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Editorial

Efforts to return to a normal society

Jong-Koo Lee

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Every year, people in the Republic of Korea have traditionally worn masks during the winter due to influenza and fine air particulate matter. However, with the outbreak of coronavirus disease 2019 (COVID-19), mandatory mask-wearing regulations were introduced. As the country now moves into the restoration stage, it is necessary to revise these guidelines. Recently, most non-pharmaceutical intervention measures in the Republic of Korea have been relaxed, and the mandatory use of indoor face masks is being reviewed. This requirement was somewhat confusing, as it differed from World Health Organization (WHO) guidelines due to shortages of supply in the early stages of the pandemic. However, the presence of asymptomatic infections and the possibility of air transmission led to mandatory mask use being implemented. Mask use was promoted when a legal requirement to wear masks was introduced due to concerns about the spread of infectious disease (Infectious Disease Control and Prevention Act, revised on August 12, 2020).

As the vaccination uptake rate, including booster shots, increased and the number of patients decreased, the mandatory outdoor mask requirement was abolished on September 26, 2022. However, wearing masks indoors, such as on buses, taxis, ships, aircraft, and in buildings, is still recommended [1]. This is due to the recent increase in the number of patients and severely ill patients, as well as the low vaccination uptake rate among high-risk groups. The trends in outbreak response are being reviewed step by step, but measures are generally promoted and viewed as desirable based on medical and public health precautions rather than compulsion. Even before the COVID-19 pandemic, mask-wearing was recommended during influenza epidemics. Currently, an influenza epidemic is being reported after a 3-year absence due to the COVID-19 pandemic. The rate of influenza-like illness has increased from 30.3 to 41.9 compared to last week, and the respiratory virus detection rate has also increased to 83.3%, so it is reasonable to recommend wearing masks as a basic health measure [2].

In addition, while China's zero-COVID policy has suppressed the Omicron epidemic, it is expected that the spread of the Omicron variant will significantly increase with the relaxation of these policies. It is difficult to obtain accurate statistics from China, but it is believed that more than 1/3 of the population in Korea was infected in the last Omicron epidemic from 4th week to 22th week (Figure 1) [3], and a similar situation is likely to occur in China. However, it is important to consider the possibility that a new variant may emerge and cause a local epidemic, potentially becoming the source of a global pandemic. Most quarantine measures have already been lifted, such as the cancellation of quarantine measures for entrants (on June 8, 2022), the cancellation of the requirement for negative test certification (on September 3, 2022), and the cancellation of the requirement for polymerase chain reaction (PCR) tests after

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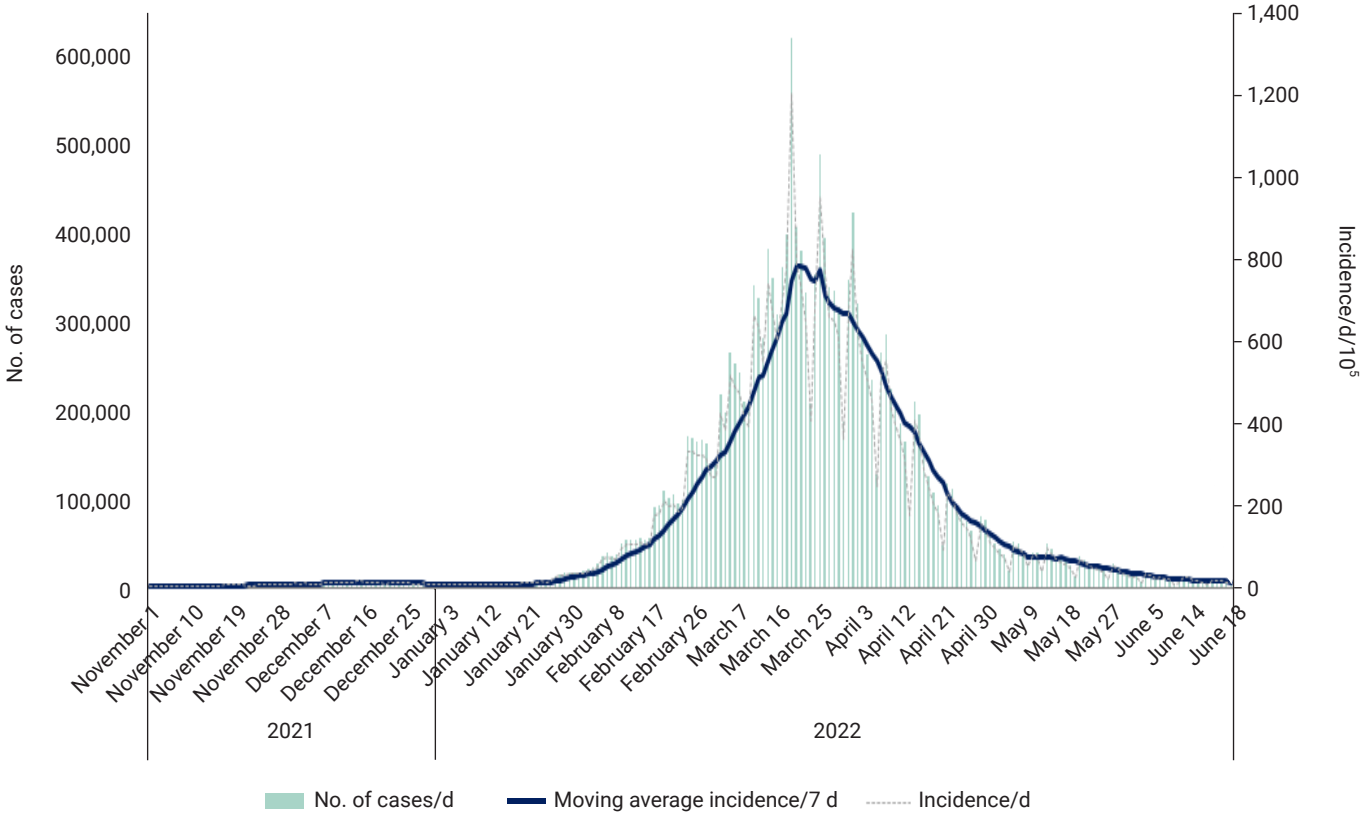

Figure 1. Confirmed cases and incidence rate (November 1, 21–June 18, 2022).
Reprinted from Korea Disease Control and Prevention Agency [3].

entry (on October 1, 2022) [4]. It is particularly important to mitigate the impact of the situation in China on Korea by strengthening fever screening tests for entrants, ensuring prompt PCR confirmation for symptomatic patients, and conducting virus sequencing tests, as it is difficult to obtain accurate information about the outbreak in China and it would not be easy to decide whether or not to go back to September.

At the end of November 2022, a ministerial meeting of the Global Health Security Agenda (GHSA) was held in Seoul, Republic of Korea. This was the second ministerial-level meeting since the Middle East respiratory syndrome outbreak in 2015, and the Minister emphasized that the country has been successfully addressing the threat of COVID-19 by strengthening its ability to respond to infectious diseases through the GHSA and active international cooperation. Twenty-seven countries, 10 international organizations, and 27 embassies participated and shared best practices. The meeting discussed the third vision for the next 5 years until 2028, which includes the full implementation of the International Health Regulations and the strengthening of technological capabilities at the national level. In particular, the Joint External Evaluation, the Global Health Security index, and the Fiscal Intervention Fund were mentioned as important achievements during the previous 2 periods. These efforts are timely in order to overcome COVID-19 and respond to new infectious diseases that may arise in the future [5]. However, above and beyond its coordinating role in addressing on-site problems, international cooperation also plays an important role in emergency relief for vulnerable populations, universal healthcare, and improving the healthcare system. As the COVID-19 situation improves, these topics will be more actively discussed and our coordinating role by New Seoul Declaration will grow accordingly.

In conclusion, it is natural to restore society to normal after the COVID-19 pandemic. Improving mask-wearing guidelines is also a step towards a more normal society. However, as the global public health crisis stage of the WHO remains unmitigated and the potential risk cannot be fully evaluated due to inadequate reporting of the outbreak in China to the international community, the importance of measures for high-risk individuals and the role of vaccines

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is underestimated. It will be necessary to gradually ease restrictions based on evidence in order to avoid giving false messages such as "the pandemic is over." At the same time, we need to be prepared for the possibility of a new outbreak, such as "Disease X."

Notes

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The author has no conflicts of interest to declare.

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Review Article

SARS-CoV-2 in brief: from virus to prevention

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ABSTRACT

The recent outbreak of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), a highly transmissible virus with a likely animal origin, has posed major and unprecedented challenges to millions of lives across the affected nations of the world. This outbreak first occurred in China, and despite massive regional and global attempts shortly thereafter, it spread to other countries and caused millions of deaths worldwide. This review presents key information about the characteristics of SARS-CoV-2 and its associated disease (namely, coronavirus disease 2019) and briefly discusses the origin of the virus. Herein, we also briefly summarize the strategies used against viral spread and transmission.

Keywords: Coronavirus; COVID-19; Pandemics; SARS-CoV-2

Introduction

Coronaviruses (CoVs) are classic, small infectious agents in both humans and animals [1]. Belonging to the family of *Coronaviridae* in the order *Nidovirales*, these viruses are divided into 2 subfamilies (*Orthocoronavirinae* and *Torovirinae*) [1]. Having 4 distinct genera in 4 major subclades, the subfamily of *Orthocoronavirinae* is classified into alpha (α)-CoVs and beta (β)-CoVs (both are infectious for mammals), as well as gamma (γ)-CoVs (infectious for birds), and delta (δ)-CoVs (infectious for mammals and birds) sharing remarkable interspecies similarities; however, differences in some features such as genome composition, transmission, pathogenicity, and associated diseases are notable (Figure 1) [1,2]. Before December 2019, 6 pathogenic CoVs had been identified as causing mild to severe human respiratory infections. Of these, 4 viruses were low-pathogenic (HCoV-OC43, HCoV-NL63, HCoV-HKU1, and HCoV-229E) associated with mild infections, and 2 viruses (severe acute respiratory syndrome coronavirus 1 [SARS-CoV-1; 2002–2003, Foshan in China] and Middle East respiratory syndrome coronavirus [MERS-CoV; 2012, Arabian Peninsula]) were highly pathogenic and linked to severe acute respiratory syndrome [3–5].

On December 31, 2019, the World Health Organization (WHO) received an alert from China and was informed of a cluster of unexplained pneumonia [6]. A week later, a new strain of CoV

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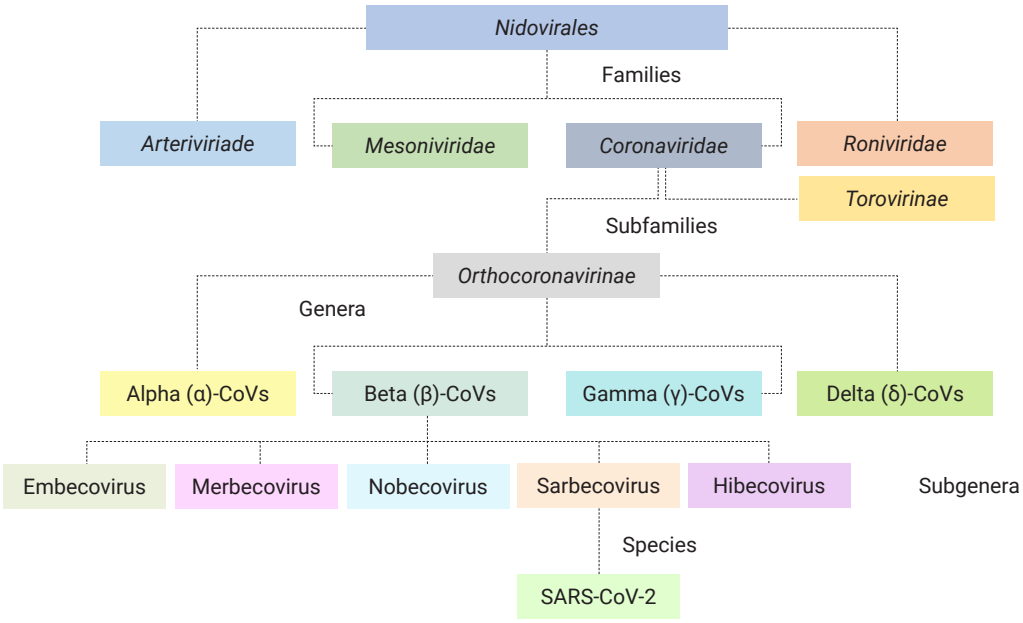

Figure 1. Classification of coronaviruses (CoVs). Based on [1].

was detected and subsequently announced by officials of the same organization [6]. Soon after, the WHO and the International Committee on Taxonomy of Viruses chose, respectively, the names 2019 novel coronavirus (2019-nCoV) and SARS-CoV-2 for the newly isolated virus [7]. Historically, SARS-CoV-2 was found after an outbreak of an unknown airway infectious disease in the city of Wuhan, China [6]. Shortly afterward, the outbreak made headlines in both regional and global news in early 2020 and plunged the world into a state of concern, and was, in fact, the beginning of a health crisis on a worldwide scale. Due to its rapid spread, the outbreak was declared a public health emergency of international concern and was deemed to constitute a global pandemic on January 30, 2020 and March 11, 2020, respectively [8].

SARS-CoV-2 is the latest infectious CoV to be identified in humans; it causes mildly symptomatic disease in about 80% of infected cases, but adverse outcomes are also predictable in the 15% and 5% of patients who develop severe and critical disease, respectively [9]. As of September 21, 2022, there have been more than 618 million confirmed coronavirus disease 2019 (COVID-19) cases, more than 6.5 million deaths, and nearly 600 million recoveries worldwide (https://www.worldometers.info/coronavirus/). To control the transmission of COVID-19 and curtail the associated infections, we should enhance our knowledge regarding the characteristics and origin of SARS-CoV-2, as well as the mechanisms underlying the associated disease. There is also a need to focus on interventions to reduce the rate of viral transmission, infection, and death.

The Virus: Structure, Genetics, Variants

Morphologically, early microscopic observations found the SARS-CoV-2 virion as a pleomorphic, rounded, and crown-shaped particle measuring 60 to 140 nm in diameter [10]. This virus contains a helical nucleocapsid protein that directly interacts with an intraparticle genomic nucleic acid as a complex of ribonucleoprotein, which are surrounded by a double-layered lipid originally derived from the membrane of infected cells [11]. In addition, the outer membrane of infectious viruses contains several projected proteins (referred to as spike proteins), which are 9 to 12 nm in diameter (Figure 2) [10].

Like other CoVs, SARS-CoV-2 has a capped and polyadenylated, large, constant, single, and positive-sense ribonucleic acid organized in a specific order into different gene sequences responsible for 3 general types of functional proteins [12]. The SARS-CoV-2 RNA encodes at least 29 different functional proteins essential for viral replication, infectivity, immunomodulation, and future therapeutic and vaccine research [13]. The genome of SARS-CoV-2 contains 2 overlapping regions (open reading frame-1a [ORF1a] and ORF1b) encoding 16 non-structural proteins (NSP1-16). In addition, it encodes 4 structural proteins (spike [S], envelope [E], membrane [M], and helical nucleocapsid [N]) and a set of accessory proteins (ORF3, ORF6, ORF7, ORF8, ORF9, ORF10) with a variable length, ranging from 13 amino acids to 1945

amino acids for NSP11 and NSP3, respectively (Figure 2) [13,14].

The nucleic acid sequence of SARS-CoV-2, with a high sequence identity, is closely related to bat coronavirus RaTG13 (96.10%), RpYN06 (94.48%), RmYN02 (93.30%), SARS-like-CoVZC45 (87.60%), SARS-like-CoVZXC21 (87.40%), SARS-CoV-1 (79.6%), and MERS-CoV (50%) [15–17]. Despite these similarities, SARS-CoV-2 differs from SARS-CoV-1 genetically. For instance, in SARS-CoV-2, ORF8b is longer (37 amino acids) and ORF3b is shorter (132 amino acids) than in SARS-CoV-1. In addition, there are no genes encoding either ORF8a or hemagglutinin esterase in SARS-CoV-2 [18,19].

The genome of SARS-CoV-2 undergoes variation, deletion, insertion, and broad mutations (estimated approximately 1×10^{-3} substitutions per year) leading to the emergence of new lineages/variants with new viral and infectious characteristics [20]. To date, 3 classifications—variant of concern (VOC), variant of interest (VOI), and variant under monitoring (VUM)—have been introduced for variants of SARS-CoV-2. The first term (VOC) refers to variants with high transmissibility that can be highly virulent, with a negative impact on vaccine efficiencies and therapeutic prospects [21]. Currently, these variants are challenging to human health. The second term (VOI) denotes variants that harbor genetic mutations predicted to have an impact on viral transmissibility and disease severity [22]. The last term (VUM) refers to variants that are genetically changed and are likely to pose a threat in the future due to their unknown phenotypic or epidemiological effects [21]. Lists of variants, countries, and selected virus spike mutations are summarized in Table 1.

Origin

The recent literature still contains no clear data to answer the question of whether SARS-CoV-2 is a natural or man-made virus; however, research on this mysterious topic is still being undertaken. Almost all human CoVs are thought to be of animal origin, as these viruses can spread to humans by cross-species transmission [23]. The SARS-CoV-2 pandemic seems to have started in the Wuhan wet market in China, where different kinds of animals were traded [24]. Bats and pangolins are likely the natural hosts of SARS-CoV-2 [25,26]. However, for more than 2 years before the start of the current pandemic, those animals were not for sale in the Wuhan wet market [24]. Therefore, additional hosts (reservoirs and intermediate ones) may need to be identified through further investigations.

To date, different scenarios have been described regarding the origin of SARS-CoV-2. In this context, 2 scenarios (zoonotic and laboratory origin) are thought to be more likely than the others. Briefly, the first one is supported by genomic data showing the same mutations in 6 residues of viral receptor-binding domains (RBDs) in both SARS-CoV-2 and pangolin-derived CoVs, suggesting the appearance of natural selection in pangolins before its transfer to humans [27]. In addition, the spike protein of SARS-CoV-2 includes a furin polybasic

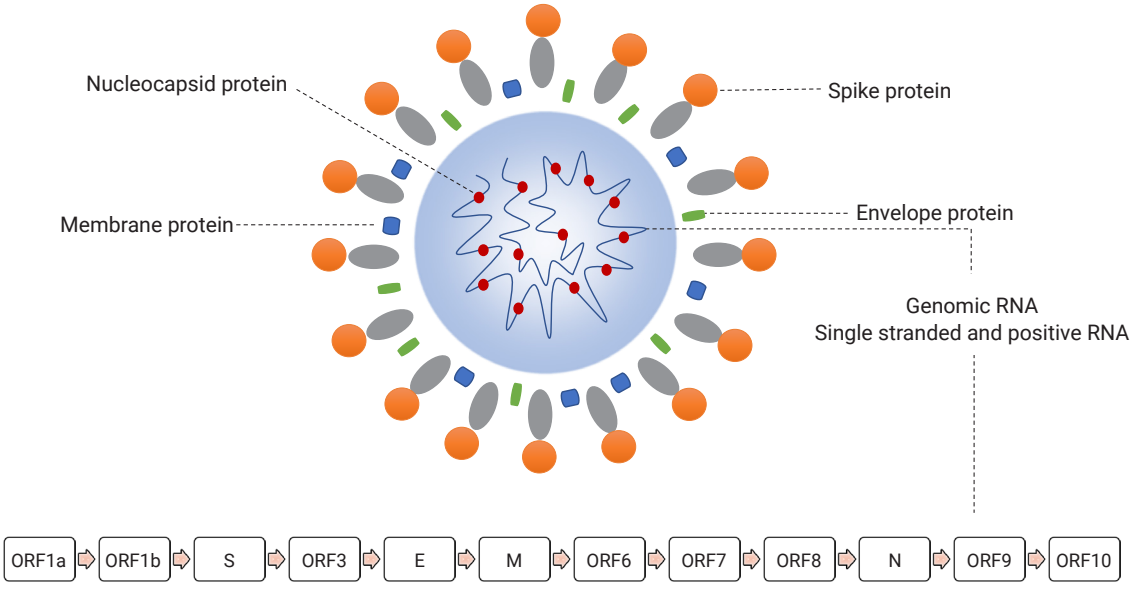

Figure 2. Virion structure and genomic organization of severe acute respiratory syndrome coronavirus 2.
ORF, open reading frame; S, spike; E, envelope; M, membrane; N, nucleocapsid.

