different surveillance systems (week 1 of 2018 to week 16 of 2021). Most of the outbreaks of acute respiratory virus infections before the coronavirus disease 2019 (COVID-19) pandemic (before week 13 of 2020) showed seasonal patterns. Infection cases of adenovirus (ADV), human bocavirus (HBov), and human rhinovirus (HRV) continued to be reported, although the number of cases decreased compared with that before the COVID-19 pandemic. Infection cases of human metapneumovirus (HMPV), human coronavirus (HCoV), respiratory syncytial virus (RSV), human parainfluenza virus (HPIV), and influenza virus (IFV) have rarely been reported since the 13th week of 2020, corresponding to the large-scale onset of the COVID-19 pandemic in Korea. Non-enveloped viruses: ADV, HBov, HRV; enveloped viruses: HMPV, HCoV, RSV, HPIV, and IFV. SARI, Severe Acute Respiratory Infection Surveillance System; KINRESS, Korea Influenza and Respiratory Viruses Surveillance System; ARI, Acute Respiratory Infection Surveillance System.

Table 2. Monthly average numbers of hospitalizations and outpatient visits for acute respiratory virus infections between the pre-COVID-19 period and during the COVID-19 pandemic

Pathogens	Total (admission+outpatient)				Admissions				Outpatient visits			
	2018–2019 Monthly average	2020– Monthly average	Difference ^{a)}	Difference ^{b)} (%)	2018–2019 Monthly average	2020– Monthly average	Difference ^{a)}	Difference ^{b)} (%)	2018–2019 Monthly average	2020– Monthly average	Difference ^{a)}	Difference ^{b)} (%)
ADV	336.9	49.9	286.9	85.2	227.6	29.6	198.0	87.0	109.3	20.3	88.9	81.4
HBoV	434.5	268.1	166.4	38.3	158.5	136.9	21.7	13.7	276.0	131.3	144.8	52.4
HRV	787.2	346.6	440.6	56.0	162.4	107.3	55.1	33.9	624.8	239.3	385.5	61.7
HMPV	604.3	50.2	554.1	91.7	386.6	29.4	357.3	92.4	217.7	20.8	196.9	90.4
RSV	2,143.9	516.9	1,627.0	75.9	1054.8	193.9	860.9	81.6	1,089.1	322.9	766.2	70.3
HCoV	0.8	4.4	-3.6	-450.0	0.7	0.3	0.4	55.9	0.3	4.4	-4.2	-1,675.0
HPIV	639.6	39	600.6	93.9	389.6	13.3	376.3	96.6	250	25.7	224.3	89.7
IFV	206,252	52,103	154,149	74.7	15,784	4,439	11,345	71.9	190,468	47,665	142,804	75.0

2018–2019: before-COVID-19, 2020–: during COVID-19. (n = 24; 12 months in each year), 2020–2021.4.24 (n = 16; 12 months in 2020+4 months in 2021). The number of infection cases of the 8 viral acute respiratory viruses was obtained according to the Health Insurance Review and Assessment Service with residential and columnar disease diagnostic codes. COVID-19, coronavirus disease 2019; ADV, adenovirus; HBoV, human bocavirus; HRV, human rhinovirus; HMPV, metapneumovirus; RSV, respiratory syncytial virus; HCoV, human coronavirus; HPIV, parainfluenza virus; IFV, influenza virus.

^{a)}Difference: absolute difference. ^{b)}Difference (%): relative change ((2018–2019)–(2020–))/(2018–2019)×100.

respiratory virus infections were 83,857,157.5 USD, and the medical expenditures for IFV infections were 74,822,896.7 USD. The direct medical costs for COVID-19 were higher than those of the other infections, which had decreased by 75% from the previous years, but were much lower than the medical expenditures from January 2018 to April 2019, including the costs for IFV infections. However, these costs for COVID-19 exclude direct costs paid by the national treasury, such as expenses for free diagnostic tests operated by public health centers; therefore, these figures do not fully represent the direct costs of COVID-19.

Outbreaks of most respiratory virus infections have markedly decreased since the onset of the COVID-19 pandemic due to intensive preventive measures such as social distancing, adherence to precautions for personal hygiene (wearing a mask and washing hands regularly), and disinfection. Among the 8 viruses analyzed in this study, 5 (HMPV, HCoV, RSV, HPIV, and IFV) had almost no associated cases. The other 3 viruses (ADV, HBoV, and HRV) continued to spread, but with fewer infections than in previous years. Our study results showed similar patterns to those reported in previous studies [8,9]. The surveillance of influenza-like illness (ILI) in Taiwan showed a rapid decrease from week 5 in 2020, after preventive measures against COVID-19 were implemented [6], and a record-low number of influenza cases was reported in February since the implementation of the national healthcare service in 1996 [6]. Wearing a mask is effective not only against COVID-19, but also against the spread of other viruses transmitted by droplets [10,11]. In a randomized controlled study, coronavirus was detected in 30% to 40% of participants who did not wear a mask, but not in those who wore a mask [10]. Although wearing a mask during the non-epidemic season did not show a statistically significant decrease in the number of acute respiratory viral infections, it was still a critical measure to reduce viral transmission during the COVID-19 pandemic [11,12].

The infection and transmission of respiratory viruses can be prevented by precautions for personal hygiene such as washing hands [13,14]. Social distancing is another way to prevent transmission of the virus by limiting the population's social contacts [15].

In line with previous studies, the reduction in the number of cases of respiratory viruses in Korea since 2020 likely occurred due to non-pharmaceutical interventions such as social distancing and adherence to precautions for personal hygiene (wearing a mask and hand sanitization) initiated due to the COVID-19 pandemic [16,17]. The precautions and preventive measures implemented to reduce the spread of COVID-19 were not only effective for COVID-19, but also for other respiratory infections. This led to a decrease in the

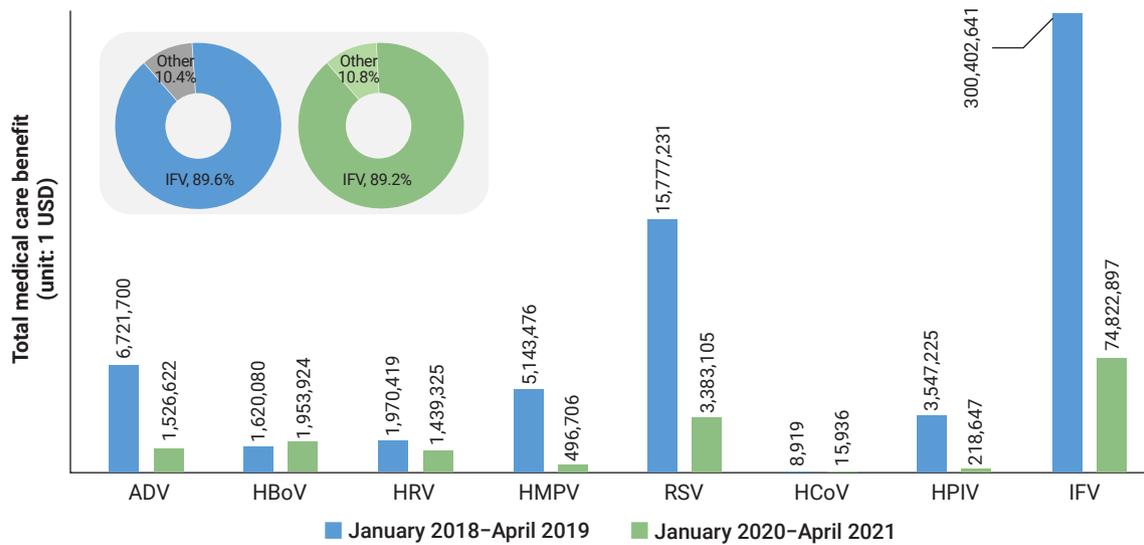


Figure 2. Medical expenses for acute respiratory virus infections between the before-COVID-19 period and during the COVID-19 pandemic (January 2018 to April 2019 vs. January 2020 to April 2021). Although there were no dramatic differences in the ratios of prevalence between the 2 time periods, the total medical costs for the 8 acute respiratory viruses decreased by 75%: adenovirus (ADV), human bocavirus (HBoV), human rhinovirus (HRV), human metapneumovirus (HMPV), human coronavirus (HCoV), respiratory syncytial virus (RSV), human parainfluenza virus (HPIV), and influenza virus (IFV). USD, US dollars; COVID-19, coronavirus disease 2019.

number of patients and a reduction in the actual disease burden (e.g., direct medical costs).

Five viruses (HCoV, HPIV, HMPV, RSV, and IFV) showed extremely low number of cases after week 13 of 2020. Of note, these are enveloped viruses. HCoV is a positive-sense single-stranded RNA virus, and the remaining 4 viruses are negative-sense single-stranded RNA viruses. They are enveloped single-stranded RNA viruses, similar to SARS-CoV-2 [18]. The 3 viruses (ADV, HBoV, and HRV) that continued to be reported even during the COVID-19 pandemic are non-enveloped viruses [19]. ADV is a non-enveloped double-stranded DNA virus [20], HBoV is a non-enveloped single-stranded DNA virus [21], and HRV is a non-enveloped single-stranded RNA virus [22].

Enveloped viruses are known to be easily inactivated by heat, dryness, detergent, and lipid solvents, unlike non-enveloped viruses [23]. Enveloped viruses are normally resistant to various environmental factors; therefore, they can survive longer in the external environment. Moreover, as they are resistant to acids and bile, they are the main cause of gastrointestinal infections [24]. Several studies have reported the inactivation of enveloped and non-enveloped viruses. Lipophilic disinfectants are mainly used to inactivate enveloped viruses, whereas glutaraldehyde or sodium hypochlorite is more effective at inactivating non-enveloped viruses [25]. The hand sanitizers widely used against COVID-19 are mainly composed of ethanol, which is

effective against SARS-CoV-2, an enveloped virus. However, they are not as effective against the non-enveloped viruses [26]. For disinfecting against enveloped viruses, the use of 0.05% to 0.1% sodium hypochlorite or grade 4-ammonium salt disinfectant for 5 minutes or longer is recommended. For non-enveloped viruses, disinfection with 0.1% sodium hypochlorite disinfectant for over 5 minutes is recommended. Furthermore, sodium hypochlorite at 6,000 ppm is needed to disinfect against ADV, a non-enveloped virus [27]. Several studies have been conducted on SARS-CoV-2, an enveloped virus, regarding its survival period and disinfection [28,29]. Of note, despite sealing the diluent bottle, leaving any disinfectant at room temperature for 30 days leads to a 50% decrease in the available chlorine content. As the disinfecting effect is the strongest shortly after production, it is desirable to use disinfectants immediately after production at the manufacturing site [30].

Although there are several ways to prevent virus transmission, the changes in the overall patterns of each virus in our study suggest the need to use different disinfectants according to the characteristics of the viruses, such as the presence or absence of an envelope. Therefore, further studies in hospital settings are required to measure the effects of different disinfectants on the spread of different respiratory viruses in healthcare facilities. Additional studies are needed on the social gains and losses that resulted from the COVID-19 pandemic in various areas. Our study results

could be adopted by other studies, as we clearly documented changes in the incidence patterns and disease burden of other viral diseases due to the COVID-19 pandemic.

This study has some limitations. First, unlike the surveillance system in which all the pathogens confirmed by diagnostic tests are reported, the main diagnosis codes from the HIRA data are filed for insurance claims and thus can be different from patients' actual diagnoses [31]. In outpatient care, patients with ILI can be reported using common diagnosis codes instead of more detailed diagnosis codes when numerous patients are treated within a short period of time. Hence, since the main diagnosis codes from the HIRA data alone cannot verify whether a specific infection has been confirmed, the frequency of a specific disease code may not represent the total incidence of that pathogen in Korea. The increase in the number of HCoV cases after the COVID-19 pandemic in outpatients reported using the main diagnosis codes could be explained by the above reason. The total costs of direct medical expenditures include health insurance coverage and copays, while excluding non-payment items. Actual medical expenditures are likely to be higher than the reported amounts, and the medical costs presented herein are very likely underestimated.