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Table 1. Overview of SARS-CoV-2 variants

Classification	Pango lineage	WHO label	First identification	The most-affected countries (selected)	Spike mutations (selected)
Variant of concern	B.1.1.7	Alpha	2020, UK	UK, USA, Germany, Sweden, Denmark	N501Y, A570D, D614G, P681H, T716I, S982A, D1118H
	B.1.351	Beta	2020, South Africa	South Africa, Philippines, USA, Sweden, Germany	D80A, D215G, K417N, E484K, N501Y, D614G, A701V
	P.1	Gamma	2020, Brazil	Brazil, USA, Chile, Argentina	L18F, T20N, P26S, D138Y, R190S, K417N/T, E484K, N501Y, D614G, H655Y, T1027I, V1176F
	B.1.617.2	Delta	2020, India	USA, India, UK, Turkey, Germany	T19R, R158G, L452R, T478K, D614G, P681R, D950N
	B.1.1.529	Omicron	2021, South Africa	UK, USA, Denmark, Germany, Brazil	G339D, S373P, K417N, N440K, G446S, S477N, T478K, E484A, G496S, Q498R, Y505H, T547K, D614G, H655Y, P681H, N764K, N856K, Q954H, N969K
Variant of interest and variant under monitoring	B.1.1.1.37	Lambda	2020, Peru	Peru, Chile, Argentina, USA, Ecuador	G75V, T76I, L452Q, F490S, D614G, T859N
	P.3	Theta	2021, Philippines	Philippines	E484K, N501Y, P681H, D614G, E1092K, H1101Y, V1176F
	P.2	Zeta	2020, Brazil	Brazil, USA, Canada, Argentina, Paraguay	E484K, D614G, V1176F
	B.1.427/B.1.429	Epsilon	2020, USA	USA, Mexico, Canada	S13I, W152C, L452R, D614G
	B.1.525	Eta	2020, Worldwide	Canada, USA, Germany, France, Denmark	A67V, E484K, D614G, Q677H, F888L
	B.1.526	Lota	2020, USA	USA, Ecuador, Canada, Puerto Rico	T95I, D253G, D614G
	B.1.617.1	Kappa	2021, India	India, Ireland, Canada, UK, USA	G142D, E154K, L452R, E484Q, D614G, P681R, Q1071H

Sources: https://cov-lineages.org and https://viralzone.expasy.org.
SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; WHO, World Health Organization.

cleavage site and o-linked glycans, which both seem to have been naturally generated, likely through immunity-induced pressure [27].

In contrast to the natural selection scenario, it has been assumed that SARS-CoV-2 was artificially synthesized under controlled conditions by a combination of RaTG13 -like and MP789- like CoVs [28]. This assumption was discussed in a recently published letter. In this letter, no sufficient data were provided in favor of the man-made origin of SARS-CoV-2 [29]. In another claim, SARS-CoV-2 was stated to be a recombinant virus having an inserted fragment (1,387 bp) corresponding to the viral spike protein; however, this statement was soon refuted by a group of researchers who found that this sequence was not unique to SARS-CoV-2, since other CoVs clearly showed the same genetic pattern in their spike proteins [30]. However, on March 30, 2021, a group of experts reported that although laboratory leakage could possibly have occurred, for SARS-CoV-2, it is an "extremely unlikely" route [31]. In general, more studies should be done to find a definitive answer to the question of whether SARS-CoV-2 is a naturally selected or laboratory-generated/leaked virus.

Transmission

It is well-established that being unprotected and close to a person infected with SARS-CoV-2 regardless of whether he or she is symptomatic or not, increases the risk of viral transmission, especially in communities with high levels of interpersonal contact [6,32]. This mode of transmission (interpersonal transmission) which was first confirmed on January 20, 2020, highlights the importance of taking appropriate precautions when attending public gatherings outside the home [8]. Horizontally, expiratory activities generate up to a few million droplets of oral fluids with sizes of <1 to 1,000 μm [33,34]. Large droplets (60–100 μm) are formed and expelled into the air primarily by defensive reflexes of the respiratory system, which throw virus-laden

liquid particles up to a distance of approximately 1 meter for exhalation to 2 meters for coughing and 6 meters for sneezing within 0.12 to 1 second in a velocity of 1 to 50 m/s [33].

SARS-CoV-2 is a contagious virus and, indeed, what has made this virus a more transmissible CoV strain than SARS-CoV-1 and MERS-CoV might be the number of detectable viruses which are shed outside the mouse/nose [34]. SARS-CoV-2-laden aerosols suspended in the air were found to travel for distances up to 4 meters and are similarly infectious to SARS-CoV-1 at a median interval of an hour after generation, increasing the likelihood of infection if inhaled or deposited on the mucosa [32,35,36]. Being in an enclosed environment (i.e., restaurants, classrooms, gyms, or prisons) where there is no proper or poor air circulation may facilitate the virus spread, increasing the risk of interhuman viral infection [37]. Although the minimum number of virions required to start an infection has not been reported, early studies estimated that around 100 infectious particles are enough to infect those who are not appropriately protected against viral transmission [38].

In indirect transmission, SARS-CoV-2 may spread through inanimate surfaces. This may occur through touching cross-contaminated or directly contaminated commonly used objects [39,40]. However, this mode of transmission is considered less important than direct contact for viral spread and transmission [41]. Nonetheless, various environmental conditions such as the level of light, pH, ultraviolet irradiation, temperature, and humidity need to be set to find how much these parameters affect the stability of the virus on contaminated surfaces. In addition to all the above routes, infection may also occur by exposure to virus-containing non-respiratory biofluids since molecular detection has confirmed the presence of viral nucleic acid in human body fluids such as breast milk, amniotic fluid, blood products, sexual secretions, and urinary and gastrointestinal excretions in SARS-CoV-2-infected individuals [42–45]. This raises concerns regarding additional modes of virus transmission.

Infection Mechanisms

Basic information exists on the pathogenic mechanisms of SARS-CoV-2 and the mechanisms underlying the progression of the disease to unfavorable outcomes. SARS-CoV-2 encodes a trimeric, mutable, and surface class I viral fusion protein called the S glycoprotein, which consists of S1 (binding) and S2 (anchoring) subunits associated together non-covalently [46]. The S1 subunit harbors a functional and antigenic domain called the RBD, which is responsible for receptor engagement in virus-cell interaction, whereas S2 fuses viral and cell membranes to help the virus enter the cell [46]. The spike protein of SARS-CoV-2 is remarkably similar (approximately 78% identity in amino acid sequences) to its equivalent presented on the SARS-CoV-1 membrane [47]. SARS-CoV-2 is a novel airway-associated infectious agent that primarily affects the host respiratory system and likely exhibits systemic involvement with non-respiratory systems due to its broad tissue tropism explained by the wide expression pattern of angiotensin-converting enzyme-2 (ACE-2) as the predominant cellular receptor (also for SARS-CoV-1) and its co-expressed molecule, the transmembrane serine protease 2, as a cellular and spike priming protease [48,49]. These molecules mediate the virus attachement penetration through the endocytic pathway, which is followed by key replicative steps that eventually form viral particles and lead to the release of new infectious particles out of the infected cell (Figure 3) [14]. For SARS-CoV-2, additional and alternative molecules have recently been proposed to serve as entry mediators [46,50,51]. In contrast to ACE-2, dipeptidyl-peptidase 4 and aminopeptidase N are often utilized by MERS-CoV and HCoV-229E, respectively, to invade the cells of choice [46].

As mentioned above, SARS-CoV-2 is a respiratory virus, meaning that the respiratory system might be the primarily affected organ system during infection [52]. Following the inhalation of virus-laden particles, the infection begins by attacking the epithelium of the respiratory tract primarily via targeting nasal multiciliated and sustentacular cells as well as oral glands, and mucous membranes enriched by cell-associated SARS-CoV-2 entry molecules [53–56]. Inside invaded cells, the viruses are sensed via cytoplasmic recognition molecules, which result in interferon (IFN)-mediated innate immune responses derived from the activation of IFN regulatory factors 3 and 7 (IRF3 and IRF7) [51].

As shown in Figure 4, by reaching the lower airway (alveoli) through the conducting airways, SARS-CoV-2 preferentially invades alveolar epithelial type II cells, allowing the virus to efficiently replicate, making more viruses and infect more cells [6]. Upon cell entry and virus replication, the activation of pattern recognition receptors and inflammatory signaling pathways initially results in cytokine and chemokine production [57]. However, SARS-CoV-2 has evolved to interfere with these intracellular recognition pathways [58]. When they fill the alveolar lumen, these inflammatory mediators mediate the recruitment of a subset of mono- and poly-morphonuclear blood cells into the site of infection, where the immune system responds to viruses that have entered [59]. The attracted leukocytes, predominantly monocyte-

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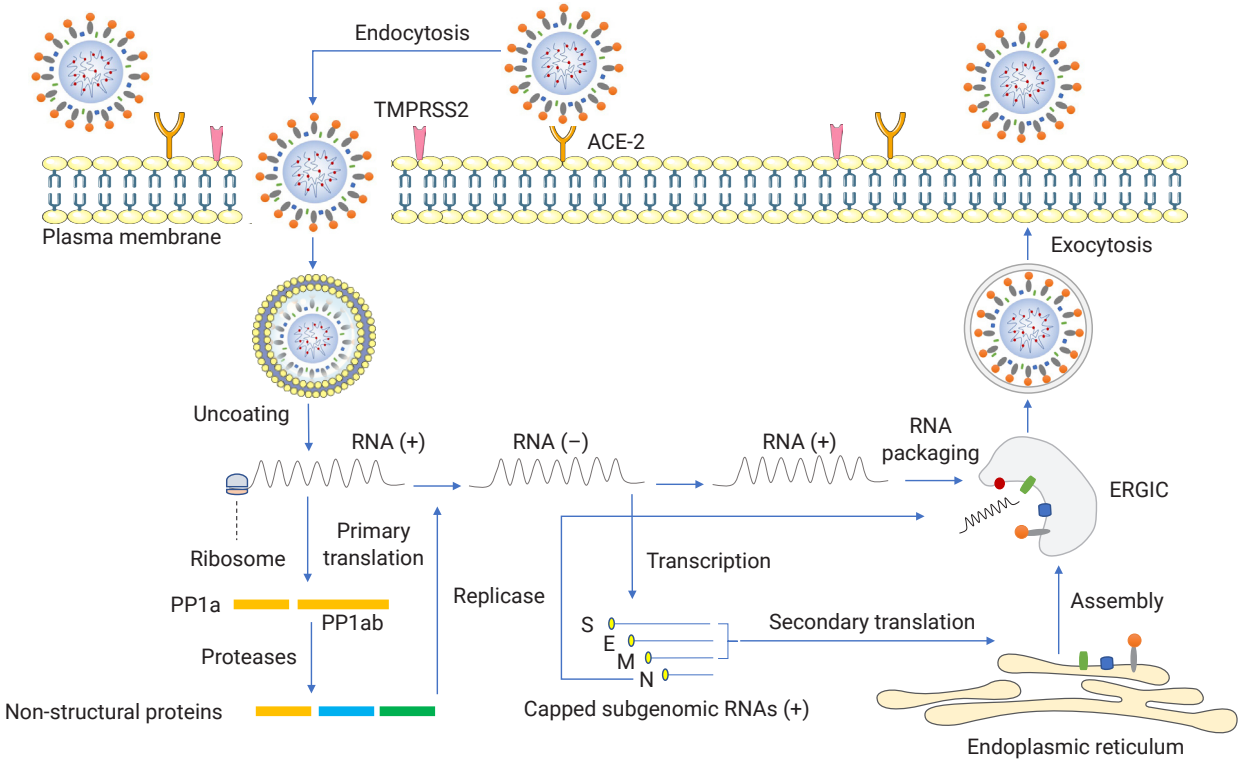

Figure 3. The severe acute respiratory syndrome coronavirus 2 life cycle.
TMPRSS2, transmembrane serine protease 2; ACE-2, angiotensin-converting enzyme 2; ERGIC, endoplasmic-reticulum–Golgi intermediate compartment; S, spike; E, envelope; M, membrane; N, nucleocapsid. Created with the help of https://smart.servier.com/. Based on [14].

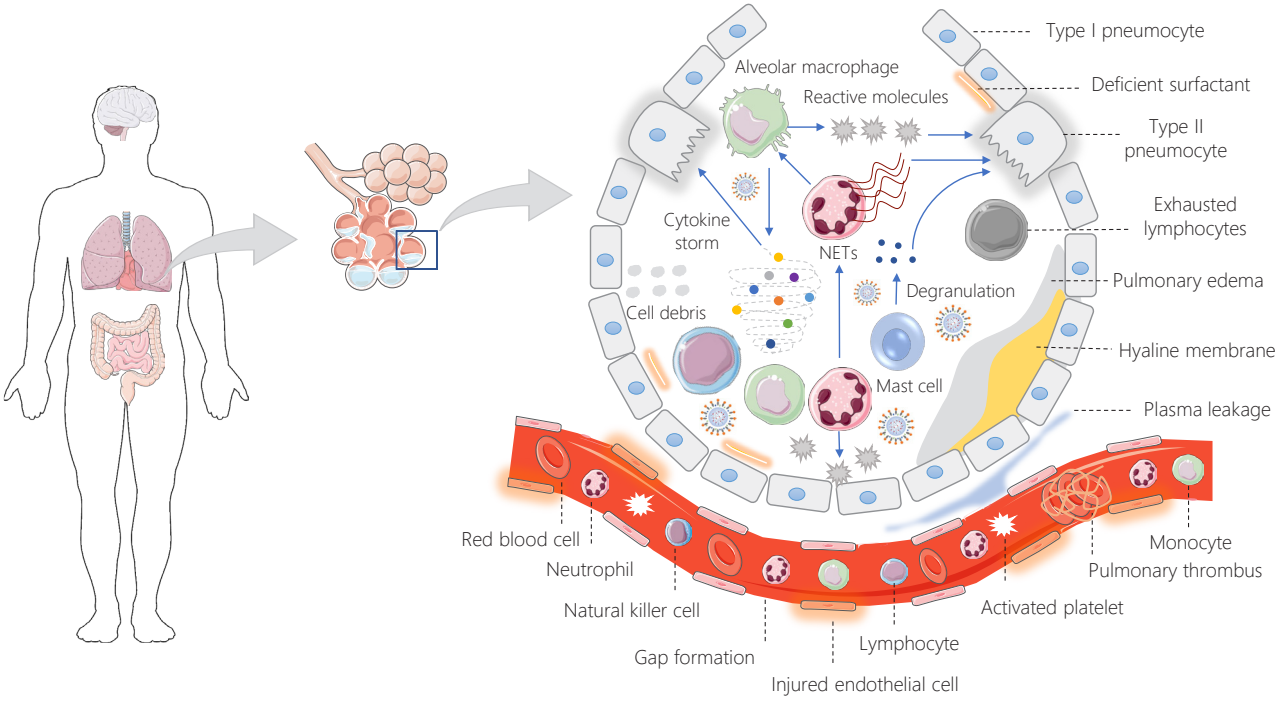

Figure 4. The pathophysiology of severe acute respiratory syndrome coronavirus 2 infection.
NETs, neutrophil extracellular traps. Created with the help of https://smart.servier.com/.

derived macrophages, contribute to the enhancement of host immune responses characterized by uncontrolled and storm-like cytokine activity [6,60]. The excessive release of cytokines results in capillary permeability and plasma leakage, and it also promotes further pulmonary inflammation and tissue injuries, which are associated with virus-induced acute respiratory distress syndrome, characterized by hypoxemia (impaired oxygenation) and organ deprivation of respiratory gases [9,61,62]. Furthermore, activated resident (e.g., macrophages) or recruited (e.g., neutrophils) immune cells contribute to injuries of both pneumocytes and endothelial barriers by inducing reactive molecules, which also play a role in defective T cell-mediated antiviral immunity [61,63]. SARS-CoV-2 induces neutrophil extracellular trap formation, which favors further inflammation triggered by macrophage-derived inflammatory cytokines [64]. The inflammation and alveolar injuries are also triggered by the rapid degranulation of mast cells, which are known as tissue-resident inflammation regulators cells [65]. SARS-CoV-2-infected cases whose lungs are seriously involved are at risk of alveolar collapse due to the loss of or low concentration of surfactant [66]. In these patients, hyaline membrane and intracapillary microthrombus formation are also expected [6]. Severe SARS-CoV-2 infection is also marked by impaired cell-mediated immunity, characterized by a numerical reduction (so-called lymphopenia) in the number of $CD4^+$ and $CD8^+$ T cells, Tregs, and γδ T cells and the functional exhaustion of peripheral $PD\text{-}1^+$ and $Tim\text{-}3^+$ expressing lymphocytes [64,67].

As a pathophysiological mechanism, since the infection presents extrapulmonary manifestations, SARS-CoV-2 can infect cells outside the respiratory system, likely through hematogenous spread, leaving lesions in infected tissues and body organs [68].

Clinical Manifestations

COVID-19 is a multifaceted and, more accurately, a multiphasic disease. While the entire course of the disease involves no or mild symptoms in most cases, severe to critical infections determined by organ involvement and the corresponding spectrum of clinical manifestations should also clinically be considered in a subset of SARS-CoV-2-infected individuals [8,69,70]. COVID-19 is a life-threatening disease, as it may lead to death at a median of 2 weeks after symptom onset; however, dying from the disease is relatively uncommon overall (case fatality rate, 1%) and most patients recover completely [8,56,71]. In this context, underlying comorbidities, such as non-communicable diseases, are among the risk factors for adverse outcomes such as hospitalization and death [72]. It was recently estimated that 84.1% of deaths due to COVID-19 occurred in patients with at least 1 medical condition [73]. Sex and age differences also affect the outcomes of infection in a non-favorable fashion [64].

Through close and unprotected contact with confirmed patients, a symptomatic infection may develop within a week (median incubation period: 4 to 5 days) after virus exposure [56]. In early 2020, a brief report was published from a series of pneumonia patients who were clinically diagnosed with fever, cough, and chest discomfort [10]. Similar to the clinical pictures of other CoVs, the symptoms of COVID-19 may present in a combined pattern based on the disease severity [74]. Children with COVID-19 were found to be less likely to develop fever as a symptom of infection than adults [75]. A recent meta-analysis found medium-grade fever (ranging from 38.1°C to 39.0°C) in the majority of included patients, independent of the disease severity [75]. This symptom may last for 10 days on average in some hospital-admitted patients [76]. In these patients, the need for health care services may be associated with fever duration [77]. In the early stages of the disease, when the infection is mild, patients with acute SARS-CoV-2 infection may complain of muscle pain, headache, diarrhea, and most importantly, respiratory symptoms including nasal and throat congestion, coughing, rhinorrhea, sore throat, and shortness of breath at varying prevalence rates [78,79].

As the disease progresses, the clinical symptoms show a moderate picture of severity approximately 1 week after symptom onset [56]. During this time, fever and coughing are likely to persist and breathlessness, tachypnea, moderate pneumonia, and abnormalities on chest computed tomography may manifest [78,80]. Coughing is a common sign that acutely presents in a non-productive pattern with no sputum production in the early days after illness onset, but as the disease progresses, the pattern changes to being productive [79]. In some patients, the infection is clinically characterized by severe and critical manifestations. In this stage, the infection towards organ dysfunction and failure, tissue injuries, severe pneumonia and dyspnea, hypoxia, cyanosis, and sepsis [78,80]. Symptomatic COVID-19 patients may also exhibit a variety of systemic symptoms, which are explained by the multiorgan involvement of the viral infection.

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Long COVID

The term "long COVID," also known as "post-COVID-19 symptoms," refers to a syndrome experienced by a subset (80%) of patients with a history of probable or confirmed COVID-19 who continue to experience for a long time (i.e., weeks after the acute infection) persistent symptoms (physical, mental, and/or cognitive symptoms) with no alternative diagnosis or explanation [81,82]. This syndrome is highly prevalent within the first 11 weeks after the onset of the disease, has a relapsing-remitting nature, and is not specific to SARS-CoV-2, since infection with other CoVs such as SARS-CoV-1 and MERS-CoV has been reported to have similar outcomes [82,83]. Long COVID appears to occur more likely in smokers, females, adults aged >35 years, those experiencing socioeconomic deprivation, patients with blood type A, people of White race, those who experienced hospital admission at the time of acute infection, patients with co-morbid conditions (e.g., asthma or obesity), and those with severe illness and poor general as well as mental health [83–88]. Patients with no or moderate symptoms at the time of acute infection are also at risk [89]. This syndrome is a multisystem disorder that can affect multiple body organs (e.g., the brain, skin, heart, kidney, lungs, etc.) characterized by different signs and symptoms (as summarized in Figure 5) [90,91]. While it is not clear how this syndrome is triggered, (1) viral-induced invasion and autoimmunity, (2) impaired immunometabolism, (3) immune exhaustion, (4) viral antigen persistence, (5) altered microbiome, (6) reactivation of latent viruses, and (7) increases and/or decreases in the renin-angiotensin system have been described as mechanisms that are likely involved in the pathophysiology of long COVID [92,93].

Prevention

Primary Prevention and Protection

To mitigate the virus spread, prevent SARS-CoV-2 transmission, and end the current pandemic, a set of personal, household, and community practices are recommended as chain-breaking measures, along with public immunization as the most effective strategy in response to viral pandemics. These include (1) physical and social distancing as general advice and an effective non-pharmaceutical intervention at both the individual and community levels, as manifested by school closures, workplace measures, public transport restrictions, and stay-at-home recommendations [94]; (2) changing social greetings (e.g., handshaking, kissing, and hugging) and face-touching behaviors [95]; (3) personal hygiene by regular handwashing with water and proper detergent like soap

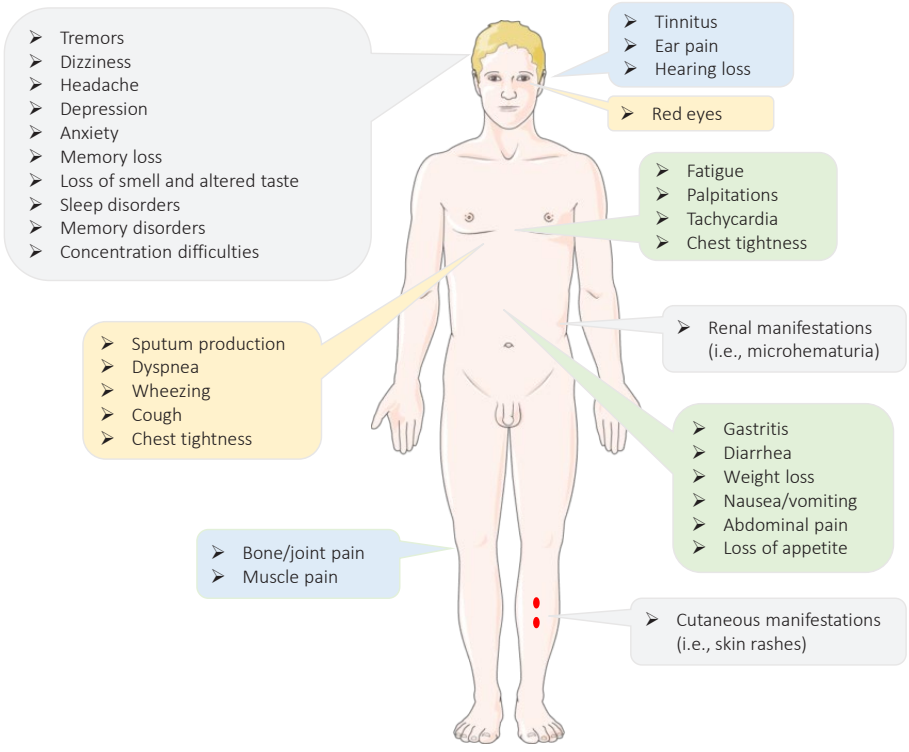

Figure 5. Long-term effects of coronavirus disease 2019.
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(at least 40–60 seconds) or sanitizing one's hands using alcohol-based sanitizers (62%–71%) for an adequate time if washing is not possible [96]; (4) employing sanitization procedures for commonly shared objects and touched areas by using ultraviolet irradiation or effective disinfectants and chemical compounds to inactivate the landed virus on physical surfaces [96]; and (5) self-protection using personal protective equipment. In this regard, wearing a well-fitted N95, medical, or even homemade mask in compliance with design standards reduces the risk of respiratory emissions, protects against virus exposure, and subsequently from being infected in high-density are where being within close contact with others is difficult to avoid [97].

For healthcare workers who are at the front line in healthcare settings, there are additional recommendations to take care of themselves and be safe against viral transmission. Although respiratory protection (wearing disposable and well-fitting facial masks [reported to be light, comfortable to wear, and easy to remove] and well-covered facial shields [reported to involve less skin irritation, and easy to breathe through] to block expelled virus-containing respiratory secretions) is highly recommended, eye protection (in addition to other required personal protective equipment) also needs to be carefully considered to limit the risk of viral transmission through the ocular mucous membranes in direct visits and care [98,99]. For this goal, facial shields as an effective barrier may offer a level of protection for the eyes, nose, mouth, and face; however, they might not be welcomed by some workers. Although goggles are not comfortable to wear for hours in daily practice and may interfere with vision, they can be an option to protect the eyes against contamination via droplets and/or splashes [100]. Healthcare workers are also required to wear protective long-sleeved gowns to cover exposed body parts against infected biofluids (i.e., respiratory secretions) and disposable medical gloves (from entry to exit of the patient's room) to keep their hands clean and avoid virus spread and self-contamination; however, skin irritation (i.e., rash, itching, and dry skin) are expected in some workers [101–103].

Vaccine, Vaccination, and Herd Immunity

To end the current viral outbreak, similar to previously reported outbreaks caused by infectious viruses, the development of prophylactic vaccines and subsequently public immunization on a large scale is an urgent priority for all at-risk and affected nations, sub-nations, and territories. Since the start of the recent outbreak, many institutions and companies have been working on both conventional and novel technological innovations using the whole virus or its functional components (e.g., the S protein) to make attenuated and inactivated virus vaccines, viral-vector vaccines, protein subunit vaccines, virus-like particle vaccines, and nucleic acid-based vaccines in a competitive environment, aiming to achieve the most desirable and broadly protective vaccines with all included standards such as high quality, favorable safety, and high efficacy at disease prevention for use in those who are at risk of viral infection [104]. To reach this goal, different SARS-CoV-2 proteins (mostly the viral spike protein) were targeted by recent efforts to find and test the best viral component for vaccine research [104]. As of September 19, 2022, 47 vaccines made by different platforms have been approved and used by 201 countries based on the decisions of national authorities and regulatory agencies; however, these vaccines are still clinically monitored under different trials in different countries to confirm their safety and efficacy (https://covid19.trackvaccines.org/). The most welcomed platforms offering a high grade of protection in vaccine receivers are BNT162b2 (an RNA-based vaccine) by Pfizer–BioNTech (efficacy, 95.0%), mRNA-1273 by Moderna (efficacy, 94.1%), and Sputnik V (adenovirus-based vaccine) by the Gamaleya Institute (efficacy, 91.6%) [105]. The following vaccines have also been tested in trials for use in humans, showing a lesser degree of protection: BBIBP-CorV (inactivated virus vaccine) by Sinopharm (efficacy, 79.34%), Covaxin (whole-virion inactivated vaccine) by Bharat Biotech (efficacy, 81.0%), Ad26.COV2.S (recombinant vaccine/adenovirus serotype 26 [Ad26]) by Johnson & Johnson (efficacy, 72.0%) and AZD1222 (recombinant vaccine) by Oxford/AstraZeneca (efficacy, 70.4%) [105]. For administration, almost all these vaccines are delivered by intramuscular injection into the muscles in 1 to 2 injections based on the type of vaccine and on a certain timetable, with the second injection occurring about 1 month after the first injection in almost all vaccines [105]. Generally, the safety of these vaccines is favorable, and most volunteers who were immunized by these vaccines had no complaints of adverse and serious reactions; however, pain and tenderness, fever, headache, fatigue, and nausea are common in some vaccinated individuals [106]. In general, the storage, handling, and transportation of almost all developed vaccines are challenging; hence, controlled conditions (2°C–8°C for most vaccines for a short period) are essential to maintain the vaccines intact and effective [107,108].

While mass vaccination programs are strongly recommended in this complicated situation to immunize people against viral infection (both symptomatic and even asymptomatic infections) and to prevent viral transmission, hospitalization, and death, herd immunity may not be reached even after natural infection [109,110]. At this time, there are some

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challenges ahead that complicate the estimation of the herd immunity threshold. Inequalities in vaccine distribution and coverage are a major concern, since these gaps allow viruses to spread worldwide, especially in low- and middle-income countries with vaccination rates <10% [111,112]. In addition, herd immunity remains difficult to achieve in societies where a large proportion of unvaccinated people have concerns about vaccine safety and necessity [109]. It also should be noted that the immune responses offered by different vaccine platforms are variable in duration, and vaccines differ from each other in terms of efficacy or effectiveness [113]. Additionally, as mentioned in section 2, SARS-CoV-2 has different strains; therefore, infection with one variant may not trigger long-lasting immunity to protect against infection with other variants [108].

Conclusion

After about 2 and a half years of struggles, the current SARS-CoV-2 pandemic is still a matter of concern as the virus tends to continue to genetically evolve into different variants, globally spread with a rapid distribution among human populations, and infect new cases among those who are not immune or do not follow the policies and recommended guidelines on the disease prevention. This virus is not the first emerging human CoV, but it is the most challenging strain, with a high degree of infectiousness and a high interhuman transmission rate. Although dozens of effective vaccines have been designed and are now available to use for public immunization, personal protection by taking appropriate precautions and following relevant guidance of the local health authorities are also essential to stop viral transmission and end the global outbreak. With little knowledge about the behavior of the virus, which seems to be the tip of the iceberg, intensive studies are recommended to comprehensively understand and find answers to open questions regarding the original, epidemiological, pathophysiological, and clinical aspects of SARS-CoV-2 and its associated disease in the near future and to design and develop new and more effective preventive and therapeutic interventions aiming to return the current complicated situation to normal.

Notes

Ethics Approval
Not applicable.

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

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

Authors' Contributions
Conceptualization: HK; Data curation: HK; Investigation: HK, ZK, NK; Supervision: HK; Writing–original draft: HK; Writing–review & editing: HK, ZK, NK.

Additional Contributions
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Review Article

Carbapenem resistance in critically important human pathogens isolated from companion animals: a systematic literature review

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ABSTRACT

This study aimed to describe the presence and geographical distribution of Gram-negative bacteria considered critical on the priority list of antibiotic-resistant pathogens published by the World Health Organization, including carbapenem-resistant *Enterobacteriaceae*, carbapenem-resistant *Acinetobacter* spp., and carbapenem-resistant *Pseudomonas aeruginosa*. A systematic review of original studies published in 5 databases between 2010 and 2021 was conducted, including genotypically confirmed carbapenem-resistant isolates obtained from canines, felines, and their settings. Fifty-one articles met the search criteria. Carbapenem-resistant isolates were found in domestic canines and felines, pet food, and on veterinary-medical and household surfaces. The review found that the so-called "big five"—that is, the 5 major carbapenemases identified worldwide in Enterobacterales (New Delhi metallo-β-lactamase, active-on-imipenem, Verona integron-encoded metallo-β-lactamase, *Klebsiella pneumoniae* carbapenemase, and oxacillin [OXA]-48-like)—and the 3 most important carbapenemases from *Acinetobacter* spp. (OXA-23-like, OXA-40-like, and OXA-58-like) had been detected in 8 species in the Enterobacteriaceae family and 5 species of glucose non-fermenting bacilli on 5 continents. Two publications used molecular analysis to confirm carbapenem-resistant bacteria transmission between owners and dogs. Isolating critically important human carbapenem-resistant Gram-negative bacteria from domestic canines and felines highlights the importance of including these animal species in surveillance programs and antimicrobial resistance containment plans as part of the One Health approach.

Keywords: Beta-lactam resistance; Carbapenem-resistant *Enterobacteriaceae*; Drug resistance; Gram-negative bacteria; One Health; Pets

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Introduction

A systematic analysis of antimicrobial resistance (AMR) in 2019 found that bacteria-related AMR accounted for 4.5 million deaths worldwide. Moreover, the global burden of AMR will be

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responsible for 10 million deaths worldwide by 2050 [1]. AMR incurs increased healthcare system costs associated with length of hospital stay, additional follow-up visits, and using drugs of last resort (DoLR) [2–4].

Antimicrobial-resistant infections in clinical and community settings are frequently associated with β-lactam-resistant Gram-negative bacteria [5–7]. Resistance to β-lactams in Gram-negative bacteria occurs due to target site modification, decreased antibiotic concentration resulting from efflux pumps, changes in outer membrane permeability caused by the loss or modifications of porins, and enzymatic inactivation of the drug by β-lactamase production. More than 4.900 β-lactamases have been reported to date [6,8]. β-lactamases can be structurally [9] or functionally classified [10]. Four types are recognized structurally. Types A, C, and D are serine enzymes, and type B includes metallo-β-lactamases [6,8,9].

Carbapenemases are extremely relevant because they hydrolyze carbapenems; β-lactam DoLRs have broad-spectrum activity and stability [6]. Carbapenem resistance (CR) is considered a marker for extensively drug-resistant (XDR) and pandrug-resistant (PDR) Gram-negative bacteria because it is associated with a wide range of co-resistance to other antimicrobial drugs [11].

According to epidemiological factors related to the degree of global spread of carbapenem-hydrolyzing enzymes, 2 groups of carbapenemases have been proposed for Enterobacterales. The first group comprises the "big five" that are widespread worldwide, and the second group includes the minor or "rare" carbapenemases that have a limited geographical spread [8]. The "big five" carbapenemases include the class A enzyme *Klebsiella pneumoniae* carbapenemase (KPC), class B enzymes active-on-imipenem (IMP), Verona integron-encoded metallo -β-lactamase (VIM), New Delhi metallo-β-lactamase (NDM), and class D enzyme active on oxacillin [OXA]-48-like [8]. Three oxacillinases from the genus *Acinetobacter* (OXA-23-like, OXA-40-like, and OXA-58-like) have been reported as of concern due to their worldwide spread [12,13].

The World Health Organization (WHO) published a global priority list of antibiotic-resistant bacteria to guide the discovery, research, and development of new antibiotics in 2017. The most important category on the list (i.e., critical-priority microorganisms) includes the carbapenem-resistant *Enterobacteriaceae* (CRE) family and 2species of carbapeem -resistant, glucose-non-fermenting bacilli (CRGNFB), namely, carbapenem-resistant *Acinetobacter baumannii* and carbapenem-resistant *Pseudomonas aeruginosa*, due to their impact on mortality, disease burden, and circulation at the human-animal-environment interface [11].

AMR involves complex human-animal-environment interface-related microbial interactions. Carbapenem use is not recommended for companion animals [14]; however, CR isolates have been reported in these animals [15]. The interactions between owners and companion animals promote AMR dissemination and maintenance through bacterial bidirectional transmission [16]. Thus, a One Health-oriented approach to analyzing carbapenemase circulation in companion animals is essential—that is, an integrated, multisector approach seeking to balance and optimize the health of humans and animals, as well as environmental sustainability [17,18].

Accordingly, this study adopted a One Health perspective for describing the presence and geographic distribution of antibiotic-resistant Gram-negative bacteria classified as critical on the WHO priority list isolated from domestic canines and felines and the contexts associated with their presence, including CRE, carbapenem-resistant *A. baumannii*, and carbapenem-resistant *P. aeruginosa*.

Materials and Methods

Search Strategy and Selection of Studies

A search for original articles that evaluated antimicrobial susceptibility to carbapenems in *Enterobacteriaceae* and glucose non-fermenting bacilli (GNFB), such as *Acinetobacter* spp. and *P. aeruginosa* obtained from domestic canines or felines, or both, and contexts associated with their presence (e.g., veterinary care, pet food, and/or the animal's home) in which genotypic CR was detected was carried out. The databases consulted were Medline, PubMed, Web of Science, Scopus, Wiley Online Library, and CABI: VetMed Resource.

Descriptors from the DeCS/MeSH thesauri were used by applying a specific search formula and combining the following terms: (carbapenemase OR CPE OR carbapenem-resistance) AND (Enterobacteriaceae OR Enterobacterales OR *Escherichia coli* OR *Enterobacter cloacae* OR *Klebsiella pneumoniae* OR *Pseudomonas* OR *Pseudomonas aeruginosa* OR *Acinetobacter* OR *Acinetobacter baumannii*) AND (companion animals OR pets OR dog OR cat) NOT review (Table S1).

Articles in English, Spanish or Portuguese, published from January 1, 2010 to April 24, 2021 were included. Publications that informed only about isolates from human sources, animals other than canines or felines (origin or unrelated environmental origin), reports of phenotypic resistance without genotypic confirmation, review articles or meta-analyses, editorials, book chapters, proceedings of academic events, evaluation of diagnostic or therapeutic methods of CR bacteria, were excluded.

Duplicates were removed using the Mendeley bibliographic manager ver. 1.19.8 (Elsevier, Amsterdam, The Netherlands).

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Two researchers carried out the search and selection independently in 2 phases. The first phase was based on the title and abstract, and the second was involved analyzing the full text. We conducted a manual search of the reference lists of included articles and selected publications according to the previous criteria to ensure better information coverage. Divergences in selection were resolved by consensus.

Data Extraction and Processing

The information was compiled in an Excel sheet (Microsoft Corp., Redmond, WA, USA). It included the main author, year, country, place, sample collected, year of isolation, animal, population, health status, history of hospitalization or antimicrobial therapy in animals and/or owners, as well as the microorganism identified, number of isolates, sequence type (ST), epidemiological classification of AMR, susceptibility assessment, and the genetic mechanism of CR.

Results

The initial search yielded 368 articles, 192 of which were duplicates. Of these, 91 were discarded according to their title and abstract, and 34 based on the full-text review (Figure 1). Fifty-one articles were included for analysis [19–69].

Study Characterization

Of the 51 articles, 48 reported isolates from domestic canines and/or felines, 3 from veterinary medical care environments,

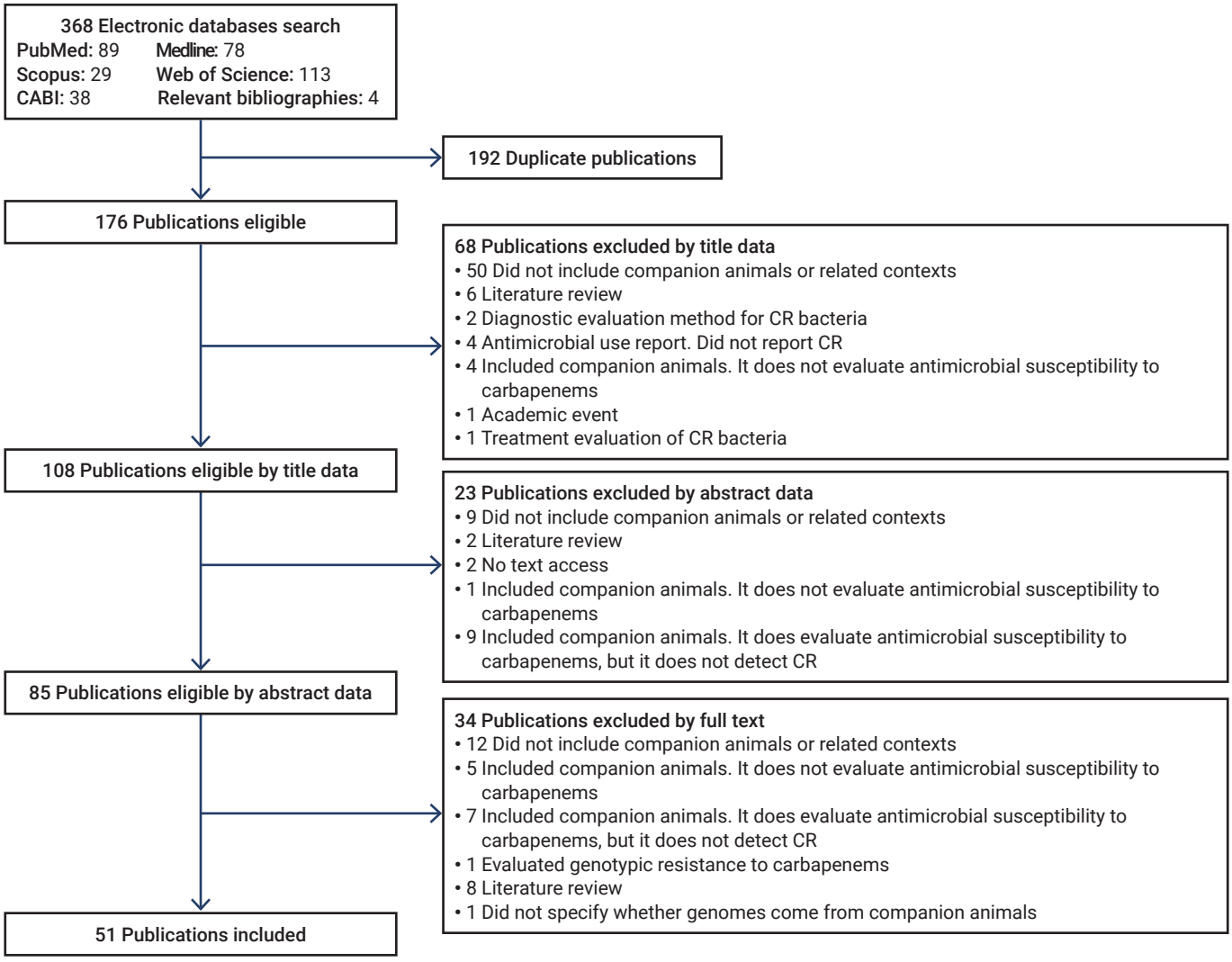

Figure 1. Flowchart of the search and selection of articles for this systematic review on carbapenem resistance (CR) in companion animals and related context.