Conclusion

Non-pharmaceutical interventions implemented due to COVID-19, such as social distancing, adherence to precautions for personal hygiene, and wearing a mask, as well as intensified disinfection in various settings, had positive effects on preventing the spread of not only COVID-19, but also other respiratory infections. As a result, there were significant reductions in the direct and indirect disease burden, as well as in medical expenditures for acute respiratory viral infections.

Notes

Ethics Approval

The requirement to obtain informed consent was exempted by the Institutional Review Board (IRB) of Korea Disease Control and Prevention Agency (IRB-2021-06-03-PE-A) as there was no personal information in the study.

Conflicts of Interest

The authors have no conflicts of interest to declare.

Funding

None.

Availability of Data

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

Authors' Contributions

Conceptualization: DL, ST; Data curation: SP, CP; Formal analysis: CP; Methodology: CP, ST; Project administration: CP; Resources: CP; Visualization: CP, SP, GL; Writing—original draft: CP; Writing—review & editing: all authors.

Additional Contributions

The opinions expressed by authors contributing to this journal do not necessarily reflect the opinions of the Korea Disease Control and Prevention Agency or the institutions with which the authors are affiliated.

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Voluntary testing for COVID-19: perceptions and utilization among the inhabitants of Saudi Arabia

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ABSTRACT

Objectives: Voluntary testing (VT) plays a crucial role in the prevention and control of infectious diseases. The present study investigated the perceptions and utilization of VT services for coronavirus disease 2019 (COVID-19) among the inhabitants of Saudi Arabia.

Methods: In total, 3,510 adult participants from all provinces of Saudi Arabia were recruited via a national online survey.

Results: Of the 3,510 participants, 88.9% were aware of the testing services available to them and of those, more than half (59.5%) had used the VT services and 96.1% were satisfied with the services. Contact with a positive COVID-19 case was the top reason for accessing VT, while a lack of awareness about the availability of VT services was the top perceived limiting factor. A history of chronic health conditions, anxiety and/or depression, and previous symptoms suggestive of COVID-19 were found to be predictors of the utilization of VT services (odds ratio [OR] 1.55, 95% confidence interval [CI] 1.22–1.96; OR 1.48, 95% CI 1.16–1.88; and OR 3.31, 95% CI 2.77–3.95), respectively.

Conclusion: The awareness of voluntary COVID-19 testing services was satisfactory among the Saudi Arabian population, but can be improved. Sociodemographic and health history predictors of the utilization of VT services were identified.

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Introduction

The prevalence of coronavirus disease 2019 (COVID-19) has exceeded 250 million confirmed cases with more than 5 million deaths worldwide. By the end of March 2022, there were

>750,000 confirmed COVID-19 cases in the Kingdom of Saudi Arabia, 9,043 reported deaths, and >62 million vaccine doses administered [1].

Voluntary testing (VT) plays a pivotal role in the early detection and treatment of infectious diseases, especially those associated with stigma such as human immunodeficiency virus (HIV). Several VT models have been developed to reach individuals and family members through their providers or clinical health settings. In addition, VT has been made easy and accessible for individuals in their communities and homes by bringing VT information to people on their smartphones and by providing home-based testing [2,3]. To detect and contain COVID-19 cases within countries and regions, mass screening strategies have been developed and executed, with the details determined according to each area's risk assessment. Studies have found wide variation in the application of these strategies in several countries. Some mass testing programs were conducted to screen large percentages of the population daily, as in the United Kingdom (UK) and Iceland. In some countries, the extensive labor and material costs involved limited mass testing, whereas nations with small populations such as Estonia and Luxembourg had higher capacities for mass screening. Despite these challenges, efficient strategies were adopted in countries with large populations, such as Republic of Korea (ROK) and Singapore. For example, ROK implemented drive-through testing, walk-through testing, and mobile examinations. Aggressive testing campaigns with multiple available testing times were implemented in Singapore and Saudi Arabia [4].

The strategic healthcare objectives of the Kingdom of Saudi Arabia for the years 2018 to 2020, in line with the Vision 2030 National Transformation Program, were defined as facilitating and promoting the prevention of health risks, increasing access to care, and enhancing quality. Therefore, the National Health Information Centre created cohesive multi-sectoral electronic health (eHealth) services to enable the healthcare transformation. In response to the COVID-19 pandemic, community-wide preventive and clinical measures were implemented by the government of Saudi Arabia. Multiple online platforms and hotlines were launched to provide COVID-19 counseling services, including pre-existing and new digital health solutions such as *Sehhaty* ("My Health") and *Tetamman* ("Rest Assured"). Moreover, a GPS-enabled application named *Tawakkalna* was launched to reveal possible infections, in association with another application called *Tabaud* ("Distancing"), which alerts individuals to confirmed case contacts. The Ministry of Health call service "937" and free-of-charge COVID-19 testing have been made available to all [5]. Individuals can

easily access any of the services, including the 937 hotline, for information on COVID-19 or to book an appointment through the *Mawid* ("Appointment") service [6].

A study by Alanzi [7] reviewed the utilization of free mobile applications related to the COVID-19 outbreak in several countries, including Saudi Arabia, Italy, Singapore, the UK, the United States (US), and India and revealed that the purposes of these applications varied. Some were used to combat the spread of the virus rather than to provide health care services information to the population. Raising awareness, booking appointments, online consultations, and contact tracing were functions that were also facilitated by these applications, highlighting their importance in combating the outbreak [7].

Studies have shown that certain characteristics and predictors contributed to the utilization of COVID-19 testing services among the population. The main factors were age, sex, occupation (healthcare workers in particular), immunocompromised status, a history of chronic disease (i.e., pulmonary diseases, diabetes, congestive heart failure, liver or renal failure), a recent trip to a major metropolitan area, or contact with a laboratory-confirmed case of COVID-19 [8]. Considering the existence of various limiting factors, VT is likely to be the most effective strategy [9].

VT for COVID-19 was encouraged by the health authorities in Saudi Arabia through widely available health education channels. An accurate assessment of the population's perception and utilization of VT enables health policy decision-makers to take the actions needed to improve the outcomes of services provided in the battle against the COVID-19 pandemic. The present study investigated the perceptions and utilization of voluntary COVID-19 testing services among the adult population of Saudi Arabia and also identified the factors that hindered or favored the utilization of these services.

Materials and Methods

Study Design and Setting

A cross-sectional analysis was conducted using data collected from June 15, 2021 to July 31, 2021 on all inhabitants of Saudi Arabia. The total population of Saudi Arabia is approximately 34.8 million people.

Study Population and Sampling Method

All adult inhabitants of Saudi Arabia over age 18 years who agreed to participate were eligible for inclusion in the study. The convenience sampling method was adopted to recruit the study sample. Invitations, including the study questionnaire, were distributed on social media platforms and groups (WhatsApp, Facebook, and Twitter). The sample

size was calculated based on a total population of 34.8 million with an expected frequency of 50%, a 0.05 level of precision, and a confidence level of 99%. Although the required sample size was 666, the sample was expanded to 3,510 to minimize the potential bias attributed to the convenience sampling method.

Study Tool and Data Collection

The data were collected using a structured, pre-designed, and self-administered online questionnaire that was developed by the researchers. The questionnaire was bilingual (Arabic and English) in the languages most commonly used by the inhabitants of Saudi Arabia. The questionnaire was composed of 4 main sections: (1) Sociodemographic and health characteristics of the participants (e.g., age, sex, nationality, education level, marital status, daily activity pattern, history of chronic conditions, and COVID-19 vaccination status). (2) The participants' perceptions of VT services in Saudi Arabia as assessed by answers to questions covering his/her knowledge of these services, whether he/she had used these services, and whether he/she would recommend these services to others. (3) Reasons for using the VT services (more than one choice was allowed). (4) Reasons for not using the VT services (more than one choice was allowed).

A pilot study was conducted to test the questionnaire on 35 participants to determine the time needed to administer it and the clarity of the questions. The pilot study participants were excluded from the final study.

The questionnaire was then formulated into an electronic version in Google Forms and distributed via social media platforms (WhatsApp, Facebook, and Twitter). All subjects meeting the inclusion criteria were invited to participate.

Ethical Considerations

Ethical approval was obtained from the Scientific and Ethical Committee of Batterjee Medical College (RES-2021-0043, June 10, 2021). The respondents were informed about the nature and aim of the study. The provision of informed consent via the user interface was a mandatory prerequisite for completion of the questionnaire. Participants were able to withdraw from the study at any stage. Data were collected anonymously and confidentiality was assured.

Variables and Data Analysis

The collected data were transferred to an Excel sheet, checked for completeness, coded, and analyzed using IBM SPSS ver. 23.0 (IBM Corp., Armonk, NY, USA). Numeric variables were presented as mean \pm standard deviation, and categorical variables were presented as numbers and percentages. The participants' perceptions of the VT services in Saudi Arabia

were presented as "yes" or "no" answers. Reasons for using the VT services for COVID-19, as well as reasons that might limit the use of these services, were presented and ranked according to frequency. The binary logistic regression model was fit to the dependent (outcome) variable, namely using or not using the VT services for COVID-19, and to the other independent variables (predictors). The model was evaluated for the prediction and estimation of the outcome. For the predictors, if the *p*-value was <0.05 , and the 95% confidence interval (CI) did not include 1 for odds ratios (ORs), then this variable was statistically significant in the model and was deemed likely to predict the outcome.

Results

The present study included 3,510 participants from all provinces of Saudi Arabia with a mean age of 37.2 ± 9.4 years. Women represented 53.1% of the study sample, and 47.6% of the participants were married. Most study participants resided in a major city and 73.4% perceived their social level as moderate. Those with chronic health conditions represented 18.0% of the study group. More than three-fourths (76.1%) reported they had received a COVID-19 vaccination (Table 1).

Regarding the perception and utilization of COVID-19 VT services, it was shown that 88.9% of participants were aware of these services and 59.5% of the aware participants had used the VT services. The overwhelming majority of the participants (96.1%) were satisfied with the service and reported that they would recommend VT to others (Table 2).

Analysis of the reasons given for visiting a COVID-19 VT site showed that contact with a positive COVID-19 case, having symptoms suggestive of COVID-19, and fear of infecting intimate persons were the top 3 reasons, reported by 49.2%, 42.0%, and 37.4% of the participants, respectively.

The top reasons limiting the utilization of VT services were ranked in a descending pattern as follows: lack of awareness of the services, fear of pain during the test procedure, and fear of the health consequences if the test is positive. These reasons were reported by 49.6%, 40.4%, and 38.3% of the participants, respectively (Table 3).

Logistic regression analysis of the predictors of VT service utilization showed that women and residents of villages were less likely to utilize the VT services than men and residents of major cities (odds ratio [OR] 0.82, 95% confidence interval [CI] 0.69–0.97; and OR 0.73, 95% CI 0.60–0.91; respectively). In addition, participants with higher education levels and those with high daily social activity levels were more likely to use VT services than participants with lower education levels and low social activity levels

Table 1. Sociodemographic and health characteristics of study participants ($n = 3,510$)

Characteristic	Value
Age (y)	37.2 ± 9.4
Sex	
Male	1,645 (46.9)
Female	1,865 (53.1)
Residence	
Major city	2,945 (83.9)
Village	565 (16.1)
Nationality	
Saudi	2,817 (80.3)
Non-Saudi	693 (19.7)
Marital status	
Married	1,672 (47.6)
Unmarried	1,838 (52.4)
Perceived social level	
High	273 (7.8)
Moderate	2,576 (73.4)
Low	661 (18.8)
Accommodation	
With family or housemates	3,266 (93.0)
Alone	244 (7.0)
Education level	
High school and lower	1,168 (33.3)
College degree and higher	2,342 (66.7)
Usual daily activity	
High social engagement	1,870 (53.3)
Low social engagement	1,640 (46.7)
Chronic health condition	
Yes	632 (18.0)
No	2,878 (82.0)
History of anxiety and/or depression	
Yes	485 (13.8)
No	3,025 (86.2)
Previous symptoms suggestive of COVID-19	
Yes	1,125 (32.1)
No	2,385 (67.9)
Received COVID-19 vaccine	
Yes	2,670 (76.1)
No	840 (23.9)

Data are presented as mean ± standard deviation or n (%).
 COVID-19, coronavirus disease 2019.