1 from home environments, and another from commercial food (wet food). Of the 48 publications, 26 included dogs, 4 involved cats, and 18 encompassed both species.

Furthermore, of the 51 publications, 40 were original studies, and 11 were from epidemiological surveillance/monitoring programs. The publications included articles spanning 11 years (2010–2021); however, some CR isolates reported a longer period of analysis (Table 1) [19–69].

Animal Clinical History

Of the 51 articles reporting CRE and CRGNFB, most (n=49) described the health status of animals. Four studies involved healthy animals, 38 included diseased animals, and 5 had animals of both statuses. In the reports of diseased animals, CRE isolates were obtained from different systems, including genitourinary, respiratory, gastrointestinal, cardiovascular, musculoskeletal, ear, skin, and soft tissues, as well as neoplasms and wounds of undescribed origin. The CRGNFB were obtained from respiratory, genitourinary, ocular and ear tissues, soft tissues, and systemic examinations (Table 2; Table S2) [19–69].

Twenty articles reported antimicrobial therapy close to the sampling date, previously, or both. Three articles reported the administration of carbapenems (meropenem) in South Korea, and 17 described the use of other antimicrobials, including tetracyclines, cephalosporins, and quinolones, β-lactams, β-lactams/β-lactamase inhibitors, aminoglycosides, lincosamides, sulfonamides, nitroimidazoles, and phosphonic acids (Table 2).

CR Bacteria Isolated from Domestic Canines and Felines

Twenty publications reported information on the frequency of animals with CR isolates. In dogs and cats, the proportions of CRE isolation ranged from 0.25% to 21.6%. The frequency of CRE was registered on 3 continents. In Europe, the highest frequency of CRE happened in an outbreak of CR *E. coli* in dogs in a veterinary hospital in Switzerland (21.65%). In Asia, the highest frequency of CRE was in dogs in veterinary hospitals in India (6.75%). In Africa, the highest frequency of CRE occurred in animals sampled at an official veterinary office in Algeria (2.5%) (Table 3) [19,20,24–28,30–33,44,45,48,56,59,61,63,67].

The frequency of companion animals from CRGNFB isolates ranged from 1.3% to 12.50%. The frequency of CRGNFB was reported on 2 continents. In Asia, the highest frequency of CRGNFB was registered in dogs in a university veterinary hospital in South Korea (12.50%). In Europe, the highest frequency of CRGNFB was in veterinary hospitals in Italy (5.34%) (Table 3).

Antimicrobial Susceptibility Evaluation

Antimicrobial susceptibility in publications was evaluated using the agar diffusion (Kirby-Bauer) and minimum inhibitory concentration (MIC) techniques with standard and automated (Vitek bioMérieux, Marcy l'Étoile, Francia; Wider (Francisco Soria Melguizo, SA, Madrid, Spain) and Sensitire (TREK Diagnostic Systems, Cleveland, OH, USA) broth microdilution and the epsilometry test (Epsilometer test (E test; AB Biodisk, Solna, Sweden). Two publications

Table 1. Geographical distribution of CR isolates obtained from canines and felines, their settings, and the study type

Country	First author	Microorganism	CR mechanism[a)]	Genetic location	Study type
Companion animals					
China	Li et al. [19]	ENB	NDM-5	Plasmid	Investigation (search)
	Wang et al. [21]	ENB	NDM-5	Plasmid	Investigation (search)
	Cui et al. [31]	ENB	NDM-1	Plasmid	Surveillance
	Liu et al. [39]	ENB	OXA-48	NR	Investigation (search)
	Wang et al. [53]	GNFB	IMP-45	Chromosome	Surveillance
South Korea	Hong et al. [22]	ENB	NDM-5	Plasmid	Investigation (report)
	Hong et al. [32]	ENB	NDM-5	Plasmid	Surveillance
	Hong et al. [45]	ENB	NDM-5	NR	Surveillance
	Oh et al. [68]	ENB	NDM-5	Plasmid	Monitoring
	Hyun et al. [61]	GNFB	VIM-2	Integron class I	Investigation (search)
India	Pruthvishree et al. [46]	ENB	NDM-1	NR	Investigation (report)
	Bandyopadhyay et al. [67]	ENB	NDM-5	Plasmid	Investigation (search)
Japan	Kimura et al. [65]	GNFB	IMP-1	NR	Surveillance
Pakistan	Taj et al. [66]	GNFB	OXA-23	NR	Investigation (report)

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Table 1. Continued

Country	First author	Microorganism	CR mechanism[a]	Genetic location	Study type
Brazil	Sellera et al. [42]	ENB	KPC-2	Plasmid	Surveillance
	Fernandes et al. [54]	GNFB	VIM-2	Chromosome	Investigation (report and search)
United States	Liu et al. [36]	ENB	OXA-48	Plasmid	Investigation (search)
	Daniels et al. [41]	ENB	KPC-4	Plasmid	Surveillance
	Shaheen et al. [47]	ENB	NDM-1	Plasmid and chromosome	Investigation (search)
	Tyson et al. [60]	ENB	NDM-5	Plasmid	Surveillance
	Cole et al. [69]	ENB	NDM-5	Plasmid	Investigation (search)
Germany	Pulss et al. [25]	ENB	OXA-48	Plasmid	Investigation (search)
	Stolle et al. [29]	ENB	OXA-48	Plasmid	Investigation (search)
	Schmiedel et al. [37]	ENB	OXA-48	NR	Investigation (search)
	Ewers et al. [55]	GNFB	OXA-23	Plasmid	Investigation (search)
	Ewers et al. [57]	GNFB	OXA-23	Plasmid	Investigation (report)
	Klotz et al. [63]	GNFB	OXA-58	Plasmid	Investigation (search)
Spain	Gonzalez-Torralba et al. [33]	ENB	VIM-1	Plasmid	Investigation (search)
Finland	Gronthal et al. [34]	ENB	NDM-5	Plasmid	Investigation (report and search)
France	Valat et al. [23]	ENB	OXA-48	Plasmid	Investigation (search)
	Melo et al. [48]	ENB	OXA-48	Plasmid	Investigation (search)
	Herivaux et al. [56]	GNFB	OXA-23	NR	Investigation (search)
	Lupo et al. [64]	GNFB	OXA-23	Chromosome	Surveillance
Italy	Alba et al. [49]	ENB	NDM-5	Plasmid	Investigation (report)
	Gentilini et al. [59]	GNFB	NDM-1, OXA-23, L1[b], LP	NR	Investigation (search)
Portugal	Brilhante et al. [26]	ENB	OXA-181	Plasmid	Investigation (search)
	Pomba et al. [58]	GNFB	OXA-23	Chromosome	Investigation (report)
United Kingdom	Reynolds et al. [24]	ENB	NDM-5	Plasmid	Surveillance
Serbia	Misic et al. [62]	GNFB	OXA-72	Plasmid	Investigation (report)
Switzerland	Nigg et al. [20]	ENB	OXA-181	Plasmid	Investigation (search)
	Brilhante et al. [38]	ENB	OXA-48	Plasmid	Investigation (report)
	Dazio et al. [40]	ENB	NDM-5, OXA-48, OXA-181	NR	Investigation (search)
	Peterhans et al. [43]	ENB	NDM- 5	Plasmid	Investigation (NR)
Algeria	Yousfi et al. [27]	ENB	OXA-48, NDM-5	NR	Investigation (search)
	Yousfi et al. [28]	ENB	OXA-48	Plasmid	Investigation (search)
	Mairi et al. [30]	ENB	OXA-48	Plasmid	Investigation (search)
Egypt	Khalifa et al. [44]	ENB	VIM-4, OXA-48, OXA-244	Plasmid	Investigation (search)
Australia	Abraham et al. [35]	ENB	IMP-4	Plasmid	Investigation (report)
Context associated with companion animals[c]					
Brazil	Fernandes et al. [54]	GNFB	VIM-2	Chromosome	Investigation (report and search)
Egypt	Ramadan et al. [51]	ENB	NDM-5, OXA-181	Plasmid	Investigation (search)
Switzerland	Brilhante et al. [38]	ENB	OXA-48	Plasmid	Investigation (report)
	Seiffert et al. [50]	ENB	OXA-48	Plasmid	Investigation (search)
	Schmidt et al. [52]	ENB	OXA-48, OXA-181	NR	Investigation (search)

CR, carbapenem resistant; ENB, enterobacteria; NDM, New Delhi metallo-β-lactamase; OXA, oxacillin; NR, not reported; GNFB, glucose non-fermenting bacilli; IMP, active-on-imipenem; VIM, Verona integron-encoded metallo-β-lactamase; KPC, *Klebsiella pneumoniae* carbapenemase; LP, loss of porine.
[a]Carbapenemase production or loss of porins. [b]Intrinsic metallo-β-lactamase L1 of the species *Stenotrophomonas maltophilia* encoded by chromosomes.
[c]Veterinary medical care surfaces, household surfaces, and companion animal food.

Table 2. CR in microorganisms isolated from canine and feline samples and their history of antimicrobial use

Study	Sample origin			Antimicrobial use		Carbapenem resistance	
	Animal	*n*	Specimen	Carbapenem	Others	Bacterial species	CR origin[a]
Li et al. [19]	Dogs	2	Stool	NR	NR	*Escherichia coli*	NDM-5
Nigg et al. [20]	Dogs, cats	21	Rectal swab	NO	PEN, BET/INHIB, QUIN, NIT, CEP, TET, SUL	*E. coli*	OXA-181 (OXA-48-like)
Wang et al. [21]	Dogs, cats	6	Stool, urine	NR	NR	*E. coli, Enterobacter cloacae, Citrobacter freundii*	NDM-5
Hong et al. [22]	Dogs, cats	2	Rectal swab	MERO	QUIN, CEP, TET	*E. coli*	NDM-5
Valat et al. [23]	Dogs	1	NR	NR	NR	*E. coli*	OXA-48
Reynolds et al. [24]	Dogs	1	Tissues[b]	NO	BET/INHIB, CEP, TET, QUIN	*E. coli*	NDM-5
Pulss et al. [25]	Dogs, cats	130	CVADs[c], urine, other fluids[d], tissues[b]	NO	CEP 2°, 3°, PEN, QUIN, BET/INHB	*Klebsiella pneumoniae/ Klebsiella oxytoca, E. cloacae, E. coli*	OXA-48
Brilhante et al. [26]	Dogs	1	Tissues[b]	NR	NR	*E. coli*	OXA-181 (OXA-48-like)
Yousfi et al. [27]	Dogs, cats	5	Rectal swab	NR	NR	*E. coli*	OXA-48, NDM-5
Yousfi et al. [28]	Dogs, cats	6	Rectal swab	NR	NR	*E. coli, K. pneumoniae, E. cloacae*	OXA-48
Stolle et al. [29]	Dogs	6	CVADs[c], tissues[b], stool, urine, other fluids[d]	NO	PEN, BET/INHIB, QUIN, CEP, 3° TET	*K. pneumoniae, E. coli*	OXA-48
Mairi et al. [30]	Dogs	1	Rectal swab	NR	NR	*K. pneumoniae*	OXA-48
Cui et al. [31]	Dogs	1	Anal swab	NR	NR	*E. coli*	NDM-1
Hong et al. [32]	Dogs	4	Rectal swab	MERO	CEP 1°, QUIN, BET/ INHIB, NIT	*E. coli*	NDM-5
Gonzalez-Torralba et al.[33]	Dogs	1	Rectal swab	NO	NO	*K. pneumoniae*	VIM-1
Gronthal et al. [34]	Dogs	2	Ear swab	NO	QUIN, CEP 1°, BET/ INHIB, LIN	*E. coli*	NDM-5
Abraham et al. [35]	Cats	4	Stool	NO	TET	*Salmonella enterica* serovar Typhimurium	IMP-4
Liu et al. [36]	Dogs, cats	NR	Urine, tissues[b]	NR	NR	*E. coli*	OXA-48
Schmiedel et al. [37]	Dogs, cats	NR	NR	NR	NR	*K. pneumoniae, E. cloacae*	OXA-48
Brilhante et al. [38]	Dogs, cats	10	Urine, other fluids[d], tissues[b]	NR	NR	*K. pneumoniae*	OXA-48
Liu et al. [39]	Dogs	NR	Urine, tissues[b]	NR	NR	*E. coli*	OXA-48
Dazio et al. [40]	Dogs, cats	25	Rectal swab	NO	NR	*E. coli*	NDM-5, OXA-48, OXA-181 (OXA-48-like)
						K. pneumoniae	OXA-48
Daniels et al. [41]	Dogs	2	Urine, tissues[b]	NO	TET	*Enterobacter. hormaechei* subsp. *xiangfangensis*	KPC-4
Sellera et al. [42]	Dogs	1	Urine	NR	NR	*K. pneumoniae*	KPC-2
Peterhans et al. [43]	Dogs	1	Tissues[b]	NR	NR	*E. coli*	NDM-5

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Table 2. Continued

Study	Sample origin			Antimicrobial use		Carbapenem resistance	
	Animal	*n*	Specimen	Carbapenem	Others	Bacterial species	CR origin[a]
Khalifa et al. [44]	Dogs, cats	7	Nasal swab, eye swab	NR	NR	*E. hormaechei* subsp. *xiangfangensis*	VIM-4
						K. pneumoniae	OXA-48
						E. coli	OXA-244 (OXA-48-like)
Hong et al. [45]	Dogs	4	Rectal swab	NR	NR	*E. coli*	NDM-5
Pruthvishree et al. [46]	Dogs	1	Other fluids[d]	NR	NR	*E. coli*	NDM-1
Shaheen et al. [47]	Dogs, cats	6	Urine, tissues[b]	NR	NR	*E. coli*	NDM-1
Melo et al. [48]	Dogs	1	Rectal swab	NO	BET/INHIB	*E. coli*	OXA-48
Alba et al. [49]	Dogs	1	Urine	NR	NR	*E. coli*	NDM-5
Wang et al. [53]	Dogs	1	Anal swab	NR	NR	*Pseudomonas aeruginosa*	IMP-45
Fernandes et al. [54]	Dogs	1	Oral swab, rectal swab, other fluids[d]	NR	NR	*P. aeruginosa*	VIM-2
Ewers et al. [55]	Dogs, cats	3	Vaginal swab, urine, other fluids[d]	NR	NR	*Acinetobacter baumannii*	OXA-23
Herivaux et al. [56]	Dogs	2	Oral swab, rectal swab	NO	NO	*A. baumannii*	OXA-23
Ewers et al. [57]	Cats	1	Urine	NR	NR	*A. baumannii*	OXA-23
Pomba et al. [58]	Cats	1	Urine	NO	BET/INHB	*A. baumannii*	OXA-23
Gentilini et al. [59]	Dogs, cats	11	Rectal swab	NO	BET/INHIB, TET, QUIN, NIT	*A. radioresistens*	NDM-1
						A. baumannii	OXA-23
						P. aeruginosa	Loss of porin[e]
						Stenotrophomonas maltophilia	L1[f]
Tyson et al. [60]	Dogs	1	Other fluids[d]	NR	NR	*E. coli*	NDM-5
Hyun et al. [61]	Dogs	10	Other fluids[d], tissues[b]	NR	NR	*P. aeruginosa*	VIM- 2
Misic et al. [62]	Dogs	1	Urine	NR	NR	*A. baumannii*	OXA-72 (OXA-40-like)
Klotz et al. [63]	Dogs, cats	4	Nasal swab, other fluids[d], tissues[b]	NR	NR	*Acinetobacter pittii*	OXA-58 (OXA-58-like)
Lupo et al. [64]	Dogs, cats	7	NR	NR	NR	*A. baumannii*	OXA-23
Kimura et al. [65]	Dogs, cats	2	Urine, other fluids[d]	NO	PHOS	*A. radioresistens*	IMP-1
Taj et al. [66]	Cats	1	Urine	NO	BET/ INHIB, QUIN	*A. baumannii*	OXA-23
Bandyopadhyay et al. [67]	Dogs	16	Rectal swab, vaginal swab, tissues[b]	NR	NR	*E. coli*	NDM-5
Oh et al. [68]	Dogs	4	Stool, nasal swab, urine	MERO	BET/ INHIB, TET	*E. coli*	NDM-5
Cole et al. [69]	Dogs, cats	6	Urine, other fluids[d], tissues[b]	NO	PEN, CEP, AMN, NIT, BET/ INHIB	*E. coli*	NDM-5

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Table 2. Continued

Study	Sample origin			Antimicrobial use		Carbapenem resistance	
	Animal	*n*	Specimen	Carbapenem	Others	Bacterial species	CR origin[a)]
Brilhante et al. [38]	Veterinary surfaces	NA	Environmental swabs	NA		*K. pneumoniae*	OXA-48
Seiffert et al. [50]	Pet food[g)]	NA	Pet food packages	NA		Enterobacterales (undetermined species)	OXA-48
Ramadan et al. [51]	Veterinary surfaces	NA	Environmental swabs	NA		*E. coli*	NDM-5, OXA-181 (OXA-48-like)
Schmidt et al. [52]	Veterinary surfaces	NA	Environmental swabs	NA		*E. coli*	OXA-48, OXA-181 (OXA-48-like)
						K. pneumoniae	OXA-48
						E. cloacae	OXA-48
Fernandes et al. [54]	Household surfaces[h)]	NA	Environmental swabs	NA		*P. aeruginosa*	VIM-2

CR, carbapenem resistant; NR, not reported; NDM, New Delhi metallo-β-lactamase; NO, non-use; PEN, penicillins; BET/INHIB, beta-lactams/beta-lactam inhibitors; QUIN, quinolones; NIT, nitroimidazoles; CEP, cephalosporins; TET, tetracyclines; SUL, sulfonamides; OXA, oxacillin; MERO, meropenem; CVADs, central venous access devices; VIM, Verona integron-encoded metallo-β-lactamase; LIN, lincosamides; IMP, active-on-imipenem; KPC, *Klebsiella pneumoniae* carbapenemase; PHOS, phosphonic acids; NA, not applicable; AMN, aminoglycosides.
[a)]Referred to the mechanism that confers resistance to the microorganism: production of carbapenemases or loss of the bacterial target. [b)]Included wound tissues, nasal structure, skin, abdominal cavity, anal sacs, intestine, and lung. [c)]Included central venous catheters. [d)]Included bronchoalveolar and tracheobronchial lavage, scrotal fluid, pus, bile, ear discharge, and eye discharge. [e)]The authors determined that the loss of the oprD porin was caused by different mutations within the gene that caused a premature stop codon because of a large insertion, a frameshift, or a nonsense mutation. [f)]Chromosome-encoded intrinsic metallo-β-lactamase L1 of *S. maltophilia* species. [g)]Mixed wet pet food with different flavors. [h)]Home surfaces (sofa, balcony, water cooler).