Table 2. Perception and utilization of VT services for COVID-19 among inhabitants of Saudi Arabia during the COVID-19 pandemic ($n = 3,510$)

Variable	Yes	No
Awareness of the VT services ($n = 3,510$)	3,120 (88.9)	390 (11.1)
Used the VT service ($n = 3,120$)	1,855 (59.5)	1,265 (40.5)
Will recommend these services to others ($n = 1,855$)	1,783 (96.1)	72 (3.9)

Data are presented as n (%).

VT, voluntary testing; COVID-19, coronavirus disease 2019.

(OR 1.22, 95% CI 1.03–1.45; and OR 1.36, 95% CI 1.16–1.59; respectively). A history of chronic disease, anxiety and/or depression, previous symptoms suggestive of COVID-19, and receiving the COVID-19 vaccine were found to be predictors of the utilization of VT services (OR 1.55, 95% CI 1.22–1.96; OR 1.48, 95% CI 1.16–1.88; OR 3.31, 95% CI 2.77–3.95; and OR 1.62, 95% CI 1.34–1.96; respectively) (Table 4).

Discussion

VT plays a crucial role in the prevention and control of infectious diseases. Therefore, it is essential to understand the numerous limiting and motivating factors for the utilization of VT. This study assessed the perception and utilization of COVID-19 VT services among the inhabitants of Saudi Arabia.

The current study showed that most participants were aware of the availability of COVID-19 VT services. This awareness was attributed to the rapid implementation of mass health education campaigns and the availability of free VT in Saudi Arabia from the start of the pandemic [5]. This high level of awareness was compatible with a study in the US which reported a high level of engagement in various testing modalities for COVID-19 [10].

More than half of the study participants who were aware of VT services stated that they used them. These results agree with a study conducted in Saudi Arabia on mass screening that found most of the study sample had used the testing services that were made available in Saudi Arabia, whether as part of mass screening or because of contact with a COVID-19 positive case [4]. Reasons for not using VT services were attributed to the absence of suggestive symptoms, symptoms similar to other infections, and the stigma of testing positive for COVID-19 [11].

Our study showed a significantly high satisfaction rate with the VT services, which reflects the quality of the service provided. Another study conducted in Saudi Arabia to assess the satisfaction level of the population with virtual clinics found an overall satisfaction rate of 68.1%. A minority of the study sample reported interest in utilizing VT and virtual clinics

Table 3. Reasons that hinder or favor visits to the COVID-19 VT service sites during the COVID-19 pandemic among inhabitants of Saudi Arabia

Rank	Participants' perception	n (%)
Reasons for visiting COVID-19 VT service sites (n = 1,855) ^{a)}		
1	I had contact with a positive COVID-19 case	912 (49.2)
2	I had symptoms that made me concerned about my COVID-19 status	780 (42.0)
3	Fear of infecting intimate persons	694 (37.4)
4	For self-assurance before travel	377 (20.3)
5	I was advised by a friend or a family member	346 (18.7)
6	Others	95 (5.1)
Reasons that may limit use of COVID-19 VT services (n = 3,120) ^{a)}		
1	Lack of awareness	1,547 (49.6)
2	Fear of pain during the test procedure	1,260 (40.4)
3	Fear of the health consequences if I test positive	1,195 (38.3)
4	Probability of getting the infection	1,024 (32.8)
5	Expected long waiting time	906 (29.0)
6	Difficult accessibility	661 (21.2)
7	Social restrictions if positive	653 (20.9)
8	Social stigma of being positive	593 (19.0)
9	Cultural beliefs	530 (17.0)
10	Cost	332 (10.6)
11	Others	50 (1.6)

COVID-19, coronavirus disease 2019; VT, voluntary testing.

^{a)}More than 1 choice was allowed.

for travel purposes [12]. This finding is consistent with the international risk classification of the in-flight transmission of severe acute respiratory syndrome coronavirus 2 [13].

The top motivating reasons for utilization of VT services were: contact with a positive COVID-19 case, presence of symptoms suggestive of COVID-19, and fear of infecting intimate people. As a motivating reason, fear of infecting intimate people is consistent with a recent study conducted in the Western Region of Saudi Arabia that revealed higher levels of fear of COVID-19 among those living with families and flat-mates compared to those who lived alone [14].

The present study showed that lack of awareness was the most common limiting reason for not using COVID-19 VT services, similar to another study in Nigeria that revealed that many students did not utilize VT for HIV, despite fear of infection, because they were unaware of the services [15]. Our study also showed fear of pain during the test procedure was a major concern that prevented participants from using the VT services. This was supported by another study in the US that showed that the nasal swab method was too painful for some participants, who described it as invasive and refused it. Responses included "I don't want a stick rammed up my nose," and "I would drive further to get tested another way that was not the nose swab." Overall, participants suggested that a more comfortable or gentle testing method would convince more people to get tested [16].

In the current study, expected long waiting times for test results were one reason that hindered people from taking the test. This result agrees with a study in the US that found that the time frame for results was important to participants [16]. In addition, our study showed that fear of the health consequences if the test is positive was a barrier to utilizing VT services. The consequences of testing positive have been classified into 3 major categories: physiological, cognitive, and behavioral [17].

The current study also revealed that the probability of getting infected while being tested was a concern for some participants. This could be explained by the prevalent fear and feelings of being unsafe at the start of the pandemic. These fears could be overcome by the implementation of standard environmental hygiene and using personal protective equipment for infection prevention and control at testing sites [18].

The present study showed that age was not a predicting factor for the utilization of VT services, unlike a study in the US that revealed significant differences in the utilization of COVID-19 testing based on age. Furthermore, our study demonstrated that men used VT services more than women. This could be explained by the fact that men are more involved in society outside the home, bringing them in contact with people and making them more likely to worry about the probability of infection. This was similar to a study

Table 4. Logistic regression analysis of the predictors of VT service utilization among inhabitants of Saudi Arabia during the COVID-19 pandemic

Variable	COR	95% CI	p-value	AOR	95% CI	p-value
Age (y)	1.01	0.99–1.01	0.82	0.99	0.98–1.00	0.06
Sex						
Male (ref.)	1			1		
Female	0.7	0.60–0.81	<0.001*	0.82	0.69–0.97	0.019*
Residence						
Major city (ref.)	1			1		
Village	0.8	0.66–0.97	0.021*	0.73	0.60–0.91	0.004*
Nationality						
Saudi Arabia (ref.)	1			1		
Non-Saudi Arabia	1.27	0.99–1.62	0.06	1.11	0.86–1.44	0.432
Marital status						
Married (ref.)	1			1		
Unmarried	0.98	0.85–1.13	0.728	1.11	0.86–1.44	0.432
Perceived social level						
High	0.89	0.65–1.21	0.449	0.95	0.67–1.34	0.762
Moderate	0.84	0.64–1.11	0.225	1.02	0.75–1.39	0.886
Low (ref.)	1			1		
Living accommodation						
With family or housemates	0.71	0.53–0.96	0.028*	0.89	0.64–1.24	0.490
Alone (ref.)	1			1		
Education level						
High school and lower (ref.)	1			1		
College degree and higher	1.25	1.07–1.45	0.004*	1.22	1.03–1.45	0.019*
Usual daily activity						
High social engagement	1.57	1.36–1.82	<0.001*	1.36	1.16–1.59	<0.001*
Low social engagement (ref.)	1			1		
Chronic health condition						
Yes	1.77	1.45–2.16	<0.001*	1.55	1.22–1.96	<0.001*
No (ref.)	1			1		
History of anxiety and/or depression						
Yes	1.88	1.50–2.35	<0.001*	1.48	1.16–1.88	0.001*
No (ref.)	1			1		
Previous symptoms suggestive of COVID-19						
Yes	3.45	2.91–4.09	<0.001*	3.31	2.77–3.95	<0.001*
No (ref.)	1			1		
Received COVID-19 vaccine						
Yes	1.59	1.33–1.88	<0.001*	1.62	1.34–1.96	<0.001*
No (ref.)	1			1		

VT, voluntary testing; COVID-19, coronavirus disease 2019; COR, crude odds ratio; CI, confidence interval; AOR, adjusted odds ratio; ref., reference category. * $p < 0.05$.

in the US that showed a predominance of male participants in testing for COVID-19 over females [9].

Study participants who lived in a major city used the VT services more than those who lived in a village. This could be explained by the availability of multiple VT centers in major cities compared to villages. Nationality was not a predictive factor of VT for COVID-19, as the service was available and free of charge for all inhabitants of Saudi

Arabia. Marital status, living accommodations, and perceived social levels were not found to be predictors of VT service utilization in Saudi Arabia, whereas a study conducted in Ethiopia on voluntary counseling and testing for HIV showed that women who were ever married were significantly more likely to be tested for HIV than those who were never married [19]. No differences were found between social levels in the utilization of VT services, as it was free and

available for all inhabitants.

The present study demonstrated that the rate of utilizing VT services for COVID-19 was higher among participants with higher education levels compared to participants with lower education levels. This finding agreed with another study conducted in England on mass testing of asymptomatic students for COVID-19 [20]. In participants with lower levels of education, this lower utilization of testing can be attributed to a lack of knowledge about the importance of testing and a perceived low risk of COVID-19 infection. In addition, some individuals were reluctant to acknowledge that they were even at risk and demonstrated behaviors at odds with professional perspectives, such as doubting the existence of the COVID-19 pandemic and denying its dangers. As a result, these individuals failed to adopt protective behaviors including testing. The same finding was also reported in a study conducted in Ethiopia about the utilization of voluntary HIV counseling and testing services [21].

In the current study, participants with high levels of daily social engagement were more likely to use VT services. Thunstrom et al. [9] also reported high rates of testing in people who had a higher chance of spreading the infection unintentionally (super-spreaders) such as people with jobs that require social interactions or extroverts with higher social activity levels. This was likely due to concerns that they could infect their family members or others at higher risk for developing serious illness from COVID-19.

Furthermore, people with chronic health conditions were more likely to use COVID-19 VT services. This is explained by the fact that people with chronic diseases such as chronic respiratory conditions, heart disease, diabetes, and obesity have a higher risk for developing severe health consequences if infected with COVID-19 [9]; therefore, concerns about their health lead to higher utilization of VT services.

This study found that having experienced symptoms suggestive of COVID-19 was a strong predictor of the utilization of VT services. A similar study in the US, using web and mobile applications to collect survey responses on health, found that respondents who reported common symptoms suggestive of COVID-19 (per the Centers for Disease Control: fever, cough, and loss of taste/smell) were more likely to be tested than asymptomatic respondents or those with less-common symptoms such as tightness in the chest [22]. This suggests that only symptomatic individuals in the US met screening criteria for determining who received a test, potentially missing asymptomatic and mildly symptomatic individuals at high risk for infection but not eligible for testing. This could lead to unfavorable consequences. This is supported by a study conducted in

the 4 regions of Northern Italy, in which 3 regions tested only symptomatic patients who needed hospitalization. A significant increase in the mortality rate was noted in contrast to the fourth region, which applied an extensive VT strategy, resulting in a lower mortality rate and reduction in unfavorable consequences [23].

People with a history of stress and depression in our study were more likely to use the COVID-19 VT services. This might be explained by high levels of health preoccupation in this group. This result is supported by a study from Haderlein et al. [24] on the association of post-traumatic stress disorder (PTSD) with COVID-19 testing and infection in US veterans seen in Veterans Health Administration services. The study reported that veterans with PTSD were more likely to test for COVID-19, indicating increased COVID-19 health concerns and hypervigilance.

The current study found that people who received COVID-19 vaccines were more likely to use VT services. This could be because people who perceived COVID-19 as a threatening disease were more likely to accept vaccines and protective measures such as handwashing, social distancing, frequent testing, and medical counseling [25]. This is supported by a study conducted in the UK stating that the possible reasons people refused the vaccine were mistrust, misinformation, and wrong beliefs about government institutions and health services, including testing and counseling. Additionally, some may question the existence of the COVID-19 pandemic, deny its dangers, and fail to adopt protective behaviors such as COVID-19 testing and counseling [26].