Table 3. Frequency of animals with CR isolates

First author	Country	Isolation place	Sampled animals (*n*)			Animals with CR microorganisms (*n*)			Frequency of animals with CR (%)		
			Dogs	Cats	Total	Dogs	Cats	Total	Dogs	Cats	Total
Li et al. [19]	China	Households with backyard pig farms	92	19	111	2	0	2	2.17	0.00	1.80
Nigg et al. [20]	Switzerland	University veterinary hospital	76	21	97	17	4	21	22.37	19.05	21.65
Reynolds et al. [24]	United Kingdom	Veterinary clinics	158	27	185	1	0	1	0.63	0.00	0.54
Pulss et al. [25]	Germany	Veterinary microbiology laboratory	3,375	932	4,307	117	13	130	3.47	1.39	3.02
Brilhante et al. [26]	Portugal	Homes and university veterinary hospital	71	27	98	1	0	1	1.41	0.00	1.02
Yousfi et al. [27]	Algeria	Local veterinary office	116	84	200	3	2	5	2.59	2.38	2.50
Yousfi et al. [28]	Algeria	Local veterinary office and homes	265	49	314	4	2	6	1.51	4.08	1.91
Mairi et al. [30]	Algeria	NR	75	37	112	1	0	1	1.33	0.00	0.89
Cui et al. [31]	China	University veterinary hospital	NR	NR	226	1	0	1	NA	NA	0.44
Hong et al. [32]	South Korea	Veterinary clinics	353	0	353	4	0	4	1.13	0.00	1.13
Gonzalez-Torralba et al. [33]	Spain	Companion animal shelter	160	0	160	1	0	1	0.63	0.00	0.63
Khalifa et al. [44]	Egypt	NR	NR	NR	1,348	3	4	7	NA	NA	0.52
Hong et al. [45]	South Korea	Veterinary hospitals	315	74	389	4	0	4	1.27	0.00	1.03

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Table 3. Continued

First author	Country	Isolation place	Sampled animals (*n*)			Animals with CR microorganisms (*n*)			Frequency of animals with CR (%)		
			Dogs	Cats	Total	Dogs	Cats	Total	Dogs	Cats	Total
Melo et al. [48]	France	University veterinary hospital	166	227	393	1	0	1	0.60	0.00	0.25
Bandyopadhyay et al. [67]	India	Veterinary clinics and university veterinary hospital	237	0	237	16	0	16	6.75	0.00	6.75
Herivaux et al. [56]	France	University veterinary hospital	104	46	150	2	0	2	1.92	0.00	1.33
Gentilini et al. [59]	Italy	Veterinary hospitals and homes	134	72	206	8	3	11	5.97	4.17	5.34
Hyun et al. [61]	South Korea	Veterinary medical teaching hospital	80	0	80	10	0	10	12.5	0.00	12.50
Klotz et al. [63]	Germany	Veterinary clinics	110	48	158	2	2	4	1.82	4.17	2.53

CR, carbapenem resistant; NA, not applicable; NR, not reported.

determined CR only with molecular techniques (Table S3). The MIC values of meropenem, imipenem, and ertapenem associated with CR isolates are presented in Table S3.

Of 49 publications reporting CR phenotypes, 46 showed susceptibility data to antimicrobials other than carbapenems. CRE and CRGNFB exhibited resistance to penicillin; penicillin/β-lactamase inhibitors; cephamycins; first-, second-, third-, and fourth-generation cephalosporins; cephalosporins/β-lactamase inhibitors; monobactams; aminoglycosides; quinolones; sulfonamides; trimethoprim; tetracyclines; phenicols; nitrofurans; glycylcyclines; and polymyxins. Resistance to macrolides was evaluated and reported only in CRE. Susceptibility to phosphonic acids was evaluated, and resistance was reported in CRE and CRGNFB (Table S3). CRE and CRGNFB presented resistance to last-resort antimicrobials such as amikacin, colistin, fosfomycin, nitrofurantoin, and tigecycline in 14, 3, 8, 4, and 3 publications, respectively (Table S3).

MDR isolates were reported in 20 articles in 4 CRE species (*E. coli*, *K. pneumoniae*, *Salmonella enterica* serovar Typhimurium, and *E. cloacae*) from companion animals and veterinary care surfaces. Four CRGNFB MDR species (*P. aeruginosa*, *A. baumannii*, *Acinetobacter radioresistens*, and *Stenotrophomonas maltophilia*) obtained from companion animals and domestic environments were reported in 7 articles (Table S3).

The XDR phenotype was reported in 1 publication that highlighted 1 species of CRE (*E. coli*) from a canine, and 2 publications recording one species of CRGNFB (*A. baumannii*) obtained from dogs and cats. No isolates showed a PDR phenotype (Table S3).

CR Genotypic Detection

Genotypic CR was confirmed in publications employing 3 single or combined techniques: polymerase chain reaction, microarrays, and whole-genome sequencing (Table S3). In CRE, resistance was associated only with the production of carbapenemases. In companion animals, the "big five" carbapenemases were detected, with higher frequencies of OXA-48-like and NDM, and smaller proportions of KPC, IMP, and VIM. In veterinary environments, only OXA-48-like and NDM were detected. Conversely, only OXA-48 was found in commercial feed. None of the minor carbapenemases were identified in the CRE reported (Table 2).

CR *Acinetobacter* spp. found in dogs and cats showed carbapenemase production as the only mechanism of resistance, with 2 of the "big five" (i.e., IMP and NDM), and the 3 important members of the genus (i.e., OXA-23-like, OXA-40-like, and OXA-58-like). CR *P. aeruginosa* was detected in dogs and home environments (sofa) and produced 2

of the 5 major carbapenemases (i.e., IMP and VIM). A CR mechanism different from carbapenemases was detected in a *P. aeruginosa* isolate from a canine. This mechanism involved the loss of the OprD outer membrane porin. CR *S. maltophilia* isolated from dogs and cats was associated with the production of L1, a species-intrinsic metallo-carbapenemase (Table 3).

Geographical Distribution of CR Bacteria

CRE and CRGNFB acquired from companion animals were reported in 19 countries on 5 continents: 5 countries from Asia, 2 from the Americas, 9 from Europe, 2 from Africa, and 1 from Oceania (Figures 2 and 3). In companion animal-associated contexts, CRE and CRGNFB were reported in 3 countries on 3 continents: 1 in the Americas, 1 in Africa, and 1 in Europe (Figure 4).

The bla_{NDM-5} gene was reported in plasmids only in CRE in Asia, the Americas, Europe, and Africa. The bla_{NDM-1} gene in CRE was detected in plasmids and chromosomes in Asia and the Americas; and in CRGNFB, without reporting its genomic location, but only in Europe. The bla_{OXA-48}, $bla_{OXA-181}$, and $bla_{OXA-244}$ genes were found in plasmids only in CRE in Europe, the Americas, Africa, and Asia. The bla_{OXA-23}, bla_{OXA-58}, and bla_{OXA-72} genes located on plasmids and chromosomes were reported only in CRGNFB in Europe and Asia. The bla_{VIM-1} and bla_{VIM-4} genes on plasmids were registered in CRE in Europe and Africa, while the bla_{VIM-2} gene located on chromosomes and integrons was present in CRGNFB in the Americas and Asia. The bla_{KPC-2} and bla_{KPC-4} genes in plasmids were found exclusively in CRE in North and South America. The bla_{IMP-4} gene located on plasmids was reported only in CRE in Oceania, while the bla_{IMP-1} gene, with no registry of its genomic location, and bla_{IMP-45} on chromosomes were detected in CRGNFB in Asia (Table 1; Figures 2–4).

Multilocus STs in CR Bacteria

In publications that established the STs of CR bacteria identified by the molecular epidemiology technique of multilocus sequence typing, 55 STs were reported in CR isolates from companion animals, and 4 had descriptions of the contexts associated with their presence. Eight publications registered no STs. In CRE carrying bla_{NDM} genes, 4 STs (ST4656, ST167, ST410, and ST9437) were reported on all continents except Oceania. CRE carrying bla_{VIM} genes were clustered into 3 STs (ST2090, ST493, and ST182) in Africa and Europe, and CRGNFB into 3 STs (ST1047, ST1203, and ST233) in Asia and the Americas. Bacteria carrying bla_{IMP} had the ST19 sequence in Oceania and the ST308 sequence in Asia in CRE and CRGNFB, respectively. Two STs (ST11 and ST171) were identified in bla_{KPC}-producing CRE in the Americas (ST11, ST171). Bacteria carrying bla_{OXA} had the widest variety of STs, with 39 in CRE in Asia, the Americas,

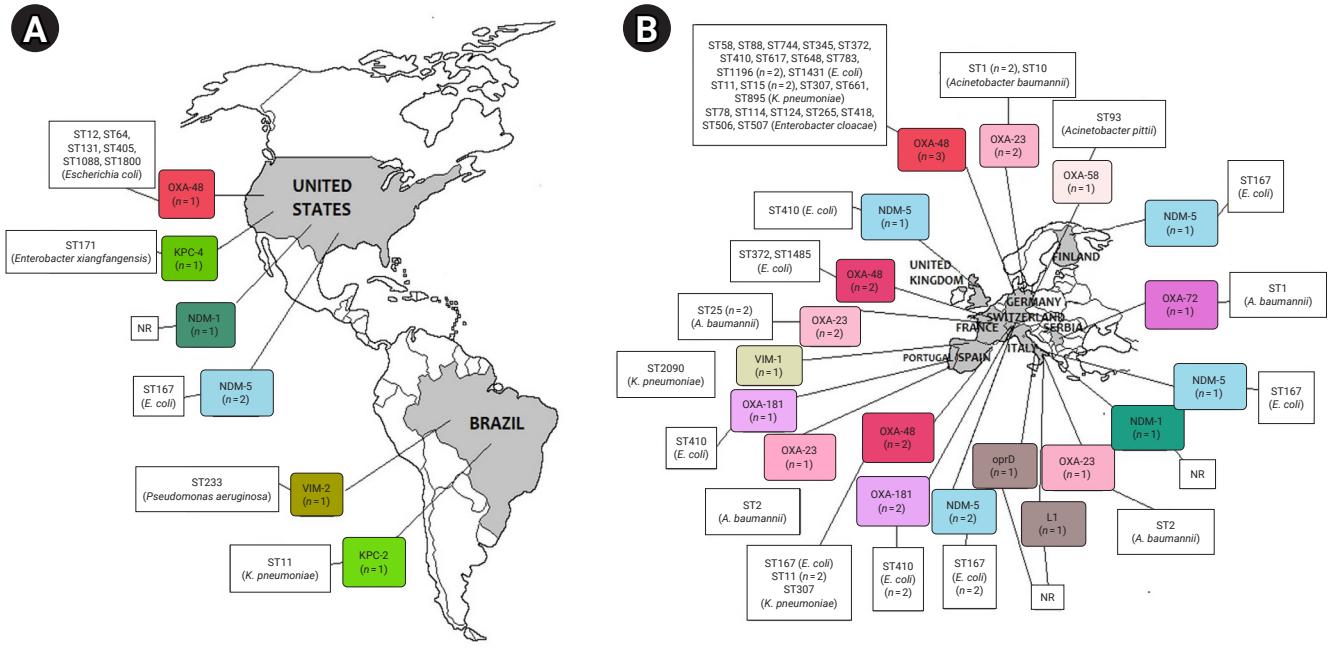

Figure 2. Number of reports and distribution of carbapenem resistance genes from *Enterobacteriaceae* and non-fermenting bacilli from domestic canines and felines in (A) America and (B) Europe.
ST, sequence type; OXA, oxacillin; KPC, *Klebsiella pneumoniae* carbapenemase; NDM, New Delhi metallo-β-lactamase; VIM, Verona integron-encoded metallo-β-lactamase; NR, not reported.

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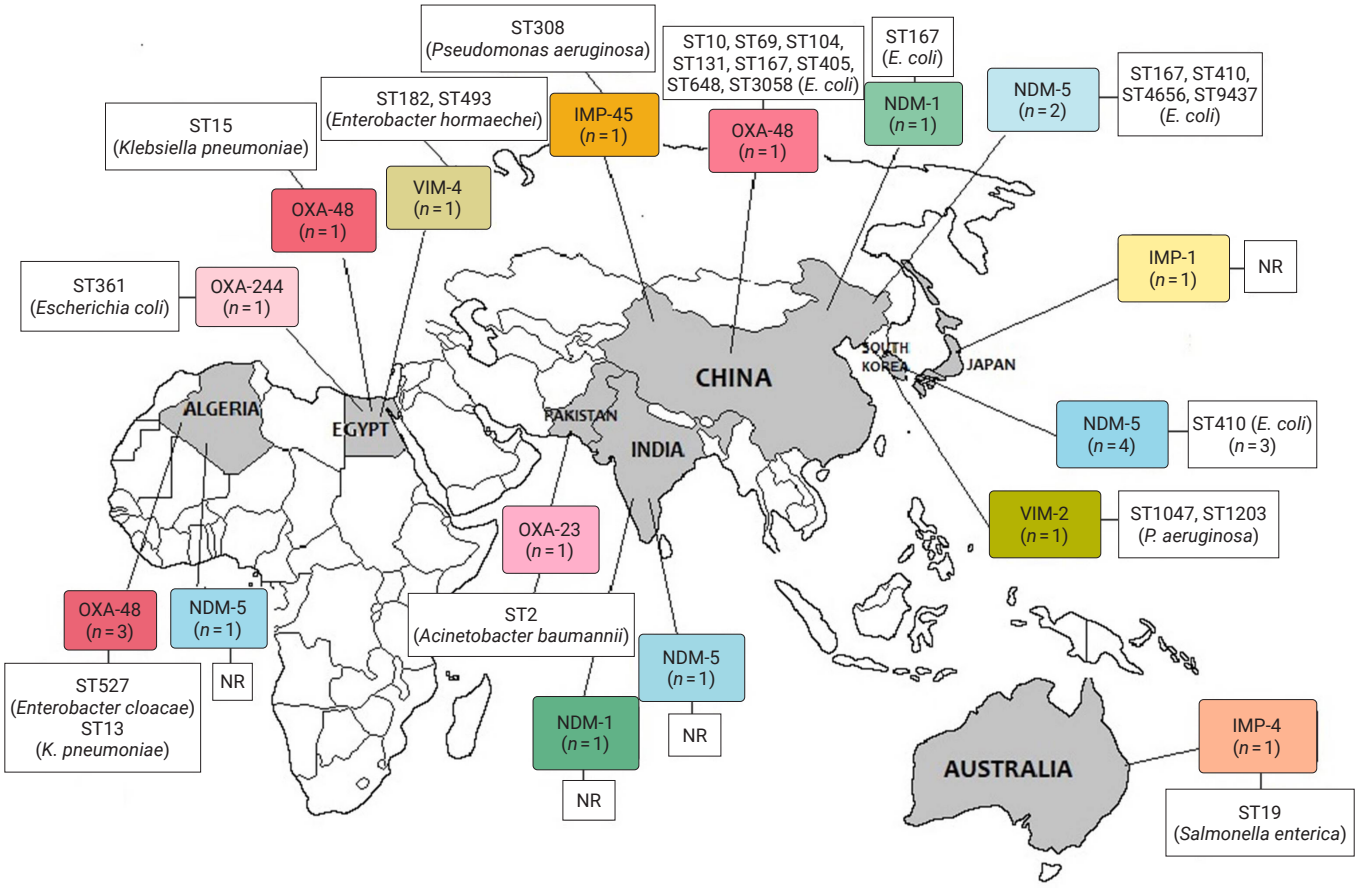

Figure 3. Number of reports and distribution of carbapenem resistance genes from *Enterobacteriaceae* and non-fermenting bacilli from domestic canines and felines in Africa, Asia, and Oceania.
ST, sequence type; OXA, oxacillin; VIM, Verona integron-encoded metallo-β-lactamase; IMP, active-on-imipenem; NDM, New Delhi metallo-β-lactamase; NR, not reported.

Europe, and Africa and 5 in CRGNFB (ST1, ST10, ST2, ST25, and ST93) in Europe and Asia (Table 1; Figures 2–4).

CR Isolations from Companion Animals Related to Humans and Other Animal Species

Eleven studies that reported CR isolates in dogs and cats also registered other animal species, including pigs, birds (poultry, pet, and wild), cattle, sheep, goats, guinea pigs, rats, mice, rabbits, horses, fish, and flies. Seven publications reported CR in humans. Two were from hospital and community settings not related to companion animals, 2 from owners and employees in veterinary care settings, and 1 from backyard swine farm residents.

In addition, 2 articles molecularly confirmed human-animal transmission from owners to dogs. CRE in Finland and CRGNFB in Brazil showed confirmed transmission with the same types of sequences and CR genes found in dogs. Both owners reported previous hospitalization, and 1 of them had also traveled internationally [34,54] (Table S4).

Discussion

The current review compiled evidence on the presence and spread on 5 continents of Gram-negative bacteria categorized as critical in the WHO priority list of antibiotic-resistant bacteria for research and development of new antibiotics, such as CRE and CRGNFB isolated from domestic canines and felines, and on the contexts associated with their presence.

Only 20% of the studies originated from surveillance programs, all in high-income and upper-middle-income countries. Since 2018, the United States has included dogs and cats in AMR surveillance programs [70,71]. In Europe, some countries included both species in their specific AMR control programs, and the European Union plans to launch the European Antimicrobial Resistance Surveillance Network in Veterinary Medicine (EARS-Vet), in which dogs and cats will be included in the scope of surveillance [72,73].

However, the role of domestic canines and felines in CR bacterial transmission is often underestimated in local

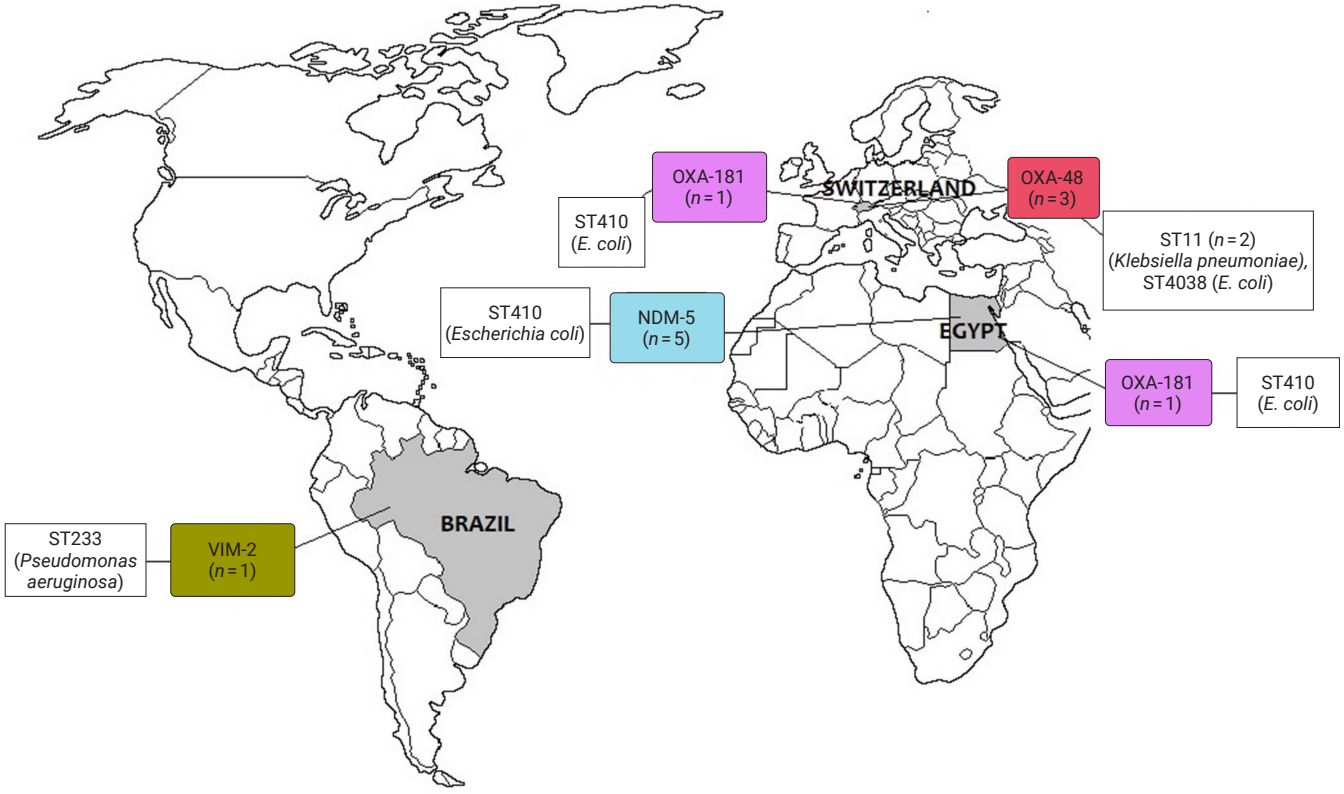

Figure 4. Number of reports and global distribution of carbapenem resistance genes from *Enterobacteriaceae* and non-fermenting bacilli from veterinary environments, homes, and commercial foods for domestic canines and felines.
ST, sequence type; VIM, Verona integron-encoded metallo-β-lactamase; OXA, oxacillin; NDM, New Delhi metallo-β-lactamase.

AMR containment programs [74,75]. Although in this study, the CR frequency in domestic canines and felines ranges from 0.4% to 6%, it is essential to integrate these animals into surveillance, control, and prevention strategies for CR, especially in low- and lower-middle-income countries where the problem may be underdiagnosed [76].