Strength and Limitation

To our knowledge, the current study is one of the few research projects assessing the VT services for COVID-19 in Saudi Arabia. Investigation of the predictors of VT service utilization is a strong point in this study. However, other aspects of this study may limit generalization of the results; for instance, only people with access to the internet could participate, and the results were based on a self-response survey from participants recruited through the convenience sampling technique. These limitations were minimized by including participants from all provinces of Saudi Arabia and by enlarging the sample size.

Conclusion

Awareness of the services available for voluntary COVID-19 testing was satisfactory among the population of Saudi Arabia, but improvement is still needed. Satisfaction with the services provided was notably high. The main motivating

factor for VT was contact with a confirmed case of COVID-19. The main limiting factors for VT were lack of awareness about service availability and fear of pain during the testing procedure. The main predictors of VT service utilization among the inhabitants of Saudi Arabia were: male sex, residence in a major city, higher education level, high daily levels of social engagement, chronic health conditions, a positive history of anxiety/depression, symptoms suggestive of COVID-19, and having received the COVID-19 vaccine. Further health education campaigns are recommended to improve the utilization of VT services, especially among hesitant users, and to enhance early case detection and proper containment of infection.

Notes

Ethics Approval

This study was approved by the Institutional Review Board of Batterjee Medical College (No. RES-2021-0043) and performed in accordance with the principles of the Declaration of Helsinki. Written informed consent was obtained for publication 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: EAAA; Data curation: EAAA, AM, SA; Formal analysis: EAAA; Investigation: all authors; Methodology: EAAA, RH, SM; Project administration: EAAA; Software: EAAA, MO; Supervision: EAAA; Validation: EAAA, AA; Visualization: EAAA; Writing-original draft: all authors; Writing-review & editing: all authors.

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Epidemiological characteristics of carbapenem-resistant *Enterobacteriaceae* and carbapenem-resistant *Acinetobacter baumannii* in a tertiary referral hospital in Korea

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ABSTRACT

Objectives: This study aimed to identify the epidemiological characteristics of patients with carbapenem-resistant *Enterobacteriaceae* and *Acinetobacter baumannii* (CRE/ CRAB) isolates in a tertiary referral hospital in Korea.

Methods: We collected and analyzed data from 528 adults admitted to a tertiary referral hospital from August 1, 2018 to February 29, 2020. The CRE/CRAB isolates were confirmed as being present at the time of patients' admission or acquired during hospitalization based on their medical records. The t-test, chi-square test, or Fisher exact test and stepwise multiple logistic regression were performed.

Results: While the proportion of community-acquired CRE/CRAB was low (6%), 20% of CRE/CRAB isolates were identified in patients at the time of hospitalization. The risk of CRAB isolation was positively associated with mechanical ventilator use (odds ratio [OR], 3.52; 95% confidence interval [CI], 1.96–6.33) and total parenteral nutrition use (OR, 3.64; 95% CI, 1.87–7.08).

Conclusion: Over 20% of CRE/CRAB isolates in a tertiary referral hospital in Korea were found at the time of patients' admission. Furthermore, patients with mechanical ventilation and/or total parenteral nutrition tended to acquire CRAB more frequently. Thus, active surveillance for CRE/CRAB at the time of hospitalization is strongly required, particularly for patients who are expected to require mechanical ventilation or total parenteral nutrition.

Keywords: *Acinetobacter baumannii*; Carbapenem-resistant *Enterobacteriaceae*; Drug resistance, multiple

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Introduction

The World Health Organization declared antibiotic resistance to be 1 of 10 international health threats to human life, and pointed out problems such as the prolongation of hospital stays, the economic burden due to the use of expensive antibiotics, death, and disability [1]. For some carbapenem-resistant organisms (CROs), genes encoding carbapenemases are located in mobile genetic elements, such as plasmids or transposons; these can cause rapid transmission of resistant bacteria between patients [2,3], making them highly likely to spread from healthcare settings to the local community [4]. In Korea, carbapenem-resistant *Enterobacteriaceae* (CRE) and multidrug-resistant *Acinetobacter baumannii* are designated as infectious diseases that must be reported to health authorities by law [5]. According to the United States Centers for Disease Control and Prevention (CDC), CRE and carbapenem-resistant *Acinetobacter baumannii* (CRAB) are classified as the most urgent threats among antibiotic-resistant microorganisms, for which reason the CDC has strengthened antibiotic resistance management [6].

Several studies have investigated the epidemiological characteristics and risk factors of acquiring CROs in patients admitted to intensive care units (ICUs) and organ transplantation wards in the United States [7], those admitted to a general hospital for CRE [8]; those admitted to the Taiwan General Hospital for CRAB [9], those admitted to an acute care health hospital for carbapenem-resistant Gram-negative bacteremia in Taiwan [10]; and CRE-infected patients in acute care health hospitals in China [11]. Those studies also sought to describe the prevalence, incidence, and epidemiological characteristics of multidrug-resistant Gram-negative bacteria and CROs, including colonization and infection in ICUs, using data entered into a German infection monitoring system [12]. However, relatively few studies have been conducted in Korea; examples include a study aiming to identify risk factors for CRE colonization in patients admitted to the ICUs of general hospitals [13,14] and a study on the acquisition of carbapenem-resistant *Escherichia coli* in hospitalized patients [15]. These studies mainly targeted patients admitted to the ICU and focused on CRE. Therefore, limited information is available on the epidemiological characteristics of CROs in other hospital settings, including general wards, and other types of CROs, such as CRAB. In addition, a case of CRE acquisition in a patient who had not visited a hospital within 3 months was reported [16], and approximately 30% of cases confirmed at hospitals are found within 48 hours of hospitalization [17]. Therefore, it is necessary to understand the characteristics

of CRE/CRAB isolates, including both healthcare-acquired (HA) and community-acquired (CA) CRE/CRAB, but few studies on CA CRE/CRAB have been reported in Korea. The purpose of this study was to identify the epidemiological characteristics of patients from whom CRE/CRAB was isolated among those admitted to a tertiary referral hospital, and to conduct a comparison between CRE and CRAB isolates, and between CA and HA CRE/CRAB.

Materials and Methods

Study Design and Participants

This was a retrospective cohort study that used patients' medical records. It was conducted at Inje University Busan Baik Hospital, an 800-bed tertiary referral hospital in Busan, Republic of Korea. The participants were CRE/CRAB cases who met all the following criteria: (1) adult patients aged 19 years or older, (2) admitted to any ward, including the emergency room and ICU, from August 1, 2018 to February 29, 2020, and (3) confirmed to have CRE/CRAB either by a CRE active surveillance culture using a rectal swab or on a culture using blood or another clinical specimen. Both colonization and infection were included. In this hospital, active CRE surveillance culture is conducted only for patients admitted to the ICU, and all departments collect clinical samples when necessary for culture and antibiotic resistance tests. During the study period, only the initial hospitalization and isolate were included in cases of rehospitalization and duplicate isolations of CRE or CRAB, and only the initial isolate was included if both CRE and CRAB were isolated. In total, 65,337 patients were hospitalized during the study period, and CRE/CRAB isolation was confirmed in 528 patients (isolation rate, 0.81%).

Definition and Variables

Cases were defined following the recommendations of the Korea Disease Control and Prevention Agency based on the recommendations of the Clinical and Laboratory Standards Institute (M100-S27) [18,19]. Antimicrobial susceptibility to carbapenems was assessed using the disk diffusion method. CRE was defined based on resistance to imipenem (≤ 19 mm), meropenem (≤ 19 mm), or ertapenem (≤ 18 mm), and CRAB was defined based on resistance to imipenem (≤ 18 mm) or meropenem (≤ 14 mm). The CA group was defined as having confirmed CRE/CRAB at the time of hospitalization or within 48 hours of hospitalization, and the HA group was defined as patients transferred from a long-term care facility, regardless of the period, or in whom isolates were obtained after 48 hours of hospitalization in an acute care hospital. The variables examined in this study were general

characteristics, multidrug-resistant organism (MDRO)-related characteristics, treatment-related characteristics, and clinical outcomes, referring to the questions used in previous studies [7,11,13] on the characteristics of CRE or CRO isolation. General characteristics included sex, age, hospitalization route, history of hospitalization within 6 months, comorbidities, and the Charlson comorbidity index score (CCIS). MDRO-related characteristics included whether the MDRO was isolated before CRE/CRAB acquisition, the CRE/CRAB acquisition time, specimen source, and strain. Treatment-related characteristics included invasive procedures performed during hospitalization and invasive devices and drugs used for more than 48 hours. Status at discharge was analyzed as a clinical outcome.

Data Collection

With the help of the infection control office of the study hospital, one researcher obtained a list of patients with confirmed CRE/CRAB isolates and selected those who met the inclusion criteria. Data were collected using structured data sheets from electronic medical records, including nursing care, hospitalization-related information, prescriptions, operations, procedures, and diagnostic test results. The CCIS was calculated directly by the researcher, referring to each patient's medical record. When a history of admission to medical institutions other than the study hospital or MDRO isolation was not confirmed, we classified these variables as "unknown." Treatment-related characteristics prior to admission to the study hospital could not be collected due to a lack of information in the medical record. For every CA or HA case transferred from a long-term care facility, data collection was based on the time of hospitalization. For HA cases with CRE/CRAB confirmed after hospitalization, the data collection period was from the time of hospitalization to the date of CRE/CRAB isolation.

Data Analysis

The collected data were analyzed using IBM SPSS ver. 26.0 (IBM Corp., Armonk, NY, USA). The 2-tailed test was

performed at a significance level (α) of 0.05. Frequency and percentage, mean and standard deviation, and median and interquartile ranges were calculated for the characteristics of the study participants. The t-test, chi-square test, or Fisher exact test was performed to compare characteristics between the CRE and CRAB groups and the CA and HA groups. With significant variables from the bivariate analysis as explanatory variables, we calculated the odds ratio and its 95% confidence interval using stepwise multiple logistic regression analysis after confirming the absence of deviation from the assumption of multicollinearity using a coefficient of determination of less than 0.80 [20].

IRB/IACUC Approval

Prior to data analysis, this study was approved by the Institutional Review Board of Inje University Busan Baik Hospital (20-0114), and the requirement for written consent was waived.

Results

Characteristics of Study Participants

Among the 528 study participants, CRAB was isolated in 67.6%, and 94.1% of cases were HA. At the time of hospitalization, 20.8% of the participants had either CRE or CRAB (Table 1). Tables 2–4 show the characteristics of the study participants. Overall, 63.4% were males, their mean age was 67.7 years, 72.2% had a history of hospitalization within the last 6 months, 49.2% had been transferred from other healthcare facilities, and 50.0% had a history of diagnosed hypertension. Regarding MDRO history, 22.0% had vancomycin-resistant *Enterococcus*, followed by extended-spectrum β -lactamase-producing organisms (16.7%). The majority of CRE/CRAB isolates occurred in respiratory specimens (60.0%), and the major strains were *A. baumannii* (67.6%) and *Klebsiella* spp. (23.9%). Almost one-third (32.6%) of participants died before discharge. During hospitalization, 51.4% underwent surgery, 90.9% used a

Table 1. Distribution of CRE and CRAB isolates ($n = 528$)

Type	CRE ($n = 171$)		CRAB ($n = 357$)		Total
	At the time of hospitalization	After hospitalization	At the time of hospitalization	After hospitalization	
HA	36 (6.8)	116 (22.0)	43 (8.1)	302 (57.2)	497 (94.1)
CA	19 (3.6)	0 (0)	12 (2.3)	0 (0)	31 (5.9)
Total	55 (10.4)	116 (22.0)	55 (10.4)	302 (57.2)	528 (100.0)

Data are presented as n (%).

CRE, carbapenem-resistant *Enterobacteriaceae*; CRAB, carbapenem-resistant *Acinetobacter baumannii*; HA, healthcare-acquired; CA, community-acquired.