Of particular concern are reports of VIM-2-producing *P. aeruginosa* [61] and an outbreak of OXA-181-producing *E. coli* [20] in veterinary hospitals in South Korea and Switzerland, with frequencies close to 12% and 20%, respectively. Although neither of those 2 reports described the administration of carbapenems, the use of meropenem in veterinary hospitals in South Korea [22,32,68] and the use of β-lactams and quinolones in the Swiss veterinary hospital have been registered, favoring the co-selection of CR isolates [34,59,77].

Carbapenemase production was the most important mechanism of CR in Enterobacterales and GNFB of companion animals. The most frequent carbapenemase was OXA. Most OXA enzymes with carbapenemase activity have been identified in *Acinetobacter* spp. and *P. aeruginosa* [78]. The carbapenemases OXA-23-like (variant OXA-23), OXA-40-like (variant OXA-72), and OXA-58-like (variant OXA-58) were only identified in *Acinetobacter* spp. in companion animals from Europe and South Asia.

However, the OXA-48-like enzyme in humans has been reported mainly in *K. pneumoniae*, *E. coli*, and *E. cloacae* [79], and it has been identified in pets, related environments, and food (variants OXA-48, OXA-181, and OXA-244). All were plasmid-encoded, confirming the risk posed by their rapid and easy transfer [79].

The bla_{OXA-48} gene detected in the European countries in animal feed might be associated with the components of the feed formulation. bla_{OXA-48} has also been reported on Enterobacteriaceae obtained from poultry and swine carcasses in Europe and Asia [80] and drinking water systems of industrialized countries (United States) [81]. Conversely, the most likely source in this case, is human intervention during manufacturing and before packing [50], suggesting the relevance of humans in contaminating animal feed with CR organisms.

The second most frequent enzyme found in this review was NDM in *E. coli*, *E. cloacae*, *Citrobacter freundii*, and *A. radioresistens* in companion animals in North America,

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Asia, Europe, and North African veterinary settings. NDM is considered endemic in the Balkan countries, the Middle East, and India, although it has spread worldwide, mainly through *E. coli*, *K. pneumoniae*, and *Acinetobacter* spp. [81–83]. *E. coli* ST101 and ST131 and *K. pneumoniae* ST11 and ST147 have been reported as epidemic clones responsible for its dissemination [81,83,84]. In *E. coli*, NDM was localized on plasmids. Nevertheless, *E. coli* presented ST167 and ST410 sequences, suggesting different dynamics in the circulation of NDM-producing *E. coli* in companion animals.

Domestic canines and felines are not considered the main sources of CR acquisition for humans [81]. However, the transmission of CRE and CRGNFB from humans to dogs, from which the same microorganisms were isolated, has been reported in Finland [34] and Brazil [54], respectively. In both cases, the owners had a history of international travel or prolonged hospitalization, which are risk factors associated with CR acquisition [78,81].

At the human-animal interface, the role of domestic canines and felines in CR dissemination in community settings should not be underestimated. In Brazil, the transmission of a CR bacterium between an owner and pet was confirmed, as well as its presence on shared household surfaces, such as the sofa [54]. The home can become a source of CR bacteria for companion animals, contributing to AMR spread in human environments. Canines, due to their generally more social behavior than felines, interact daily with other congeners and with people outside their family context, including at parks, daycare centers, shelters/kennels, and veterinary hospitals [85], favoring the spread/increase of the presence of CR bacteria in community settings.

The presence of plasmid-borne IMP carbapenemase detected in the zoonotic bacterium *Salmonella* serovar Typhimurium in hospitalized cats in Australia [35] is of particular concern. Its presence could be attributed to human factors, considering that the circulation of the bla_{IMP} gene has been demonstrated in Gram-negative bacteria in Australian human clinical settings and in migratory birds carrying CR *Salmonella* spp. acquired from human environments and genetically related to human isolates [86].

Companion animals may also be involved in the spread of AMR in rural settings. A Chinese backyard pig farm reported CRE circulation in humans, birds, and flies, predominantly originating from canine gene complexes [19]. Human and animal populations that coexist in small-scale agricultural productions with insufficient biosecurity measures have been reported to be more vulnerable to acquiring CR [76]. In rural settings, the use of carbapenems may be lower due to the associated cost. However, using other antimicrobials that may favor co-selection and the occurrence of CR cannot be ruled out [34,59,77].

The limitations of the current review include the fact that it was based only on studies published in electronic databases, and some valid reports of carbapenemases in companion animals in the gray literature may not have been identified unknown. Furthermore, low- and lower-middle-income countries may have been underrepresented due to the absence of publications in electronic databases. In addition, methods of isolation and detection of CR bacteria, phenotypic interpretation criteria, and the classification of resistant, intermediate, and susceptible isolates varied between the studies, and these factors may have influenced the collective results.

Conclusion

In conclusion, evidence of the presence of CRE and CRGNFB from companion animals and associated contexts in the 5 continents is compiled in this review. Domestic canines and felines are recognized as a possible source of dissemination and maintenance of carbapenemases for animals and humans. Thus, there is an urgent need for in-depth studies on the dynamics of CR circulation, including companion animals, under the concept of One Health in CR surveillance programs and plans for the containment of AMR, especially in low- and lower-middle-income countries, where the magnitude of the problem may be underestimated.

Supplementary Material

Table S1. Search formula details and results from the included databases; **Table S2.** Health status and antimicrobial use of the animals from which carbapenem-resistant isolates were derived; **Table S3.** Minimum inhibitory concentration (MIC), inhibition zone diameter (IZD), and carbapenem resistance (CR) mechanisms of isolates obtained from companion animals and the contexts associated with their presence; **Table S4.** Carbapenem resistant (CR) isolates from companion animals linked to humans and other species. Supplementary data are available at https://doi.org/10.24171/j.phrp.2022.0033.

Notes

Ethics Approval
Not applicable.

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

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None.

Availability of Data

All data generated or analyzed in this study were included in this published article. More information can be requested from the corresponding author.

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Original Article

Time-series comparison of COVID-19 case fatality rates across 21 countries with adjustment for multiple covariates

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ABSTRACT

Objectives: Although it is widely used as a measure for mortality, the case fatality rate (CFR) of coronavirus disease 2019 (COVID-19) can vary over time and fluctuate for many reasons other than viral characteristics. To compare the CFRs of different countries in equal measure, we estimated comparable CFRs after adjusting for multiple covariates and examined the main factors that contributed to variability in the CFRs among 21 countries.

Methods: For statistical analysis, time-series cross-sectional data were collected from Our World in Data, CoVariants.org, and GISAID. Biweekly CFRs of COVID-19 were estimated by pooled generalized linear squares regression models for the panel data. Covariates included the predominant virus variant, reproduction rate, vaccination, national economic status, hospital beds, diabetes prevalence, and population share of individuals older than age 65. In total, 21 countries were eligible for analysis.

Results: Adjustment for covariates reduced variation in the CFRs of COVID-19 across countries and over time. Regression results showed that the dominant spread of the Omicron variant, reproduction rate, and vaccination were associated with lower country-level CFRs, whereas age, the extreme poverty rate, and diabetes prevalence were associated with higher country-level CFRs.

Conclusion: A direct comparison of crude CFRs among countries may be fallacious, especially in a cross-sectional analysis. Our study presents an adjusted comparison of CFRs over time for a more proper comparison. In addition, our findings suggest that comparing CFRs among different countries without considering their context, such as the epidemic phase, medical capacity, surveillance strategy, and socio-demographic traits, should be avoided.

Keywords: COVID-19; Least-squares analysis; Linear models; Mortality

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Introduction

Since the pandemic of coronavirus disease 2019 (COVID-19) started in December 2019, mortality due to severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), the viral agent that causes COVID-19, has been a matter of concern. In the early days of the pandemic, questions were raised regarding the severity of COVID-19 infection and whether COVID-19 is more severe than other existing respiratory ailments, such as seasonal influenza, SARS or Middle East respiratory syndrome (MERS), in terms of mortality [1].

The case fatality rate (CFR) is one of the main measures used to calculate the mortality risk of COVID-19. The estimated CFR of COVID-19 is reported lower than those of Ebola, SARS, and MERS, but still reportedhigher than that of the seasonal flu [2–4].

However, it has been pointed out that the CFR does not fully reflect the risk of dying from COVID-19 [5]. This is because the CFR changes not only due to biological characteristics of the virus, but also due to particular aspects of the context, such as environmental, social, and individual risk factors, as well as potential biases related to the surveillance strategy.

The confounding issues of the CFR become even more critical when comparing CFRs among different countries. In many cases, CFRs are not compared in equal measure considering multiple covariates; these misleading results could lead to a faulty risk assessment and scientifically unsupported decisions by public health agencies in urgent public health emergencies. Therefore, when comparing CFRs among different countries, it is important to take multiple covariates into account to examine whether differences in CFRs among countries simply reflect a probabilistic phenomenon caused by chance or are a consequence of different levels of underlying conditions or response capabilities across countries.

Some prior studies have compared CFRs with adjustments for well-known covariates. The most common method of estimating the CFR has been through meta-analyses pooling various individual studies to estimate the CFR [6–9]. Although this approach succeeded in identifying some possible confounding factors, it could not take into account multiple covariates at the same time.

To complement the limitations of meta-analyses, several studies have estimated the CFR using a regression model to consider multiple risk factors and confounders. However, these studies were conducted using cross-sectional data [10] or for intra-country comparisons rather than inter-country comparisons [11]. Other research using time-series cross-sectional data appears to have underestimated the impact of autocorrelation and heteroscedasticity [12,13] or could not control for the effect of SARS-CoV-2 variants, especially during the emergence of the Delta and Omicron variants [14].

Based on prior studies, this study conducted a panel data analysis using time-series cross-sectional data to address 2 main objectives: (1) to estimate comparable CFRs adjusted for country-level multiple covariates, and (2) to examine potential factors that cause variation in the CFR among countries after adjustment for multiple covariates.

Materials and Methods

Data Collection

COVID-19-related data were collected from the Our World in Data, an open-source resource on COVID-19 data [15]. This database provides overall information on COVID-19 in each country, including the number of daily cases and deaths, the percentage of vaccinated people, the number of tests, and several characteristics of each country, including the gross domestic product (GDP) per capita, median age, extreme poverty, and number of hospital beds. Among all available countries in the database, we selected 38 countries in the Organisation for Economic Co-operation and Development (OECD) because they had more available data than non-OECD countries. In addition, by focusing on OECD countries, we aimed to compare countries with similar socio-economic conditions.

To examine the effect of SARS-CoV-2 variants on the CFR, the proportion of the Delta and Omicron variants for each country was collected. We collected this data from CoVariants.org, whose original data were derived from GISAID [16,17]. This provided proportions of each variant at 2-week intervals at the country level. Among all time periods since the emergence of COVID-19, we only selected data for the 28 weeks between September 20, 2021 and April 4, 2022 in order to measure the effect of COVID-19 variants on the CFR. The selected time period was a transition period from the predominance of the Delta variant to the predominance of the Omicron variant (BA.1 and BA.2), enabling an analysis of the effects of COVID-19 variants on the CFR.

For statistical analysis, data from Our World in Data and data from CoVariants.org were merged. After the exclusion of some countries due to missing values, 21 of the 38 OECD countries were selected for the final analysis: Australia, Belgium, Canada, Chile, Colombia, Denmark, Estonia, Greece, Ireland, Israel, Italy, Latvia, Lithuania, Mexico, Norway, Portugal, South Korea, Spain, Turkey, United Kingdom, and the United States. While most countries included in the final analysis had 196 days of observations (from September 20, 2021 to April 4, 2022), some countries had fewer than 196

days of observations due to missing data.

This study did not need approval from the Institutional Review Board or an informed consent procedure because we used country-level open-source data without any individual information.

Statistical Analysis

As the dataset was in a time-series cross-sectional format, we applied panel data regression to estimate the CFRs. The natural logarithm of the biweekly CFR was used as the response (dependent) variable. The biweekly CFR was calculated by dividing the sum of new deaths in the preceding 2 weeks by the sum of new cases in the preceding 2 weeks. There were 2 reasons to use the biweekly CFR as a response variable instead of the daily CFR. First, smoothing the daily CFR across 14 days can provide more information about overall trends in the CFR by reducing daily variance due to differences in the number of tests between weekdays and weekends. Second, the biweekly CFR can reflect the time lag between infection and death by COVID-19, unlike the daily CFR. In the final regression model, we used the natural logarithm of the biweekly CFR to address the problem of distribution.

Country-level variables known to be associated with the CFR were included in the final regression model, including the predominance of the Omicron variant, population share of vaccinated people, population share of individuals older than age 65, diabetes prevalence, and cardiovascular deaths. These variables were measured at the country level and retained in our final regression model [18–27]. Additional variables included 7-day smoothed numbers of newly confirmed cases and deaths per million, the reproduction rate, the stringency index, natural logarithm of GDP per capita, the extreme poverty rate, hospital beds per thousand, and life expectancy [28–31].

The predominance of the Omicron variant was included after creating a dummy variable for the share of the Omicron variant as 0 or 1, based on the proportion of the variants. If the Delta variant proportion was greater than 50%, the dummy variable was 0. If the Omicron variant proportion was higher than 50%, the dummy variable was 1.

Fixed- or random-effects models are commonly used for panel data regression because of the permanent error term induced by unobserved characteristics of the panel group. Fixed- and random-effects models can be effective estimators only when there is no autocorrelation in the error term. However, the Wooldridge test [32] detected first-order autocorrelation in the error term. In addition, when first-order autocorrelation was considered in the regression model, there was no need to consider the permanent error term induced by unobserved characteristics of the country. Additionally, the modified Wald test detected group-wise heteroscedasticity in the regression model. Therefore, we used a pooled feasible generalized least squares (GLS) model that assumed heteroscedasticity and first-order autocorrelation of the error term instead of fixed- and random-effects models.

We formulated 4 regression models. Model 1 was a baseline model including all research variables except 7-day smoothed cases and deaths per million. Models 2 and 3 were mediation models to measure the mediation effects of cases and deaths on the CFR. In model 2, we added 7-day smoothed new cases per million as a mediation variable to model 1, and in model 3, we added 7-day smoothed new deaths per million to model 1. Lastly, model 4 was a full model with the simultaneous addition of both 7-day smoothed new cases per million and 7-day smoothed new deaths per million added to model 1 at the same time. All panel analysis was conducted using Stata ver. 16.1 SE (StataCorp LLC, College Station, TX, USA).

Results

Descriptive Statistics

Table 1 shows descriptive statistics for all variables included in the final regression models. The variables can be categorized as time-varying and fixed variables. The time-varying variables included the biweekly CFR, 7-day smoothed new cases and deaths, share of the Omicron variant, reproduction rate, percentage of fully vaccinated people, and stringency index over time.

The mean of the biweekly CFR was 0.79, and the median was 0.42. The biweekly CFR of all countries showed a right-skewed distribution with large variance, ranging from 0.01 to 8.41. The average number of new cases and the number of new deaths per million were smoothed over 7 days. New deaths refer to the number of deaths attributed to COVID-19. The variables for cases and deaths showed a right-skewed distribution with large maximum values compared to their means.

The mean proportion of the Omicron variant was 52%, since the study period reflected the transition period from the Delta variant to the Omicron variant. Full vaccination was defined as having received all recommended doses were received (usually 3 times). The mean proportion of fully vaccinated people over the study period was 70.9%. The proportion of fully vaccinated people steadily increased and exceeded 60% in all countries in the middle of February 2022.

The stringency index referred to the COVID-19 response stringency of each country based on 9 indicators including school closures, workplace closures, and travel bans. The

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Table 1. Description of variables used in the analysis (n = 3,328)

Variable	Mean	Median	Minimum	Maximum
Time-varying variables				
Biweekly CFR (%)	0.79	0.42	0.01	8.41
7-Day smoothed new cases (per million)	1,058.8	618.0	11.8	10,968.2
7-Day smoothed new deaths (per million)	3.04	2.09	0.03	21.20
Share of the Omicron variant (%)	52	50	0	100
Reproduction rate	1.09	1.06	0.46	2.33
People fully vaccinated (%)	70.9	72.0	34.8	92.6
Stringency index	47.6	47.2	11.1	80.1
Fixed Variables				
People aged older than 65 (%)	16.1	17.0	6.9	23.0
Natural logarithm of GDP per capita	10.46	10.47	9.49	11.12
Extreme poverty rate (%)	0.85	0.50	0.20	4.50
Hospital beds (per thousands)	3.86	2.99	1.38	12.27
Diabetes prevalence (%)	6.54	5.31	3.28	13.06
Cardiovascular deaths (per 100,000)	148.3	122.1	86.0	350.0
Life expectancy (y)	80.6	81.6	75.0	83.5

Data from 21 countries for 28 weeks between September 20, 2021 and April 4, 2022.
CFR, case fatality rate; GDP, gross domestic product.

scores were transformed and rescaled from 0 to 100; a closer score to 100 indicated a more stringent response [33].

Unlike time-varying variables, fixed variables had constant values throughout the entire research period. GDP per capita before transformation to its natural logarithm ranged from 13,254 to 67,335 in constant 2011 international dollars. The extreme poverty rate was defined as share of the population living in extreme poverty (less than 10% of the national average income per person) in the most recent year available since 2010. Diabetes prevalence was the percentage of people diagnosed with diabetes among all aged 20 to 79, and cardiovascular deaths referred to the annual number of deaths by cardiovascular disease per 100,000 people in 2017, which was the most recent data available. Life expectancy was the expected lifespan at birth in 2019.

Adjusted CFRs for Each Country

Table 2 shows the mean of the crude biweekly CFRs and adjusted CFRs for individual countries. The adjusted CFRs were computed from regression model 4 (Table 3), which included all possible covariates in this study. The overall CFR, along with each country's CFR, is reported as a percentage and listed in descending order of the adjusted CFRs.

Compared to crude CFRs, the variance of the adjusted CFRs was much smaller. The range between minimum and maximum values decreased from 8.40 to 4.58 after adjustment. The variance of the CFRs of individual countries also decreased after adjustment. The overall decreases in the variance and daily fluctuations after adjustment can be seen in Figures 1 and 2.

The variance in CFRs among countries was reduced, as shown by comparing a graph of the adjusted CFRs to the crude CFRs. Fluctuations in the adjusted CFRs throughout the entire time period in individual countries are much smaller compared to crude CFRs. As a result, compared to the graph of crude CFRs in Figure 1, the lines of the adjusted CFRs in Figure 2 are more smoothed.

The adjusted CFRs of most countries were below 1%, except for the top 3 ranked countries: Colombia, Mexico, and the United States (Table 2; Figure 2). These 3 countries showed higher CFRs than the other countries during the entire study period. Thus, the overall high CFRs of 3 countries may have been mainly due to the baseline effects of fixed variables (i.e., the country's characteristics).

Latvia was ranked fourth place in the average adjusted CFR, but demonstrated a different pattern over time compared to Colombia, Mexico, and the United States (Table 2; Figure 2). Whereas the adjusted CFRs of Colombia, Mexico, and the United States were already high in October 2021, and maintained their high levels through April 2022, Latvia (represented as a gray dashed line in Figure 2) started with an estimated CFR of about 1%. Latvia's adjusted CFR soared to about 2.5% until mid-November 2021, and then decreased to below 1% around January 2022. Therefore, compared to Colombia, Mexico, and the United States, this fluctuation in the adjusted CFR over time in Latvia could have mainly been driven by time-varying variables, not by Latvia's specific characteristics.