Table 2. Comparison of general characteristics, MDRO-related characteristics, and clinical outcome between patients with CRE and those with CRAB

Variable	Category	Total (n = 528)	CRE (n = 171)	CRAB (n = 357)	p
Sex	Male	335 (63.4)	107 (62.6)	228 (63.9)	0.773
	Female	193 (36.6)	64 (37.4)	129 (36.1)	
Age (y)		67.7 ± 14.0	68.7 ± 13.7	67.2 ± 14.1	0.251
History of hospitalization within 6 months	No	147 (27.8)	33 (19.3)	114 (30.9)	0.006
	ACH	301 (57.0)	113 (66.1)	188 (52.7)	
	LTCF	80 (15.2)	25 (14.6)	55 (15.4)	
Route of hospitalization	ACH, transfer	184 (34.8)	64 (37.4)	120 (33.6)	0.680
	LTCF, transfer	76 (14.4)	23 (13.5)	53 (14.8)	
	Community	268 (50.8)	84 (49.1)	184 (51.5)	
Comorbidities ^{a)}	Hypertension	264 (50.0)	100 (58.5)	164 (45.9)	0.007
	Diabetes mellitus	186 (35.2)	70 (40.9)	116 (32.5)	0.057
	CVD	158 (29.9)	48 (28.1)	110 (30.8)	0.520
	Cancer	140 (26.5)	49 (28.7)	91 (25.5)	0.441
	CKD	64 (12.1)	24 (14.0)	40 (11.2)	0.351
	Liver disease	52 (9.8)	23 (13.5)	29 (8.1)	0.055
	CRD	49 (9.3)	15 (8.8)	34 (9.5)	0.781
Charlson comorbidity index score		4.6 ± 2.3	4.4 ± 2.1	4.7 ± 2.4	0.281
Treatment in ICU	No	190 (36.0)	79 (46.2)	111 (31.1)	0.001
	Yes	338 (64.0)	92 (53.8)	246 (68.9)	
MDRO history ^{a)}	VRE	116 (22.0)	48 (28.1)	67 (19.0)	0.019
	MRSA	55 (10.4)	20 (11.7)	35 (9.8)	0.505
	ESBL	88 (16.7)	46 (26.9)	42 (11.8)	<0.001
	MRPA	11 (2.1)	3 (1.8)	8 (2.2)	1.000 ^{b)}
Specimen source of CRE/CRAB	Respiratory	317 (60.0)	15 (8.8)	302 (84.6)	<0.001
	Rectal swab	126 (23.9)	125 (73.1)	1 (0.3)	
	Urine	33 (6.3)	15 (8.8)	18 (5.0)	
	Blood	18 (3.4)	2 (1.2)	16 (4.5)	
	Others	34 (6.4)	14 (8.2)	20 (5.6)	
Strain of CRE/CRAB ^{a)}	<i>Acinetobacter baumannii</i>	357 (67.6)	0 (0)	357 (100.0)	<0.001
	<i>Klebsiella</i> spp.	126 (23.9)	126 (100.0)	0 (0)	<0.001
	<i>Escherichia coli</i>	36 (6.8)	36 (21.1)	0 (0)	<0.001
	<i>Enterobacter</i> spp.	11 (2.1)	11 (6.4)	0 (0)	<0.001 ^{b)}
	Others	3 (0.6)	3 (1.8)	0 (0)	<0.001 ^{b)}
Status at discharge	Alive	356 (67.4)	119 (69.6)	237 (66.4)	0.462
	Dead	172 (32.6)	52 (30.4)	120 (33.6)	

Data are presented as n (%) or mean ± standard deviation.

MDRO, multidrug-resistant organism; CRE, carbapenem-resistant *Enterobacteriaceae*; CRAB, carbapenem-resistant *Acinetobacter baumannii*; ACH, acute care hospital; LTCF, long-term care facilities; CVD, cardiovascular disease; CKD, chronic kidney disease; CRD, chronic respiratory disease; ICU, intensive care unit; VRE, vancomycin-resistant *Enterococcus*; MRSA, methicillin-resistant *Staphylococcus aureus*; ESBL, extended-spectrum β-lactamase; MRPA, multidrug-resistant *Pseudomonas aeruginosa*.

^{a)}Multiple responses, ^{b)}Fisher exact test.

urinary catheter, 84.2% used a central venous catheter, and 54.5% used carbapenem as an antimicrobial agent.

Comparison of Characteristics between the CRE and CRAB Group, and the CA and HA Group

There were significant differences in the characteristics of the CRE and CRAB groups with regard to the history of

hospitalization within 6 months, hypertension, treatment in the ICU, MDRO history, the source of the specimen from which CRE/CRAB was isolated, and the use of arterial catheters, mechanical ventilation, and total parenteral nutrition (TPN) (Tables 2 and 3). Compared to the CRE group, the CRAB group showed lower frequencies of hospitalization within 6 months (p = 0.006), hypertension

Table 3. Comparison of treatment-related characteristics between patients with CRE and those with CRAB

Variable	Category	Total (n = 418)	CRE (n = 116)	CRAB (n = 302)	p
Invasive procedures	Surgery	215 (51.4)	63 (54.3)	152 (50.3)	0.466
	Bronchoscopy	94 (22.5)	22 (19.0)	72 (23.8)	0.285
	G-endoscopy	63 (15.1)	22 (19.0)	41 (13.6)	0.168
Invasive device	Urinary catheter	380 (90.9)	103 (88.8)	277 (91.7)	0.351
	Central catheter	352 (84.2)	93 (80.2)	259 (85.8)	0.161
	Gastrointestinal tube	336 (80.4)	88 (75.9)	248 (82.1)	0.149
	Arterial catheter	322 (77.0)	77 (66.4)	245 (81.1)	0.001
	Mechanical ventilator	275 (65.8)	58 (50.0)	217 (71.9)	< 0.001
	Drainage tube	138 (33.0)	42 (36.2)	96 (31.8)	0.390
Antibiotics	Penicillin	274 (65.6)	68 (58.6)	206 (68.2)	0.065
	Quinolone	237 (56.7)	59 (50.9)	178 (58.9)	0.136
	Carbapenem	228 (54.5)	58 (50.0)	170 (56.3)	0.247
	Cephalosporin	225 (53.8)	62 (53.4)	163 (54.0)	0.923
	Vancomycin	165 (39.5)	43 (37.1)	122 (40.4)	0.533
Medication	Antiacids	375 (89.7)	103 (88.8)	272 (90.1)	0.701
	Steroids	187 (44.7)	46 (39.7)	141 (46.7)	0.195
	TPN	369 (88.3)	90 (77.6)	279 (92.4)	< 0.001

Data are presented as n (%).

CRE, carbapenem-resistant *Enterobacteriaceae*; CRAB, carbapenem-resistant *Acinetobacter baumannii*; TPN, total parenteral nutrition.

Table 4. Factors associated with CRAB isolation (n = 418)

Variable	OR (95% CI)	p
Hypertension ^{a)}	0.56 (0.35–0.89)	0.014
Treatment in ICU ^{a)}	0.34 (0.16–0.72)	0.005
History of vancomycin-resistant <i>Enterococcus</i> ^{a)}	0.49 (0.29–0.83)	0.008
History of extended-spectrum β -lactamase ^{a)}	0.48 (0.26–0.87)	0.017
Use of mechanical ventilator ^{a)}	3.52 (1.96–6.33)	< 0.001
Use of total parenteral nutrition ^{a)}	3.64 (1.87–7.08)	< 0.001

CRAB, carbapenem-resistant *Acinetobacter baumannii*; OR, odds ratio; CI, confidence interval; ICU, intensive care unit.

^{a)}Reference group = No (carbapenem-resistant *Enterobacteriaceae*/CRAB-isolated patients without the corresponding condition).

($p = 0.007$), VRE history ($p = 0.019$), and broad-spectrum β -lactamase-producing organism history ($p < 0.001$), but higher frequencies of ICU stay ($p = 0.001$), arterial catheter use ($p = 0.001$), mechanical ventilator use ($p < 0.001$), and TPN use ($p < 0.001$). CRE was more prevalent in rectal swab specimens at the time of hospitalization, whereas CRAB was more prevalent in respiratory specimens after hospitalization (both $p < 0.001$) (Tables 2 and 3). Multiple logistic regression analysis showed that CRAB isolation was positively associated with mechanical ventilator use and TPN use. The risk of CRAB isolation was 3.52 times higher in those who used a mechanical ventilator and 3.64 times higher in those who used TPN compared to their counterparts (Table 4).

The CA and HA groups showed significant differences in hospitalization route, hypertension, cerebrovascular disease, treatment in the ICU, MDRO history, and the source of the specimen from which CRE/CRAB was isolated (Table 5). The HA group showed higher frequencies of transfer from other healthcare facilities ($p < 0.001$), cerebrovascular disease ($p = 0.011$), and treatment in the ICU ($p < 0.001$), and lower frequencies of hypertension ($p = 0.016$), MDRO history ($p < 0.001$), and extended-spectrum β -lactamase-producing organism history ($p = 0.004$) compared to the CA group (Table 5). Multiple logistic regression analysis showed that the risk of HA-CRE/CRAB isolation was 6.30 times higher in patients diagnosed with cardiovascular disease than in those without cardiovascular disease (Table 6).

Discussion

In this study, we identified the epidemiological characteristics of patients with confirmed CRE or CRAB isolation among inpatients in wards and the ICU, and compared the characteristics between the CRE and CRAB groups and between the HA and CA groups.

CRAB isolation was common in this tertiary hospital in Korea, suggesting that *A. baumannii* constitutes a large proportion of carbapenem-resistant bacteria in domestic medical institutions. According to the results of the global antimicrobial resistance surveillance system in Korea (Kor-GLASS) from 2016 to 2019, the imipenem resistance rates were 0.1% in blood and 0.1% in urine for *E. coli*, 1.0% in blood

Table 5. Comparison of general characteristics between patients with healthcare-acquired and community-acquired infections

Variables	Category	Total (n = 528)	HA (n = 497)	CA (n = 31)	p
Sex	Male	335 (63.4)	315 (63.4)	20 (64.5)	0.899
	Female	193 (36.6)	182 (36.6)	11 (35.5)	
Age (y)		67.7 ± 14.0	67.5 ± 14.0	71.2 ± 14.0	0.146
History of hospitalization within 6 months	No	147 (27.8)	136 (27.4)	11 (35.5)	0.310
	ACH	301 (57.0)	283 (56.9)	18 (58.1)	
	LTCF	80 (15.2)	78 (15.7)	2 (6.5)	
Source of hospitalization	ACH, transfer	184 (34.8)	184 (37.0)	0 (0)	< 0.001
	LTCF, transfer	76 (14.4)	76 (15.3)	0 (0)	
	Community	268 (50.8)	237 (47.7)	31 (100.0)	
Comorbidities ^{a)}	Hypertension	264 (50.0)	242 (48.7)	22 (71.0)	0.016
	Diabetes mellitus	186 (35.2)	171 (34.4)	15 (48.4)	0.114
	CVD	158 (29.9)	155 (31.2)	3 (9.7)	0.011
	Cancer	140 (26.5)	132 (26.6)	8 (25.8)	0.927
	CKD	64 (12.1)	61 (12.3)	3 (9.7)	1.000 ^{b)}
	Liver disease	52 (9.8)	49 (9.9)	3 (9.7)	1.000 ^{b)}
	CRD	49 (9.3)	45 (9.1)	4 (12.9)	0.517 ^{b)}
Charlson comorbidity index score		4.6 ± 2.3	4.6 ± 2.3	4.3 ± 2.4	0.541
Treatment in ICU	No	190 (36.0)	159 (32.0)	31 (100.0)	< 0.001
	Yes	338 (64.0)	338 (68.0)	0 (0)	
MDRO history ^{a)}	VRE	116 (22.0)	113 (22.7)	3 (9.7)	0.088
	MRSA	55 (10.4)	53 (10.7)	2 (6.5)	0.760 ^{b)}
	ESBL	88 (16.7)	77 (15.5)	11 (35.5)	0.004
	MRPA	11 (2.1)	9 (1.8)	2 (6.5)	0.132 ^{b)}
Specimen source of CRE/CRAB	Respiratory	317 (60.0)	307 (61.8)	10 (32.3)	0.001 ^{b)}
	Rectal swab	126 (23.9)	117 (23.5)	9 (29.0)	
	Urine	33 (6.3)	27 (5.4)	6 (19.4)	
	Blood	18 (3.4)	15 (3.0)	3 (9.7)	
	Others	34 (6.4)	31 (6.2)	3 (9.7)	
Strain of CRE/CRAB ^{a)}	<i>Acinetobacter baumannii</i>	357 (67.6)	345 (69.4)	12 (38.7)	< 0.001
	<i>Klebsiella</i> spp.	126 (23.9)	113 (22.7)	13 (41.9)	0.015
	<i>Escherichia coli</i>	36 (6.8)	31 (6.2)	5 (16.1)	0.051 ^{b)}
	<i>Enterobacter</i> spp.	11 (2.1)	10 (2.0)	1 (3.2)	0.489 ^{b)}
	Others	3 (0.6)	2 (0.4)	1 (3.2)	0.166 ^{b)}
Status at discharge	Alive	356 (67.4)	335 (67.4)	21 (67.7)	0.969
	Dead	172 (32.6)	162 (32.6)	10 (32.3)	

Data are presented as n (%) or mean ± standard deviation.

HA, healthcare-acquired; CA, community-acquired; ACH, acute care hospital; LTCF, long-term care facilities; CVD, cardiovascular disease; CKD, chronic kidney disease; CRD, chronic respiratory disease; ICU, intensive care unit; MDRO, multidrug-resistant organism; VRE, vancomycin-resistant *Enterococcus*; MRSA, methicillin-resistant *Staphylococcus aureus*; ESBL, extended-spectrum β-lactamase; MRPA, multidrug-resistant *Pseudomonas aeruginosa*; CRE, carbapenem-resistant *Enterobacteriaceae*; CRAB, carbapenem-resistant *Acinetobacter baumannii*.

^{a)}Multiple responses, ^{b)}Fisher exact test.

Table 6. Factors associated with healthcare-acquired CRE and CRAB isolation (n = 528)

Variable	OR	95% CI	p
Hypertension ^{a)}	0.35	0.15–0.83	0.016
Cardiovascular disease ^{a)}	6.30	1.82–21.85	0.004

CRE, carbapenem-resistant *Enterobacteriaceae*; CRAB, carbapenem-resistant *Acinetobacter baumannii*; OR, odds ratio; CI, confidence interval.

^{a)}Reference group = No (CRE/CRAB-isolated patients without the corresponding conditions).

and 1.2% in urine for *Klebsiella pneumoniae*, and 90.3% in blood for *A. baumannii*, which was a very alarming finding [21]. The reported types of CROs differ across studies. CROs isolated from carbapenem-resistant bloodstream infections in Taiwan were higher in *Acinetobacter* spp. and *Pseudomonas* spp. than in CREs, including *E. coli*, *Klebsiella* spp., and *Enterobacter* spp. [10]. In contrast, a study on carbapenem-resistant Gram-negative bacteremia at a

university hospital in the United States [22] and a study in the ICU and transplant ward of a university hospital in the United States [7] showed the order of *Pseudomonas aeruginosa* and *K. pneumoniae*, indicating that the isolation rate of *Actinobacter* spp. was lower than that of other strains.

A. baumannii is commonly found in hospital environments and is known to cause various healthcare-associated infections, such as sepsis, pneumonia, urinary tract infections, wound infections, and postoperative infections [23]. Most strains are resistant to various antibiotics, including carbapenem [24,25]. In the Kor-GLASS analysis, the majority of *Enterobacteriaceae* cases were community-associated, whereas 86.9% of *Actinobacter* spp. Cases were healthcare-associated [21]. Although *A. baumannii* is a Gram-negative bacterium, it tolerates a dry environment well [26]. Many CRAB epidemics have been reported in healthcare settings, including ICUs, and the vulnerability to these outbreaks has been increasing due to the growing number of patients with underlying diseases, invasive catheters, and mechanical ventilation, as well as the use of broad-spectrum antibiotics [27–29]. In this study, 64% of participants received ICU treatment, and many participants underwent invasive procedures and received antibiotic treatment, which may explain the higher rate of CRAB isolation.

The risk of CRAB isolation increased with mechanical ventilator use and TPN use. TPN use was also confirmed as a risk factor for CRAB bloodstream infection in a of patients at the Taiwan Veterans Hospital [9]. In this study, TPN was used by approximately 88% of the participants. Therefore, we can expect that MDRO prevention and control measures, including thorough hand hygiene, will lead to significant reductions in MDROs, including CRAB, among TPN-using patients [18,30].

Approximately 6% of the participants in this study were found to have CA infections. The percentage of CA infections relative to HA infections varied from 6% [31] to 10% [8] in the United States and from 12% [32] to 30% [17] in Taiwan. According to the results of this study, it would be difficult to say that CRE/CRAB is prevalent in communities in Korea; however, continuous monitoring is required considering the possibility of its spread to the community. CRE and CRAB are designated as legally notifiable infectious diseases and are under mandatory and sentinel surveillance systems, respectively [5,33]. Therefore, it is possible to determine whether spread has occurred to the local community by reporting HA and CA separately to health authorities. Although there were relatively few CA infections in this study, 1 out of 5 CRE/CRAB was isolated at the time of hospitalization among CRE/CRAB isolated patients, suggesting

that CRE/CRAB management at the time of hospitalization is important.

Similar to previous studies [7], the primary hospitalization route of patients was from the community, followed by transfer from acute care hospitals and transfer from long-term care facilities. Approximately half of the participants were transferred from acute care hospitals and long-term care facilities. Approximately 70% of the study participants had a history of hospitalization within 6 months, and about 65% to 90% of patients had a history of hospitalization within 1 year in a previous study in the United States [8]. Thus, for patients with a history of hospitalization within 6 months to 1 year, a system for active surveillance cultures is required at the time of hospitalization. However, for hospitals to which a large number of patients are transferred, such as the hospital in this study, the application of active surveillance culture for all inpatients and outpatients would be burdensome in terms of time and cost. As an alternative, selectively performing active monitoring cultures for high-risk groups by applying a previously developed risk model can be considered [8,13,14].

Most patients had invasive devices within 3 months of the survey, with urinary catheters being the most prevalent, followed by central venous catheters, gastrointestinal tubes, arterial catheters, and mechanical ventilators. According to previous studies, although the duration of keeping invasive devices varied from 30 days to 3 months from the point of the survey, the most common type of invasive device was the urinary catheter [7,9,10,13]. Among drugs other than antibiotics, gastric acid inhibitors (including proton pump inhibitors or histamine H₂ receptor antagonists) were frequently used among the patients in this study, consistent with a previous study [7].

The mortality rate at discharge in this study was 32.6%, which was higher than the 17.0% reported in a previous domestic study [13] on the isolation of CRE from patients admitted to the ICU, with a 30-day mortality rate of 14.2% to 24.8% [22], in patients whose culture was positive for carbapenem-resistant Gram-negative bacteremia during hospitalization between 2000 and 2017 at a hospital in the United States. Patients with CRAB have been reported to have a lower survival rate than those with other carbapenem-resistant Gram-negative bacteremia [22]. Considering the previous study [22], the relatively high mortality rate in this study may be related to the higher proportion of CRAB compared to CRE.

Strengths and Limitations

This study is significant in that it identified and analyzed the characteristics of all hospitalized patients in whom CRE or CRAB was isolated, including those in the emergency

department and the ICU. However, this study has the following limitations that need to be considered when interpreting its results. First, the number of CRE/CRAB cases may have been underestimated because active surveillance cultures were only performed for patients admitted to the ICU, and only the first case was included in the analysis when both CRE and CRAB were isolated. Second, this study was limited to CRE and CRAB among carbapenem-resistant Gram-negative bacteremia, according to the MDRO management policy of the research institution. Third, for cases of HA infections in patients who were transferred from long-term care facilities or acute care hospitals, the length of stay and treatment-related characteristics at the previous institutions could not be considered due to data limitations. Fourth, the data on patients' general characteristics were based on the "history taking" results in patients' electronic medical records, as collected at the time of hospitalization. Therefore, the responses for certain items, such as history of hospitalization within 6 months and comorbidities, may have been biased. Finally, this study cannot be generalized to other types of medical institutions because the data were collected from a tertiary referral hospital.

Conclusion

Over 20% of CRE/CRAB isolates in a tertiary referral hospital in Korea were found at the time of admission. Furthermore, CRAB isolation occurred more frequently in patients with mechanical ventilation and/or TPN than in those without. Thus, active surveillance of CRE/CRAB at the time of hospitalization is strongly required, particularly for patients who are expected to require mechanical ventilation or TPN.

Notes

Ethics Approval

This study was approved by the Institutional Review Board of Inje University Busan Baik Hospital (20-0114), and performed in accordance with the principles of the Declaration of Helsinki. Written informed consent was waived.

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.

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Safety monitoring of COVID-19 vaccination among adolescents aged 12 to 17 years old in the Republic of Korea

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ABSTRACT

Objectives: This study aimed to disseminate information on coronavirus disease 2019 (COVID-19) vaccine safety among adolescents aged 12 to 17 years in the Republic of Korea.

Methods: Two databases were used to assess COVID-19 vaccine safety in adolescents aged 12 to 17 years who completed the primary Pfizer-BioNTech vaccination series. Adverse events reported to the web-based COVID-19 vaccination management system (CVMS) and collected in the text message-based system were analyzed.

Results: From March 5, 2021 to February 13, 2022, 12,216 adverse events among 12- to 17-year-olds were reported to the CVMS, of which 97.1% were non-serious adverse events and 2.9% were serious adverse events, including 85 suspected cases of anaphylaxis, 74 suspected cases of myocarditis and/or pericarditis, and 2 deaths. From December 13, 2021 to January 26, 2022, 10,389 adolescents responded to a text message survey, and local/systemic adverse events were more common after dose 2 than after dose 1. The most commonly reported events following either vaccine dose were pain at the injection site, headache, fatigue/tiredness, and myalgia.

Conclusion: The overall results are consistent with previous findings; the great majority of adverse events were non-serious, and serious adverse events were rare among adolescents aged 12 to 17 years following Pfizer-BioNTech COVID-19 vaccination.

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

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Introduction

Coronavirus disease 2019 (COVID-19) vaccination has been available since February 26, 2021 in the Republic of Korea (ROK) to prevent the occurrence of severe cases leading to hospitalization and death by reducing the risk of infection and transmission [1]. To date, only the Pfizer-

BioNTech mRNA COVID-19 vaccine has been authorized for use in adolescents aged 12 to 17 years by the Korea Ministry of Food and Drug Safety (MFDS), on the basis of safety and efficacy data from controlled trials conducted in the United States (US) [2,3]. The Korea MFDS initially approved the use of the Pfizer-BioNTech vaccine for persons aged ≥ 16 years on March 5, 2021 [4], and expanded it to include adolescents aged ≥ 12 years on July 16, 2021 [5]. Following the 19th Korea Advisory Committee on Immunization Practices (KACIP), the Pfizer-BioNTech vaccine was offered 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, with a 3-week interval between dose 1 and dose 2 [6,7].

Since then, COVID-19 vaccines have been widely distributed to adolescents aged 12 to 17 years across the nation, and vaccination coverage in this population trended upward, reaching 46.9% for dose 1 and 24.9% for dose 2 as of December 1, 2021 [8]. To make COVID-19 vaccinations more accessible and boost the vaccinations rate for adolescents, the Korea Disease Control and Prevention Agency (KDCA) announced a 2-week mass vaccination strategy during December 13–24, 2021, to vaccinate adolescents aged 12 to 17 years at schools, vaccination centers, public health centers in cooperation with the Korea Ministry of Education [8]. In addition, a text message survey for those aged 12 to 17 years was launched when the mass vaccination strategy was initiated to monitor and investigate adverse events or health conditions after COVID-19 vaccination.