Table 2. Crude and adjusted CFRs of COVID-19 by country

Country	Crude CFRs (%)				Adjusted CFRs (%)[a]			
	Mean	Median	Minimum	Maximum	Mean	Median	Minimum	Maximum
Colombia	1.83	1.97	0.24	4.45	3.02	3.15	2.03	3.87
Mexico	4.35	3.27	0.47	8.41	2.96	2.87	2.19	4.59
United States	1.55	1.45	0.23	3.55	2.00	2.10	1.10	2.52
Latvia	1.56	1.36	0.27	3.40	1.23	1.01	0.38	2.63
Lithuania	0.91	1.15	0.16	1.57	0.75	0.85	0.26	1.16
Turkey	0.58	0.70	0.21	0.96	0.71	0.72	0.53	0.84
Italy	0.57	0.51	0.13	1.58	0.68	0.74	0.37	0.89
Greece	0.90	0.90	0.22	1.91	0.62	0.66	0.26	0.91
Chile	0.94	0.67	0.10	3.46	0.44	0.47	0.27	0.59
Canada	0.77	0.83	0.12	1.45	0.42	0.44	0.31	0.50
Estonia	0.49	0.41	0.06	1.26	0.42	0.46	0.11	0.72
Spain	0.68	0.36	0.06	2.20	0.42	0.44	0.20	0.58
South Korea	0.65	0.79	0.05	1.45	0.37	0.42	0.05	0.63
Portugal	0.25	0.22	0.06	1.14	0.36	0.40	0.13	0.58
Norway	0.21	0.17	0.02	1.30	0.30	0.33	0.12	0.48
Israel	0.37	0.32	0.01	0.91	0.26	0.30	0.01	0.40
Australia	0.34	0.22	0.03	0.94	0.26	0.25	0.08	0.46
Denmark	0.18	0.15	0.04	0.59	0.26	0.32	0.04	0.44
Belgium	0.28	0.27	0.05	0.63	0.26	0.27	0.09	0.36
United Kingdom	0.26	0.28	0.07	0.45	0.24	0.24	0.14	0.30
Ireland	0.21	0.21	0.02	0.47	0.18	0.19	0.06	0.24

Countries are arranged in descending order of mean of adjusted CFR.
CFR, case fatality rate; COVID-19, coronavirus disease 2019.
[a]Adjusted for 7-day smoothed new cases (per million), 7-day smoothed new deaths (per million), the predominance of the Omicron variant, reproduction rate, people fully vaccinated (%), stringency index, people aged older than 65 (%), natural logarithm of gross domestic product per capita, extreme poverty rate (%), hospital beds (per thousand), diabetes prevalence (%), cardiovascular deaths (per 100,000), and life expectancy (years).

Effects of Factors on Differences in the Estimated CFRs

Table 3 shows the results of the pooled GLS analysis of our panel data. Marginal changes in the biweekly CFR (converted from a natural logarithm by exponential transformation) in percentages by single-unit increases in independent variables are reported in the right column of coefficients in model 4 (Table 3). As time-varying variables, the predominance of the Omicron variant (>50% of the total variant share), reproduction rate, and proportion of fully vaccinated people significantly lowered the biweekly CFR ($p < 0.001$).

In model 2, the coefficients of the predominance of the Omicron variant and reproduction rate were reduced compared to model 1 once the variable for 7-day smoothed new cases per million was added. The mediation effect of 7-day smoothed new deaths per million was much smaller in model 3 than for the corresponding variable in model 2. Given the meaning of the reproduction rate and the high transmission of the Omicron variant, these results suggest that the predominance of the Omicron variant and a high reproduction rate reduced the CFR by increasing the number of new cases. Meanwhile, the proportion of fully vaccinated people significantly reduced the CFR in all models, with statistical significance ($p < 0.05$), as has been observed in previous studies [34–37].

Among the fixed variables, only 4 variables demonstrated a significant effect at the $p < 0.05$ level on the CFR: the proportion of individuals older than age 65, the share of the population living in extreme poverty, the number of hospital beds per thousand, and diabetes prevalence. These 4 factors were associated with an increased CFR, but the effect of the population share living in extreme poverty was particularly strong (a 173.15% increase in the CFR per unit increase of the proportion living in extreme poverty). Diabetes prevalence and age also contributed to the CFR. Single-unit increases in diabetes prevalence and the population share of people older than age 65 raised the CFR by 115.49% and 103.94%, respectively. In contrast, the effects of the stringency index, cardiovascular deaths, and life expectancy were not significantly associated with the CFR.

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Table 3. Pooled generalized least squares estimates from 4 different models

Variable	Model 1	Model 2	Model 3	Model 4	
	Coef.	Coef.	Coef.	Coef.	Marginal effect (%)[a]
Time-varying variables					
7-Day smoothed new cases (per million)		−0.0003***		−0.0003***	99.97
7-Day smoothed new deaths (per million)			0.0500***	0.0639***	106.60
Predominance of the Omicron variant	−0.0737***	−0.0596***	−0.0703***	−0.0532***	94.82
Reproduction rate	−0.306***	−0.256***	−0.262***	−0.186***	83.03
People fully vaccinated (%)	−0.0182***	−0.0096*	−0.0203***	−0.0144**	98.57
Stringency index	0.0001	0.0004	−0.0002	0.0000	100.00
Fixed variables					
People aged older than 65 (%)	0.0307	0.0418*	0.0338	0.0386*	103.94
Natural logarithm of GDP per capita	0.282	0.552	0.412	0.506	165.86
Extreme poverty rate (%)	0.485***	0.565***	0.491***	0.549***	173.15
Hospital beds (per thousands)	0.0139	0.0593*	0.0100	0.0567*	105.83
Diabetes prevalence (%)	0.101**	0.159***	0.110**	0.144***	115.49
Cardiovascular deaths (per 100,000)	0.0024	0.0022	0.0006	0.0005	100.05
Life expectancy (y)	−0.0503	−0.0689	−0.0704	−0.0656	93.65

The dependent variable is the natural logarithm of the biweekly case fatality rate. Coefficients (coef.) are rounded up to the fourth digit after the decimal point.

GDP, gross domestic product.

[a]Changes in the biweekly case fatality rate in percentage by single-unit increases in independent variables.

*$p < 0.05$, **$p < 0.01$, ***$p < 0.001$.

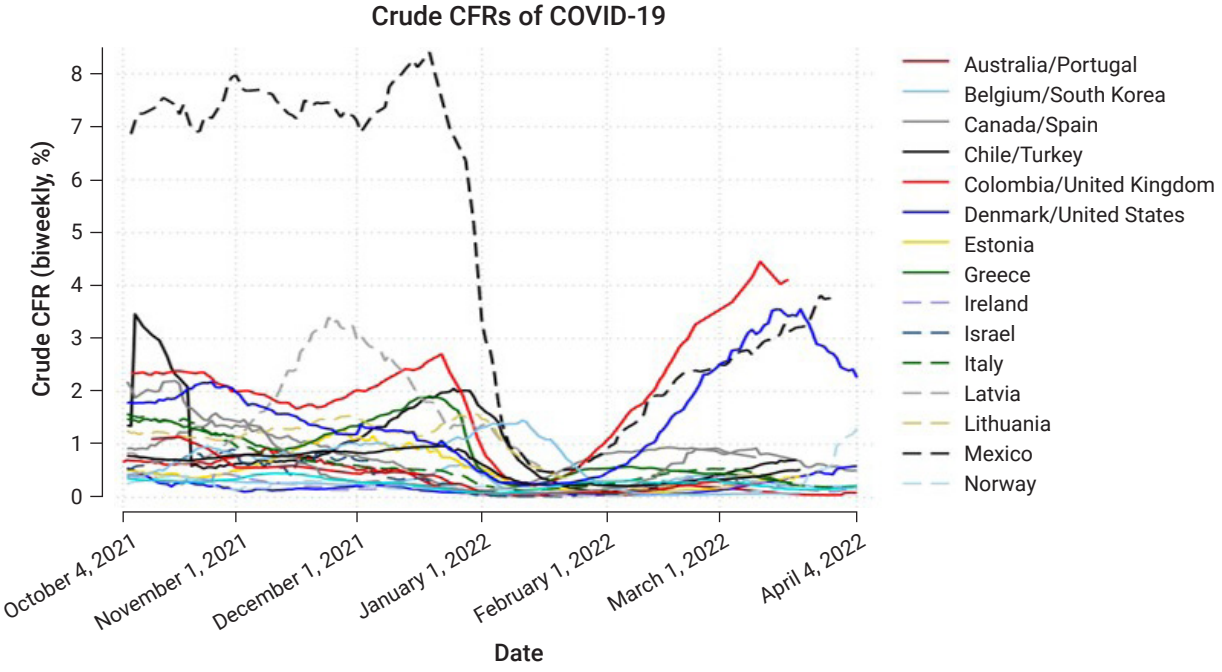

Figure 1. Time-series graph of crude case fatality rates (CFRs) of coronavirus disease 2019 (COVID-19) by country.

Discussion

Previous studies have pointed out several factors associated with the CFR. First, the CFR could be distorted by selection biases. There is a high likelihood that mild and asymptomatic cases would not be counted as confirmed cases, resulting in an overestimation of the CFR by decreasing the denominator (number of cases), especially in some countries with low

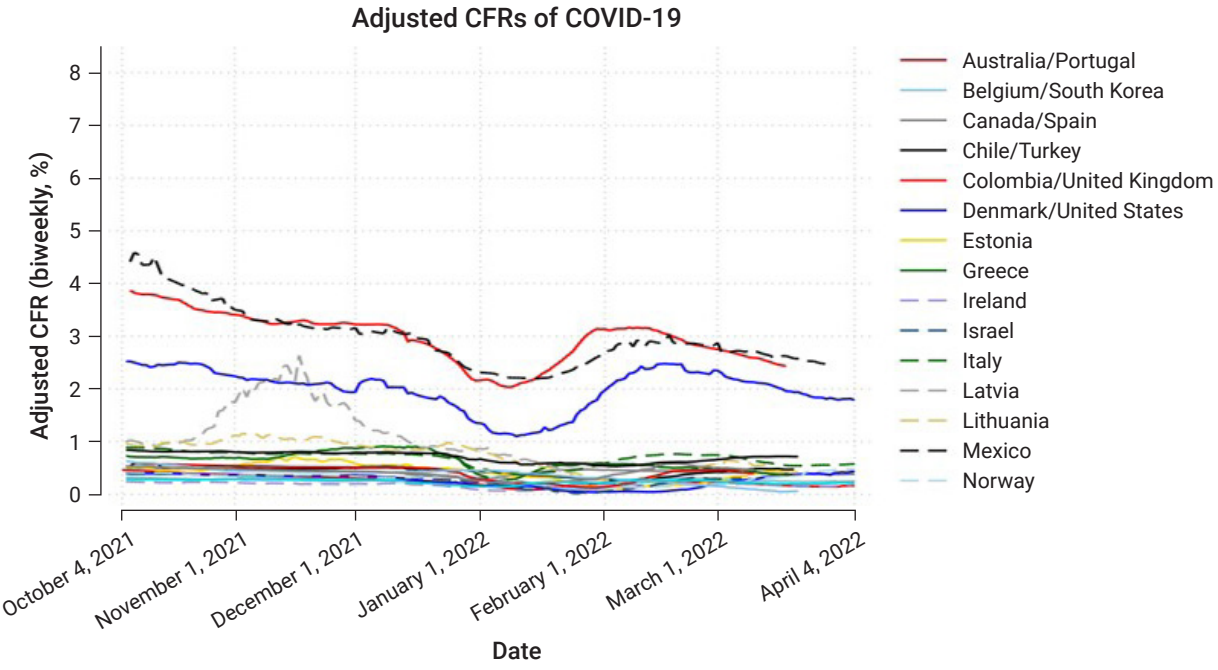

Figure 2. Time-series graph of adjusted case fatality rates (CFRs) of coronavirus disease 2019 (COVID-19) by country. Adjusted for 7-day smoothed new cases (per million), 7-day smoothed new deaths (per million), the predominance of the Omicron variant, reproduction rate, people fully vaccinated (%), stringency index, people aged older than 65 (%), natural logarithm of GDP per capita, extreme poverty rate (%), hospital beds (per thousand), diabetes prevalence (%), cardiovascular deaths (per 100,000), and life expectancy (years).

laboratory test access. The time lag between infection and confirmation, or between infection and death by COVID-19, could also influence the CFR. If infected cases are not counted as confirmed cases, this would overestimate the CFR [38]. In addition, the surveillance scheme of the country-wide reporting system, overall testing strategies, and an active screening program can cause biases in the CFR [39,40].

Individual risk factors, such as comorbidities, or demographic factors, such as age, sex, and race within the study population, are known to affect the CFR [20,41–45]. Furthermore, national-level factors, such as preventive policies (including mask-wearing or quarantine measures), poverty, income, capacity for disease, and healthcare, could affect the CFR by altering the number of cases or number of deaths [9,11,29–31,46–48].

In this analysis, we found that (1) CFRs adjusted by multiple covariates were less likely to vary over time and place, and (2) country-level CFRs were affected most by the following variables: the predominant variant at the time, the reproduction rate, vaccination, age, extreme poverty, and diabetes prevalence.

The significant effects of the Omicron variant, reproduction rate, vaccination, and older age on the CFR reconfirmed previously reported results about COVID-19 [34–37,42,49–56].

It is thought that the prevalence of the Omicron variant and reproduction rate reduce the CFR by increasing the number of new cases. It is straightforward that a high reproduction rate lowers the CFR because more infections result in a larger denominator for the CFR. The Omicron variant (BA.1 and BA.2) is known to have higher transmissibility and has actually driven the global pandemic [52,53]. The inverse relationship of the reproduction rate and the Omicron variant with the CFR, since those factors increase the number of new cases, was identified by the mediation effect in model 1 and model 2 (Table 3). We found that the coefficient of the reproduction rate and the Omicron variant became much smaller after adding the variable for 7-day smoothed new cases per million in model 2.

Older age has been repeatedly suggested as a factor that increases mortality from COVID-19 in most previous studies [8,23,42,56]. In that sense, our findings reconfirmed that a high proportion of elderly individuals is associated with an increased country-level CFR. We also found that vaccination robustly reduced the CFR. We hypothesize that vaccination affects the CFR by preventing severe cases and death, rather than by reducing new infections, because if the effect of vaccination on preventing new cases was much larger than its effects on preventing new deaths, the

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coefficient of vaccination would have been positive.

Following our analysis of country-level characteristics that may affect the CFR, we found that the extreme poverty rate and diabetes prevalence remarkably increased CFR. The overall high CFR in the top 3 countries (Colombia, Mexico, United States) was primarily driven by high extreme poverty rates. The extreme poverty rates in the top 3 countries were in the 75th percentile or higher among all countries (4.5 in Colombia, 2.5 in Mexico, and 1.2 in United States, whereas the median extreme poverty rate among all analyzed countries was only 0.5).

Although it is possible to overestimate the effect of extreme poverty due to its skewed distribution, the positive direction of the effect was robust in all regression models. Two hypotheses for why the extreme poverty rate has a positive effect on CFR can be suggested. First, it could be due to the differential inclusion of cases in the denominators. If individuals could not visit the hospital due to financial barriers, it would induce overestimation of the CFR because infections among the poor would not be counted as confirmed cases. Second, living in extreme poverty could raise the risk of death by COVID-19. For example, individuals living in extreme poverty might not be able to afford medical fees or might not be able to take sick leave from employment depending on their occupation. Comorbidities such as diabetes, possibly due to malnutrition or insufficient medical services, may also have played a role in this association.

The baseline effect of diabetes prevalence on the CFR in Colombia, Mexico, and United States was significantly high. As with the extreme poverty rate, the diabetes prevalence in the top 3 countries was in the 75th percentile or above among all countries (7.44 in Colombia, 13.6 in Mexico, and 10.79 in the United States, whereas the median diabetes prevalence in all countries was 5.91). This finding is consistent with previous studies about the burden imposed by comorbidities in COVID-19 patients because diabetes has been repeatedly identified as a significant comorbidity that increases severity and mortality of COVID-19 [20,26,28,31,57].

Meanwhile, it is notable that hospital beds per thousand showed a positive effect on the CFR. However, it would not be proper to interpret this result as meaning that more hospital beds for patients are "bad." One possible explanation for this result could be selection bias, as more beds could enhance the detection of deaths at hospital beds. In the same way, it is not necessarily "good" that some variables reduced the CFR, because the CFR does not provide direct information about the biological characteristics of the virus.

For example, as we have shown, the Omicron variant reduced the CFR because the growth rate of new cases caused by the Omicron variant was much higher than the growth rate of new deaths by the Omicron variant. However, it still needs to be carefully examined whether the lower CFR of the Omicron variant is a result of inflated new cases, or a signal that SARS-CoV-2 has changed into a less severe form of the virus that manifests fewer deaths for the same number of infections.

Furthermore, as we noticed, it is very important to consider the theoretical path when interpreting the significance of the effects of included variables. Logically, given the definition of the CFR, there are only 2 possible paths to affect the CFR: through the number of cases or the number of deaths. A precise understanding of the effect of risk factors is only possible if we determine whether they affect the CFR through the number of cases or the number of deaths. For example, we have shown a mediation effect of cases in the relationship between the predominance of the Omicron variant and the CFR. However, this interpretation of the mediation effect is only possible if there are enough preceding studies and knowledge about the biological mechanisms underlying the path of the effect. Thus, one should take care not to interpret the mediation effect of fixed variables in Table 3 too impetuously.

As we mentioned in the results, Latvia showed major fluctuations compared to countries such as Ireland, South Korea, Belgium, and Norway, where low CFRs were maintained steadily. The fluctuation in Latvia's CFR was largely driven by the number of deaths in the preceding 2 weeks. Thus, more research is needed to clarify whether epidemic events, such as seasonal spread, mass gatherings, or spread in vulnerable facilities, affected the large increase in deaths by COVID-19 at a specific time point in Latvia.

In conclusion, our findings suggested that the comparison of CFRs between multiple countries should consider the viral, immunological, medical, and social context of each country, as we observed significant effects of the predominant variant, reproduction rate, vaccination, age, poverty, and diabetes on the CFR. Therefore, when comparing CFRs of different countries, especially in contexts such as the epidemic phase, the medical capacity, surveillance strategy, and socio-demographic traits of the periods being compared should be considered, and one should be cautious when interpreting crude cross-sectional comparisons of CFRs.

Two limitations of this study should be noted. First, there is a possibility of a false effect caused by unaccounted variables. Such variables could include environmental factors such as temperature, altitude, seasonality, and air pollution, or population-based factors such as population immunity, age-specific cases, and the proportion of people

with health insurance [48]. Second, our study used only country-level data for analysis. To tease out a better estimate of country-level effects, a multi-level analysis with both individual and country-level data could be conducted. For example, it is well-known that comorbidities have a negative impact on an individual's disease severity and risk of mortality by COVID-19. An analysis without individual-level data could mask the impact of disparities among subnational entities [47].

Though our findings support a significant effect of some country-level variables on the CFR, further research is needed to examine whether these country-level characteristics, such as extreme poverty or medical capacity, may also affect the CFR by changing either the number of deaths or the number of cases. More covariates (e.g., seasonal and environmental factors) that might affect the CFR should be considered, and aggregating individual and country-level data would also be helpful for a multi-level analysis in the future.

Notes

Ethics Approval

This study did not need approval from the Institutional Review Board or an informed consent procedure because we used country-level open-source data that did not include any individual information.

Conflicts of Interest

The authors have no conflicts of interest to declare.

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None.

Availability of Data

The datasets generated and analyzed during the current study are available on the websites of Our World in Data (https:// ourworldindata.org/coronavirus) and CoVariants.org (https://covariants.org).

Authors' Contributions

Conceptualization: all authors; Data curation: YK; Formal analysis: YK; Investigation: YK; Methodology: all authors; Project administration: all authors; Supervision: BIK, ST; Visualization: YK; Writing–original draft: YK; Writing–review & editing: all authors.

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Original Article

mRNA vaccine effectiveness against SARS-CoV-2 B.1.617.2 (Delta) and B.1.1.529 (Omicron) variant transmission from home care cases to household contacts in South Korea

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ABSTRACT

Objectives: Household contacts of confirmed cases of coronavirus disease 2019 (COVID-19) are exposed to a high risk of viral transmission, and secondary incidence is an important indicator of community transmission. This study analyzed the secondary attack rate and mRNA vaccine effectiveness against transmission (VET) for index cases (patients treated at home) confirmed to be infected with the Delta and Omicron variants.
Methods: The subjects of the study were 4,450 index cases and 10,382 household contacts. Logistic regression analysis was performed to compare the secondary attack rate by vaccination status, and adjusted relative risk and 95% confidence intervals were identified.
Results: The secondary attack rate of the Delta variant was 27.3%, while the secondary attack rate of the Omicron variant was 29.8%. For the Delta variant, groups with less than 90 days and more than 90 days after 2 doses of mRNA vaccination both showed a VET of 37%. For the Omicron variant, a 64% VET was found among those with less than 90 days after 2 doses of mRNA vaccination.
Conclusion: This study provides useful data on the secondary attack rate and VET of mRNA vaccines for household contacts of COVID-19 cases in South Korea.

Keywords: COVID-19; Delta variant; Omicron variant; Vaccine efficacy; Vaccine effectiveness against transmission

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Introduction

A new variant of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) was reported to the World Health Organization (WHO) from South Africa in November 2021. This variant is characterized by its potential immune escape and high transmission rate. The WHO designated

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this a variant of concern, naming it Omicron [1,2]. As of April 1, 2022, the Omicron variant was further classified as follows: BA.1.1.529, BA.1, BA.2, and BA.3 [3]. As of April 5, 2022, the Health and Safety Executive (UK) reported 1,125 cases of XE, a mix of the BA.1 and BA.2 sub-variants [4].