As information on COVID-19 vaccine safety for adolescents aged 12 to 17 years is currently limited in real-world settings, this study aimed to identify and disseminate information on COVID-19 vaccine safety for adolescents aged 12 to 17 years in the ROK who completed the primary Pfizer-BioNTech vaccination series, including the first and second doses. This study analyzed data on adverse events reported to the COVID-19 vaccination management system (CVMS; a web-based passive vaccine safety surveillance system) and the text message-based vaccine safety surveillance system.

Materials and Methods

COVID-19 Vaccination Management System

In order to monitor adverse events following immunization (AEFIs) and identify potential safety signals for further evaluation, the KDCA manages the CVMS, in which doctors and forensic pathologists can report AEFIs regardless of a causal association between the events and the vaccines in accordance with the Infectious Disease Control and Prevention Act [9]. From March 5, 2021 to February 13, 2022, a total of 4,340,710 primary doses of the Pfizer-BioNTech

vaccination series were administered to adolescents aged 12 to 17 years in the ROK, and 12,216 adverse events after vaccination were reported to the CVMS. Data on an additional dose (dose 3) and vaccines other than the Pfizer-BioNTech vaccine were excluded as they were not authorized for use in adolescents aged 12 to 17 years during the study period in the ROK. Adverse events reported to the CVMS are classified into non-serious and serious events as per the Guidelines for Adverse Events Following COVID-19 Immunization in the ROK [9]. Non-serious events include common symptoms, such as redness at the injection site, pain, swelling, myalgia, fever, headache, chills, and others. The following adverse events are classified as serious: death, suspected 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 adolescents aged 12 to 17 years were stratified by sex, age groups, and vaccine doses, and the types of symptoms and signs reported as adverse events were described in descending order of the number of cases. Since adverse events reported to the CVMS are suspected cases, the events do not indicate medically confirmed diagnoses.

Text Message-Based Vaccine Safety Surveillance System

The KDCA operates a text message-based vaccine safety surveillance system that surveys adverse events and health conditions after COVID-19 vaccination for specific population groups, such as pregnant women who consent to receive text message surveys through their smartphones on the day of their first vaccination [9]. Text messages were sent on a daily basis until day 7 post-vaccination to check health conditions. In total, 10,398 adolescents aged 12 to 17 years in the ROK who received the primary series of the Pfizer-BioNTech vaccine responded to text message surveys from December 13, 2021 to January 26, 2022. The surveys included questions about any health problems experienced after vaccination, fever, local and systemic adverse events, limits to normal daily activities, and visits to medical facilities. The respondents were able to report multiple adverse events on various days. The characteristics of 10,398 respondents aged 12 to 17 years were described according to sex and age, and adverse events and health conditions were assessed in terms of age groups and vaccine doses.

SAS ver. 9.4 (SAS Institute Inc., Cary, NC, USA) was used to conduct all the analyses in this study. The passive surveillance activity was conducted and authorized by the KDCA; the study was not subject to the institutional review board approval under government regulations. The study with the

text message-based surveillance was exempted from review by the Korea Public Institutional Review Board designated by the Ministry of Health and Welfare (P01-202203-01-035).

Results

COVID-19 Vaccination Management System

From March 5, 2021 to February 13, 2022, the CVMS confirmed 12,216 adverse events among adolescents aged 12 to 17 years after primary doses of the Pfizer-BioNTech vaccination series (Table 1); 11,867 (97.1%) were non-serious and 349 (2.9%) were serious. Serious adverse events included death (2, 0%), suspected anaphylaxis (85, 0.7%) and major adverse events, including AESIs for COVID-19 vaccines (262, 2.1%). In total, 4,340,710 doses were administered to adolescents aged 12 to 17 years during the study period and the overall reporting rate per 100,000 doses was 281.4 (295.8 after receipt of dose 2 and 268.1 after receipt of dose 1). The reporting rate per 100,000 doses after the primary vaccination series was 271.5 in males and 291.9 in females, and 16- to 17-year-olds (370.0) showed a higher reporting rate than 12- to 15-year-

olds (224.6). Two deaths were reported in males aged 16 to 17 years after receipt of dose 2. Among 11,867 (97.1%) non-serious adverse events, the most commonly reported symptoms based on the reporting rate per 100,000 doses were headache (74.0), chest pain (72.0), myalgia (42.5), dizziness (39.9), and nausea (36.2) (Table 2). Among 349 (2.9%) serious adverse events, acute cardiovascular injury (2.1), including 74 cases of suspected myocarditis and/or pericarditis, showed the highest reporting rate per 100,000 doses, followed by anaphylaxis, including anaphylactoid reactions (2.0), convulsions or seizures (0.9), acute paralysis (0.8), and vaccine-associated enhanced disease (0.7).

Text Message-Based Vaccine Safety Surveillance System

From December 13, 2021 to January 26, 2022, a total of 10,389 adolescents aged 12 to 17 years responded to at least 1 text message survey on days 0 to 7 after Pfizer-BioNTech COVID-19 vaccination (Table 3); 8,909 (85.8%) were 12- to 15-year-olds and 1,480 (14.2%) were 16- to 17-year-olds. Among them, 4,828 (46.5%) were male and 5,561 (53.5%) were

Table 1. Characteristics of adverse events reported to the CVMS for adolescents aged 12 to 17 years after Pfizer-BioNTech COVID-19 vaccination, Republic of Korea, March 5, 2021 to February 13, 2022

Variable	Number of doses administered	Adverse events (n = 12,216) ^{a)}					
		Total	Non-serious adverse events ^{b)}	Serious adverse events ^{c)}			
				Sub-total	Death	Anaphylaxis	Others
Total	4,340,710	12,216 (281.4)	11,867 (273.4)	349 (8.0)	2 (0)	85 (2.0)	262 (6.0)
Dose 1	2,254,487	6,044 (268.1)	5,845 (259.3)	199 (8.8)	0	71 (3.1)	128 (5.7)
Dose 2	2,086,223	6,172 (295.8)	6,022 (288.7)	150 (7.2)	2 (0.1)	14 (0.7)	134 (6.4)
Sex							
Male	2,229,864	6,055 (271.5)	5,854 (262.5)	201 (9.0)	2 (0.1)	38 (1.7)	161 (7.2)
Dose 1	1,158,684	2,915 (251.6)	2,809 (242.4)	106 (9.1)	0	30 (2.6)	76 (6.6)
Dose 2	1,071,180	3,140 (293.1)	3,045 (284.3)	95 (8.9)	2 (0.2)	8 (0.7)	85 (7.9)
Female	2,110,846	6,161 (291.9)	6,013 (284.9)	148 (7.0)	0	47 (2.2)	101 (4.8)
Dose 1	1,095,803	3,129 (285.5)	3,036 (277.1)	93 (8.5)	0	41 (3.7)	52 (4.7)
Dose 2	1,015,043	3,032 (298.7)	2,977 (293.3)	55 (5.4)	0	6 (0.6)	49 (4.8)
Age (y)							
12–15	2,644,362	5,940 (224.6)	5,762 (217.9)	178 (6.7)	0	42 (1.6)	136 (5.1)
Dose 1	1,424,052	3,026 (212.5)	2,918 (204.9)	108 (7.6)	0	36 (2.5)	72 (5.1)
Dose 2	1,220,310	2,914 (238.8)	2,844 (233.1)	70 (5.7)	0	6 (0.5)	64 (5.2)
16–17	1,696,348	6,276 (370.0)	6,105 (359.9)	171 (10.1)	2 (0.1)	43 (2.5)	126 (7.4)
Dose 1	830,435	3,018 (363.4)	2,927 (352.5)	91 (11.0)	0	35 (4.2)	56 (6.7)
Dose 2	865,913	3,258 (376.3)	3,178 (367.0)	80 (9.2)	2 (0.2)	8 (0.9)	70 (8.1)

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 calculated using the information on suspected adverse events after COVID-19 vaccination reported by medical facilities or doctors. The results do not indicate an accurate diagnosis 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 major adverse events including adverse events of special interest, intensive care unit admission, life-threatening events, permanent disability or sequelae, and others.

Table 2. Types of symptoms and signs reported to the CVMS for adolescents aged 12 to 17 years after Pfizer-BioNTech COVID-19 vaccination, Republic of Korea, March 5, 2021 to February 13, 2022

Symptoms and signs (<i>n</i> = 12,216) ^{a)}	Case (per 100,000)
Non-serious adverse events (<i>n</i> = 11,867)	
Headache	3,214 (74.0)
Chest pain	3,127 (72.0)
Myalgia	1,845 (42.5)
Dizziness	1,732 (39.9)
Nausea	1,573 (36.2)
Fever	1,183 (27.3)
Vomiting	754 (17.4)
Abdominal pain	748 (17.2)
Allergy reactions	745 (17.2)
Chills	692 (15.9)
Pain, redness or swelling at the injection site within 3 days after	455 (10.5)
Diarrhea	451 (10.4)
Lymphadenitis	381 (8.8)
Abnormal uterine bleeding	130 (3.0)
Cellulitis	58 (1.3)
Arthritis	44 (1.0)
Severe local adverse events	29 (0.7)
Abscess at the injection site	2 (0)
Systemic disseminated Bacillus Calmette-Guerin infection	1 (0)
Severe adverse events (<i>n</i> = 349) including reports of death	
Acute cardiovascular injury	90 (2.1)
Anaphylaxis (including anaphylactoid reactions)	85 (2.0)
Convulsions or seizures	40 (0.9)
Acute paralysis	33 (0.8)
Vaccine-associated enhanced disease	30 (0.7)
Acute respiratory distress syndrome	14 (0.3)
Encephalopathy or encephalitis	11 (0.3)
Thrombocytopenic purpura	6 (0.1)
Thrombocytopenia	5 (0.1)
Acute kidney injury	4 (0.1)
Osteitis or osteomyelitis	4 (0.1)
Erythema multiforme	3 (0.1)
Coagulation disorder	3 (0.1)
Thrombosis with thrombocytopenia syndrome	3 (0.1)
Anosmia or ageusia	3 (0.1)
Acute liver injury	2 (0)
Meningoencephalitis	2 (0)
Multisystem inflammatory syndrome	2 (0)
Single organ cutaneous vasculitis	2 (0)
Acute disseminated encephalomyelitis	1 (0)
Chilblains	1 (0)
Guillain-Barre syndrome	1 (0)

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 calculated using the information on suspected adverse events after COVID-19 vaccination reported by medical facilities or doctors. The results do not indicate an accurate diagnosis or causality between the events and the vaccines.

Table 3. Characteristics of adolescents aged 12 to 17 years^{a)}

Characteristic	Dose 1 (n = 10,389)	Dose 2 (n = 3,147)
Sex		
Male	4,828 (46.5)	1,436 (45.6)
Female	5,561 (53.5)	1,711 (54.4)
Age (y)		
12–15	8,909 (85.8)	2,744 (87.2)
12	1,948 (18.8)	639 (20.3)
13	2,432 (23.4)	766 (24.3)
14	1,857 (17.9)	584 (18.6)
15	2,672 (25.7)	755 (24.0)
16–17	1,480 (14.2)	403 (12.8)
16	864 (8.3)	247 (7.8)
17	616 (5.9)	156 (5.0)

Data are presented as n (%).

COVID-19, coronavirus disease 2019.

^{a)}Adolescents aged 12 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 January 26, 2022.

female. During days 0 to 7 post-vaccination, health problems among those aged 12 to 15 years were more common after dose 2 (58.9%) than after dose 1 (53.9%) (Table 4). The reporting trend was similar for those aged 16 to 17 years: health problems were reported by 58.1% of respondents after dose 2 and 51.8% after dose 1. Fewer than one-quarter of adolescents in both age groups reported fever or a sensation of heat after dose 2. Among those aged 12 to 15 years, local adverse events (53.2%) and systemic adverse events (52.3%) were reported more frequently after dose 2 than after dose 1. The reporting trends were similar for those aged 16 to 17 years, of whom 52.6% reported local adverse events and 53.8% reported systemic adverse events after dose 2. The most commonly reported adverse events among both age groups following either dose 1 or dose 2 were as follows: pain at the injection site, headache, fatigue or tiredness, myalgia, and fever or a sensation of heat. Almost one-fifth

Table 4. Adverse events and health conditions reported by adolescents aged 12 to 17 years following Pfizer-BioNTech COVID-19 vaccination, Republic of Korea, December 13, 2021 to January 26, 2022

Events ^{a)}	Age group (12–15 y)		Age group (16–17 y)	
	Dose 1 (n = 8,909)	Dose 2 (n = 2,744)	Dose 1 (n = 1,480)	Dose 2 (n = 403)
Health problems ^{b)}	4,803 (53.9)	1,617 (58.9)	766 (51.8)	234 (58.1)
Fever or sensation of heat	694 (7.8)	634 (23.1)	103 (7.0)	89 (22.1)
Local adverse events	4,323 (48.5)	1,460 (53.2)	686 (46.4)	212 (52.6)
Pain	3,978 (44.7)	1,346 (49.1)	634 (42.8)	200 (49.6)
Redness	195 (2.2)	88 (3.2)	39 (2.6)	20 (5.0)
Swelling	843 (9.5)	316 (11.5)	130 (8.8)	55 (13.6)
Itching	232 (2.6)	95 (3.5)	44 (3.0)	12 (3.0)
Urticaria	42 (0.5)	13 (0.5)	9 (0.6)	1 (0.2)
Others	506 (5.7)	164 (6.0)	86 (5.8)	31 (7.7)
Systemic adverse events	3,736 (41.9)	1,434 (52.3)	615 (41.6)	217 (53.8)
Chills	494 (5.5)	386 (14.1)	102 (6.9)	66 (16.4)
Headache	1,455 (16.3)	853 (31.1)	262 (17.7)	146 (36.2)
Joint pain	218 (2.4)	146 (5.3)	48 (3.2)	35 (8.7)
Myalgia	2,070 (23.2)	729 (26.6)	404 (27.3)	136 (33.7)
Fatigue or tiredness	1,753 (19.7)	748 (27.3)	338 (22.8)	144 (35.7)
Nausea	577 (6.5)	267 (9.7)	103 (7.0)	55 (13.6)
Vomiting	35 (0.4)	24 (0.9)	12 (0.8)	4 (1.0)
Diarrhea	188 (2.1)	68 (2.5)	36 (2.4)	13 (3.2)
Abdominal pain	326 (3.7)	145 (5.3)	53 (3.6)	26 (6.5)
Rash	25 (0.3)	11 (0.4)	10 (0.7)	5 (1.2)
Armpit tenderness	347 (3.9)	286 (10.4)	65 (4.4)	41 (10.2)
Others	450 (5.1)	152 (5.5)	73 (4.9)	28 (6.9)
Unable to perform normal daily activities	867 (9.7)	510 (18.6)	185 (12.5)	103 (25.6)
Visits to medical facilities	100 (1.1)	39 (1.4)	16 (1.1)	5 (1.2)
Emergency department visit	15 (0.2)	6 (0.2)	3 (0.2)	1 (0.2)
Hospitalization	2 (0)	0	0	0
Clinic visit	87 (1.0)	34 (1.2)	13 (0.9)	5 (1.2)

Data are presented as n (%): the percentage of respondents who reported health problems and adverse events at least once during days 0–7 post-vaccination. COVID-19, coronavirus disease 2019.

^{a)}Events were reported by respondents who completed at least 1 text message-based survey on days 0 to 7. They could report multiple adverse events on various days. ^{b)}The proportion of respondents who answered that they had experienced any health problems after vaccination.

(18.6%) of adolescents aged 12 to 15 years responded that they were unable to perform normal daily activities after dose 2. This reporting rate was slightly higher in those aged 16 to 17 years (25.6%). More than 1% of adolescents aged 12 to 17 years visited medical facilities, including emergency departments, clinics, or hospitals, during days 0 to 7 after receiving either dose.

Discussion

The results of the text message survey on AEFIs and subjective health problems among adolescents aged 12 to 17 years after the primary series of Pfizer-BioNTech COVID-19 vaccination are consistent with the safety data including adolescents aged 12 to 17 years reported in the US [10] and a controlled trial [2]; local and systemic adverse events, including fever, following vaccination were more common after dose 2 and were mostly mild and did not limit daily activities. Moreover, similar to the findings reported in the US and a controlled trial [2,10], the most common local adverse event was pain at the injection site, and the most common systemic adverse events were headache, fatigue, and myalgia in this study. Those adverse events were more frequently reported in 16- to 17-year-olds than in 12- to 15-year-olds in both the ROK and the US [10].

Among the adverse events reported to the CVMS for adolescents aged 12 to 17 years after Pfizer-BioNTech COVID-19 vaccination, 97.1% were non-serious and 2.9% were serious. These proportions are slightly different from those in safety data in adolescents reported in the US, where 90.7% were non-serious reports and 9.3% were serious reports [10]. This might be attributed to different standards used in the 2 surveillance systems to assess and define non-serious and serious adverse events. However, the great majority of adverse events reported by adolescents aged 12 to 17 years following vaccination were non-serious in both the ROK and the US.

Based on the early safety monitoring for adolescents aged 12 to 17 years after Pfizer-BioNTech COVID-19 vaccination, serious adverse events, including 85 cases of suspected anaphylaxis (2.0 cases per 100,000 doses administered) and acute cardiovascular injury (including 74 cases of suspected myocarditis and/or pericarditis; 1.7 cases per 100,000 doses administered) appear to be rarely reported. Reviewing these 2 major serious adverse events, the number of suspected anaphylaxis reports in adolescents after vaccination was greater after dose 1 (71, 83.5%) than after dose 2 (14, 16.5%), but similar between females (47, 55.3%) and males (38, 44.7%). In previous reports from the ROK and the US, most cases of confirmed anaphylaxis based on the Brighton

Collaboration case definition criteria among all age groups after Pfizer-BioNTech COVID-19 vaccination were reported in women (70.9%–93.6%) [11,12]. Moreover, the number of suspected myocarditis and/or pericarditis reports was higher in males (59, 79.7%) than in females (15, 20.3%), and after dose 2 (50, 67.6%) than after dose 1 (24, 32.4%) in this study; these findings are consistent with a meta-analysis showing that the incidence of myopericarditis was significantly higher in males and after receiving dose 2 [13]. However, since the current study is based on reports of suspected cases including anaphylaxis and myocarditis and/or pericarditis due to limited information available in early safety monitoring, diagnostic bias might exist and the assessment of causality between adverse events and vaccines is constrained at this stage. Therefore, we suggest that follow-up work should be conducted with the confirmation of suspected cases in adolescents after COVID-19 vaccination for further evaluation.

Although a few COVID-19 vaccine-associated myocarditis and/or pericarditis cases have been reported among adolescents aged 12 to 17 years, predominantly among males, after dose 2 of Pfizer-BioNTech vaccination, most cases were mild [14–18]. Since those cases are rarely reported and patients can recover quickly if responded to and treated well, the benefits of COVID-19 vaccination, including for adolescents, are considered to outweigh the risks of myocarditis and/or pericarditis [19–22]. Furthermore, a systematic review concluded that the COVID-19 vaccine for children and adolescents is effective with no major safety issues based on 36 clinical studies [23], and a meta-analysis also demonstrated that the incidence of myopericarditis after COVID-19 vaccination was not higher than that reported after other standard vaccinations including smallpox and influenza vaccines [13]. In this respect, this study does not support actions to exclude adolescents aged 12 to 17 years from vaccination; instead, we recommend that adverse events, including myocarditis and/or pericarditis after COVID-19 vaccination, should be closely monitored to respond and provide further information on COVID-19 vaccine safety [24].

The number of deaths reported among adolescents aged 12 to 17 years after Pfizer-BioNTech COVID-19 vaccination was 2, and both were among males aged 16 to 17 years after receipt of dose 2 in this study. For rapid responses in the ROK, the Vaccine Injury Investigation Committee (VIIC) has been reviewing all death reports to evaluate the causality between death and vaccination [11]. These 2 deaths were assessed not to be associated with the vaccination based on medical records, death certificates, autopsy, and epidemiological investigation results.

This study has some limitations. First, data were calculated using information on suspected adverse events after COVID-19 vaccination; thus, the results do not indicate an accurate diagnosis or causality between the events and the vaccines. Second, since adverse events reported to the CVMS are based on persons who visit medical institutions, the reports might have been subject to underreporting. Third, the results of text message surveys solely relied on self-reported responses; thus, the number of adverse events reported might have been overestimated due to the likelihood of responding by their parents or guardians. Fourth, as text messages were sent to adolescents aged 12 to 17 years during a particular period of time, the findings cannot be generalized to the entire adolescent population in the ROK; therefore, caution needs to be exercised in interpreting the results. Nevertheless, to the best of our knowledge, this is the first study on COVID-19 vaccine safety in adolescents aged 12 to 17 years in real-world settings in the ROK using national vaccine safety surveillance data managed by the Korean government. This study found consistent safety information on Pfizer-BioNTech COVID-19 vaccination with the US and a controlled trial; serious adverse events following vaccination were extremely rare among adolescents aged 12 to 17 years. No deaths associated with the vaccine were demonstrated as a result of the causality assessment conducted by the VIIC. We will continue to closely monitor any adverse events, including anaphylaxis and myocarditis and/or pericarditis cases, after COVID-19 vaccination for adolescents and share up-to-date information on vaccine safety with policymakers and committees to support the development of evidence-based guidelines.

Notes

Ethics Approval

The passive surveillance activity was conducted and authorized by the public health authority; the study was not subject to institutional review board approval under government regulations. The study with 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. P01-202203-01-035).

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: YK, YKL; Data curation: SK, IH, MK; Formal analysis: SK, IH; Investigation: SK, MK; Methodology: all authors; Validation:

YK, YKL; Writing-original draft: SK, YKL; Writing-review & editing: all authors.

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

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Please refer to the following examples.

• Journal articles

1. Park AK, Kim IH, Kim J, et al. Genomic surveillance of SARS-CoV-2: distribution of clades in the Republic of Korea in 2020. *Osong Public Health Res Perspect* 2021; 12:37-43.
2. Hyun J, Lee JH, Park Y, et al. Interim epidemiological and

clinical characteristic of COVID-19 28 cases in South Korea. *Public Health Wkly Rep* 2020;13:464-74. Korean.

3. Gultekin V, Allmer J. Novel perspectives for SARS-CoV-2 genome browsing. *J Integr Bioinform* 2021 Mar 15 [Epub]. <https://doi.org/10.1515/jib-2021-0001>.

• **Books**

4. Riffenburgh RH, Gillen DL. *Statistics in medicine*. 4th ed. London: Academic Press; 2020.
5. Miller DD. Minerals. In: Damodaran S, Parkin KL, editors. *Fennema's food chemistry*. 5th ed. Boca Raton, FL: CRC Press; 2017. p. 627-80.
6. Ministry of Employment and Labor. *Statistics on occupational injuries and illnesses, 2008*. Gwacheon, KR: Ministry of Employment and Labor; 2009.

• **Websites**

7. World Health Organization (WHO). COVID-19 vaccines [Internet]. Geneva: WHO; 2021 [cited 2021 Mar 15]. Available from: <https://www.who.int/emergencies/diseases/novel-coronavirus-2019/covid-19-vaccines>.

• **Conference papers**

8. Christensen S, Oppacher F. An analysis of Koza's computational effort statistic for genetic programming. In: *EuroGP 2002: Proceedings of the 5th European Conference on Genetic Programming*; 2002 Apr 3-5; Kinsdale, IE. Berlin: Springer; 2002. p. 182-91.

• **Dissertation**

9. Park HY. *The role of the thrombomodulin gene in the development of myocardial infarction [dissertation]*. Seoul: Yonsei University; 2000.

Tables and Figures

Tables should be simple, self-explanatory, and supplemental, and should not duplicate the text or figures. Each table must be on a separate page, not exceeding 1 page when printed, and have a concise and informative title. The tables should be numbered with Arabic numerals in consecutive order. Each column should be appropriately headed with units in parentheses if numerical measures are given. All units of measurements and concentrations must be indicated. Footnotes are followed by the source notes, other general notes, abbreviation, notes on specific parts of the table (^a, ^b, ^c, ^d...), and notes on level of probability (*, **, *** for *p*).

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

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