In Korea, the first case of the Omicron variant was detected on November 30, 2021 [5]. On January 24, 2022, the predominant variant in Korea changed from the Delta variant to the Omicron variant [6]. As of January 3, 2022, 83.0% of Korea's population had received vaccines against coronavirus disease 2019 (COVID-19) [7].

A South African study reported that confirmed cases of the Omicron variant increased by approximately 2-fold compared with the previous number of confirmed cases and that the basic reproduction number of the Omicron variant could increase up to 4.2-fold compared with that of the Delta variant [8]. A study conducted at 9 nursing homes in Korea reported that the incidence rate of the Omicron variant was 11.18-fold higher than that of the Delta variant [9]. Previous studies have indicated that a reduction in vaccine effectiveness (VE) due to immune escape may have contributed to the higher incidence rates of the Omicron variant [10,11]. Furthermore, previous studies have reported that the vaccine effectiveness against transmission (VET) was lower for the Omicron variant than for the Delta variant [12,13].

Studies from the UK and Denmark have reported that identifying VE and quantifying VET are essential for estimating the transmission of new variants [14,15]. A recent study conducted among 10 million inhabitants in Korea showed the effectiveness of 3 doses of the mRNA vaccine against infection [16]. The household contacts of confirmed cases of COVID-19 are at a high risk of viral transmission [14]. In the UK, the incidence rates of infected household members increased concomitantly with the increased incidence rate of confirmed cases of the Delta variant [17]. Thus, the secondary attack rate (SAR) among household contacts is an important indicator of community transmission [18]. This study aimed to identify the SAR and mRNA VET among index cases (patients treated at home) with laboratory-confirmed cases of the Delta and Omicron variants.

Materials and Methods

Participants

This study included 4,450 index COVID-19 cases with either the Delta or Omicron variant, as confirmed by whole genome sequencing (WGS) in the laboratory, and their 10,382 household contacts from June 25, 2021, to January 22, 2022. Index cases were defined as those who had positive results on a SARS-CoV-2 polymerase chain reaction (PCR) test and were being isolated and treated at home. Confirmed cases were monitored for their health twice a day via phone calls or a mobile phone application, and if necessary, they had a telephone consultation and obtained a prescription for medication. The household contacts of the index cases were defined as those who were registered in the contact management system of the Korea Disease Control and Prevention Agency (KDCA).

When the Delta variant became predominant, household contacts were isolated at home for 14 days from the last day of contact with index cases, and they were required to undergo PCR tests at a public health center when they were made aware that they were contacts, if they became symptomatic during isolation, and when they were released from isolation [19].

When the Omicron variant became predominant, household contacts were isolated at home for 10 days, unless they met all of the following criteria at the time of contact with index cases: (1) fully vaccinated at the time of close contact; (2) asymptomatic; and (3) not residents, users, or employees at high-risk facilities, such as long-term care facilities. Household contacts had PCR tests at a public health center near their jurisdiction on the day when they became aware that they were contacts of COVID-19 cases and 6 to 7 days after their last contact with confirmed index cases [20]. Moreover, the staff of the public health center educated all household contacts about home-quarantine guidelines.

Data were obtained from a total of 44,573 index cases and 97,300 household contacts for analysis. Those who met the following criteria were excluded: did not undergo a test for a variant, had other variants, had incorrectly registered information, had unidentifiable vaccination status (VS); underwent a diagnostic test ≥15 days after the date when the index case was diagnosed, and had non-mRNA vaccines (Figure 1). VS was defined as at least 14 days having passed after a certain number of vaccinations. All index cases had received mRNA vaccines (Pfizer or Moderna) and the duration post-vaccination was analyzed using a cut-off of 90 days after vaccination.

Data Sources

Data on home healthcare and WGS of index cases were obtained from the COVID-19 patient management information system of the KDCA. Information about household contacts was obtained from the COVID-19 information management system of the KDCA. Data on VS were obtained from the COVID-19 vaccination system of the KDCA.

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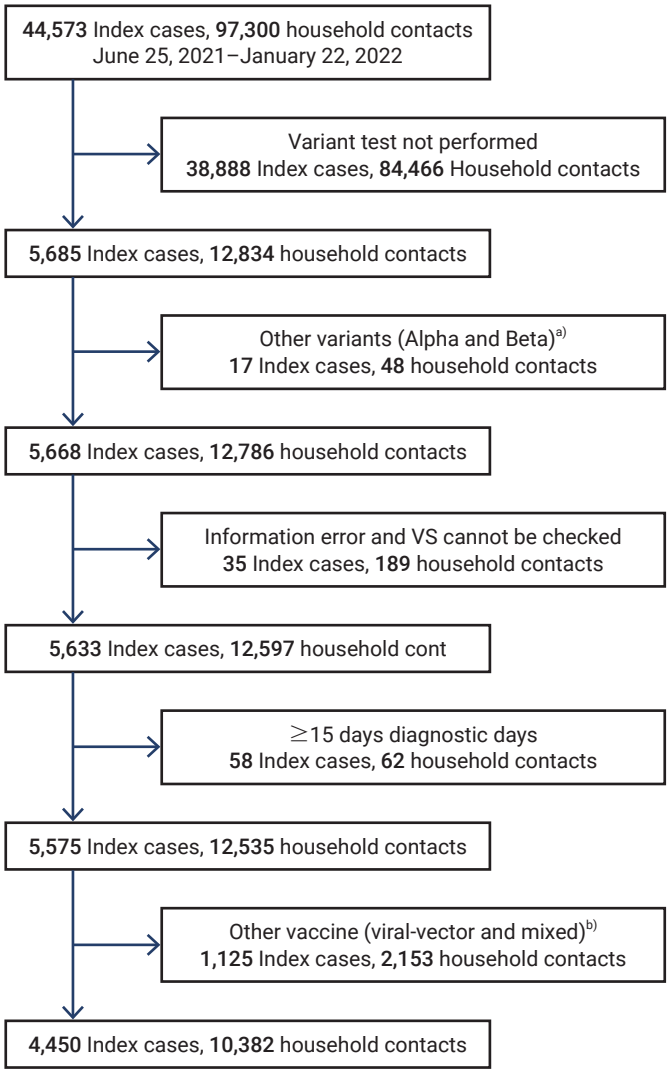

Figure 1. Inclusion criteria for index cases and household contacts in South Korea, June 25, 2021 to January 22, 2022.
a)Alpha: 15 index cases, 43 household contacts; Beta: 2 index cases, 5 household contacts. b)Viral-vector: 831 index cases, 1,574 household contacts; mixed: 294 index cases, 579 household contacts.
VS, vaccination status.

Statistical Analysis

Descriptive statistics were used to analyze participants' demographic characteristics and SAR, which were expressed as percentages (%). Logistic regression analysis was performed to compare the SAR according to the number of vaccine doses, and the adjusted related risk (aRR) was estimated. In an analysis model, sex, age, VS, and the diagnosis date of index cases and household contacts were adjusted. A p-value < 0.05 was considered to indicate statistical significance, and a 95% confidence interval (CI) was presented. All data were analyzed using the R software ver. 4.1.2 (The R Foundation, Vienna, Austria).

IRB/IACUC Approval

Information about all study participants was obtained after obtaining consent based on the Infectious Diseases Control and Prevention Act. The present study was reviewed and approved by the Institutional Review Board of the KDCA (2022-05-02-PE-A).

Results

Of the total of 14,832 participants, 4,450 (30.0%) were index cases and 10,382 (70.0%) were household contacts. Among both index cases and household contacts, the proportion of women was higher than that of men. The largest age group among index cases was ≤19 years (40.7%), whereas 37.1% of household contacts were in the age group of 30 to 49 years. In terms of VS, unvaccinated status predominated among the index cases, whereas the most common status among the household contacts was 2 doses of an mRNA vaccine (≤90 days) (Tables 1, 2).

Among household contacts, 2,877 (27.7%) participants were confirmed cases. The SAR of female index cases was 27.8%, which was higher than that of male cases. The index cases aged ≥75 years showed the highest SAR (38.3%). In an analysis of the index group according to VS, the unvaccinated group showed the highest SAR (30.8%), and the group that received the third dose of the vaccine showed the lowest SAR (13.6%). The aRR was estimated to identify risk factors for secondary transmission and the VET for index cases. In terms of age, the aRR was 1.87 (95% CI, 1.23–2.84) for individuals aged ≥75 years and 0.62 (95% CI, 0.54–0.70) for those aged ≤19 years compared to the age group of 30–49 years. In the association of VS with secondary transmission, the aRR of 1 dose was 0.68 (95% CI, 0.54–0.87), that of 2 doses (≤90 days) was 0.56 (95% CI, 0.48–0.65), that of 2 doses (>90 days) was 0.68 (95% CI, 0.58–0.79), and that of 3 doses was 0.28 (95% CI, 0.18–0.46) compared to the unvaccinated group.

Among the total of 4,450 index cases, 3,690 (82.9%) were infected with the Delta variant, and they had 8,719 (84.0%) household contacts. Among these, 2,382 confirmed cases were found, corresponding to a SAR of 27.3%. The index cases aged ≥75 years showed the highest SAR (38.2%). In an analysis according to VS, the unvaccinated group showed the highest SAR (30.2%), and the group that received the third dose of the vaccine showed the lowest SAR (15.5%). We estimated the aRR to identify risk factors for secondary

Table 1. General characteristics of index cases in South Korea from June 25, 2021 to January 22, 2022

Characteristic	Index case (%)
Total	4,450 (100)
Sex	
Male	2,142 (48.1)
Female	2,308 (51.9)
Age (y)	
≤ 19	1,812 (40.7)
20–29	577 (13.0)
30–49	1,287 (28.9)
50–74	704 (15.8)
≥ 75	70 (1.6)
Vaccination status	
Unvaccinated	2,412 (54.2)
1 Dose	211 (4.7)
Viral-vector	0
mRNA	211 (4.7)
2 Doses	1,740 (39.1)
Viral-vector (≤ 90 d)	0
Viral-vector (> 90 d)	0
mRNA (≤ 90 d)	917 (20.6)
mRNA (> 90 d)	823 (18.5)
Mixed (≤ 90 d)	0
Mixed (> 90 d)	0
3 Doses	87 (2.0)
2 Viral+1mRNA	0
1 Viral+2 mRNA	0
3 mRNA (≤ 90 d)	87 (2.0)

Table 2. General characteristics of household contacts in South Korea, from June 25, 2021 to January 22, 2022

Characteristic	Household contacts	
	Total (%)	Confirmed (%)
Total	10,382 (100)	2,877 (100)
Sex		
Male	4,872 (46.9)	1,299 (45.2)
Female	5,510 (53.1)	1,578 (54.8)
Age (y)		
≤ 19	2,524 (24.3)	929 (32.3)
20–29	911 (8.8)	181 (6.3)
30–49	3,853 (37.1)	1,045 (36.3)
50–74	2,753 (26.5)	634 (22.0)
≥ 75	341 (3.3)	88 (3.1)
Vaccination status		
Unvaccinated	2,942 (28.3)	1,270 (44.1)
1 Dose	466 (4.5)	110 (3.8)
Viral-vector	28 (0.3)	6 (0.2)
mRNA	438 (4.2)	104 (3.6)
2 Doses	5,912 (56.9)	1,351 (47.0)
Viral-vector (≤ 90 d)	225 (2.2)	68 (2.4)
Viral-vector (> 90 d)	734 (7.1)	207 (7.2)
mRNA (≤ 90 d)	2,961 (28.5)	606 (21.1)
mRNA (> 90 d)	1,679 (16.2)	395 (13.7)
Mixed (≤ 90 d)	81 (0.8)	20 (0.7)
Mixed (> 90 d)	232 (2.2)	55 (1.9)
3 Doses	1,062 (10.2)	146 (5.1)
2 Viral+1 mRNA	555 (5.3)	80 (2.8)
1 Viral+2 mRNA	108 (1.0)	13 (0.5)
3 mRNA (≤ 90 d)	399 (3.8)	53 (1.8)

transmission and VET among index cases confirmed to have the Delta variant. In terms of age, the aRR was 2.04 (95% CI, 1.32–3.17) for individuals aged ≥ 75 years and 0.67 (95% CI, 0.58–0.78) for those aged ≤ 19 years compared to the age group of 30 to 49 years. The aRRs of 1 dose, 2 doses (≤ 90 days), 2 doses (> 90 days), and 3 doses were 0.70 (95% CI, 0.54–0.89), 0.63 (95% CI, 0.53–0.74), 0.63 (95% CI, 0.52–0.77), and 0.41 (95% CI, 0.19–0.87), respectively, compared with the unvaccinated group.

Among the total of 4,450 index cases, 760 (17.1%) were infected with the Omicron variant. They had 1,663 (16%) household contacts, of whom 495 (29.8%) participants were confirmed to have become infected. The SAR for female index cases was 30.1%, which was higher than that of male index cases. The index cases aged ≥ 75 years showed the highest SAR (40%). Unvaccinated index cases showed the highest SAR (36.7%), and patients who had received the third dose of the vaccine showed the lowest SAR (12.6%). The aRR was estimated to identify risk factors for secondary transmission and VET among index cases confirmed to have the Omicron variant.

The aRR was 0.44 (95% CI, 0.31–0.64) in the index cases aged 20 to 29 years and 0.49 (95% CI, 0.35–0.67) in those aged ≤ 19 years compared to the index cases aged 30 to 49 years. In terms of the VS of index cases, the aRR was 0.36 (95% CI, 0.25– 0.51) in the group that had received the second dose (≤ 90 days) and 0.22 (95% CI, 0.11–0.42) in the group that had received the third dose compared to the unvaccinated group. In the Omicron group, the aRRs for those who had received the first dose and the second dose > 90 days ago were not statistically significant (Figure 2; Table S1–S3).

Discussion

This study confirmed the SAR and VET for index cases infected with the Delta or Omicron COVID-19 variants in terms of transmission to their household contacts. The SAR of index cases infected with the Delta variant was 27.3%, while that of index cases infected with the Omicron

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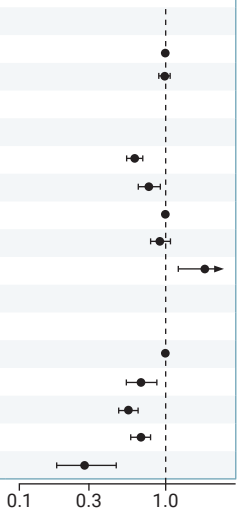
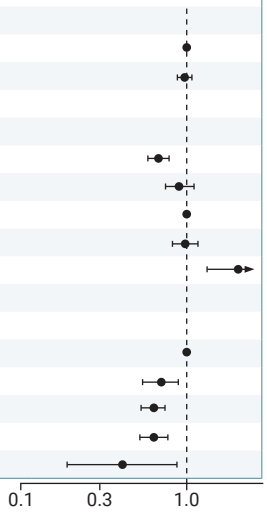
A

Total				
Index	**SAR**	**cRR**	**(95% CI)**	**aRR (95% CI)**
Sex				
Male	27.6	1.00	(–)	1.00 (–)
Female	27.8	1.01	(0.93–1.10)	0.99 (0.90–1.08)
Age (y)				
≤19	26.8	0.78	(0.70–0.86)	0.62 (0.54–0.70)
20–29	22.7	0.63	(0.53–0.73)	0.77 (0.65–0.92)
30–49	32.0	1.00	(–)	1.00 (–)
50–74	25.3	0.72	(0.63–0.83)	0.92 (0.79–1.08)
≥75	38.3	1.32	(0.90–1.94)	1.87 (1.23–2.84)
Vaccine status				
Unvaccinated	30.8	1.00	(–)	1.00 (–)
1 Dose, mRNA	24.9	0.75	(0.60–0.93)	0.68 (0.54–0.87)
2 Dose, mRNA (≤90)	22.2	0.64	(0.57–0.72)	0.56 (0.48–0.65)
2 Dose, mRNA (>90)	25.7	0.78	(0.69–0.88)	0.68 (0.58–0.79)
3 Dose, mRNA (≤90)	13.6	0.35	(0.23–0.55)	0.28 (0.18–0.46)



B

Delta variant				
Index	**SAR**	**cRR**	**(95% CI)**	**aRR (95% CI)**
Sex				
Male	27.3	1.00	(–)	1.00 (–)
Female	27.3	0.99	(0.91–1.10)	0.97 (0.88–1.07)
Age (y)				
≤19	26.4	0.80	(0.72–0.90)	0.67 (0.58–0.78)
20–29	24.3	0.72	(0.60–0.86)	0.90 (0.74–1.10)
30–49	30.8	1.00	(–)	1.00 (–)
50–74	24.9	0.75	(0.64–0.87)	0.98 (0.82–1.17)
≥75	38.2	1.39	(0.94–2.06)	2.04 (1.32–3.17)
Vaccine status				
Unvaccinated	30.2	1.00	(–)	1.00 (–)
1 Dose, mRNA	24.1	0.73	(0.59–0.92)	0.70 (0.54–0.89)
2 Dose, mRNA (≤90)	22.5	0.65	(0.59–0.76)	0.63 (0.53–0.74)
2 Dose, mRNA (>90)	22.2	0.66	(0.57–0.77)	0.63 (0.52–0.77)
3 Dose, mRNA (≤90)	15.5	0.42	(0.21–0.86)	0.41 (0.19–0.87)



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Omicron variant				
Index	**SAR**	**cRR**	**(95% CI)**	**aRR (95% CI)**
Sex				
Male	29.4	1.00	(–)	1.00 (–)
Female	30.1	1.04	(0.84–1.28)	1.06 (0.84–1.33)
Age (y)				
≤19	29.9	0.72	(0.56–0.92)	0.49 (0.35–0.67)
20–29	18.8	0.39	(0.28–0.54)	0.44 (0.31–0.64)
30–49	37.3	1.00	(–)	1.00 (–)
50–74	27.9	0.65	(0.46–0.93)	0.68 (0.46–1.01)
≥75	40.0	1.12	(0.19–6.78)	3.07 (0.41–22.96)
Vaccine status				
Unvaccinated	36.7	1.00	(–)	1.00 (–)
1 Dose, mRNA	34.2	0.90	(0.45–1.80)	0.73 (0.36–1.50)
2 Dose, mRNA (≤90)	20.7	0.45	(0.33–0.61)	0.36 (0.25–0.51)
2 Dose, mRNA (>90)	32.1	0.82	(0.64–1.04)	0.73 (0.53–1.01)
3 Dose, mRNA (≤90)	12.6	0.25	(0.14–0.45)	0.22 (0.11–0.42)

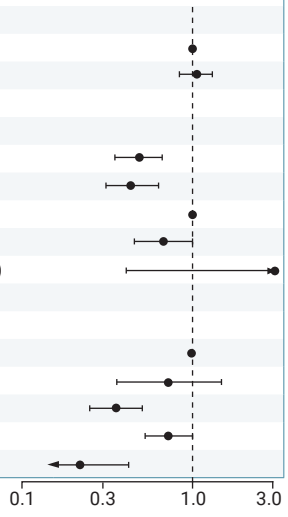

Figure 2. Adjusted relative risks (aRR) by sex, age and vaccination status of index cases in South Korea, from June 25, 2021 to January 22, 2022. (A) Total, (B) Delta variant, (C) Omicron variant. SAR, secondary attack rate; cRR, crude attack rate; CI, confidence interval.

variant was 29.8%. Among the index cases infected with the Delta variant, the VET was approximately 37% in cases who had received the second dose and approximately 59% in those who had received the third dose compared to the unvaccinated group. Among index cases infected with the Omicron variant, the VET was approximately 64% in those who had received the second dose (≤90 days) and approximately 78% in those who had received the third dose compared to the unvaccinated group. Our results can be used as evidence on the SAR and VET for household contacts of index cases infected with the Delta or Omicron variant in Korea, supporting the evidence from previous international and domestic studies.

Our study confirmed that the SAR of the Omicron variant was approximately 2.5 percentage points higher than that of the Delta variant. Since the first confirmed case of the Omicron variant, the number of confirmed cases has been rapidly increasing [6]. Our study results are in accordance with the findings of studies conducted in other countries that the emergence of the Omicron variant led to a more rapid increase in the number of confirmed COVID-19 cases than observed with the Delta variant [8,21]. Previous studies have reported that the SAR for the Delta variant was 11% to 36% [15,22,23], while the SAR for the Omicron variant was 51% to 52.7% [23,24]. The SAR for the Delta variant was approximately 1.7-fold higher than that of the Alpha variant [17], and SAR for the Omicron variant was approximately 1.41- to 1.48-fold higher than that of the Delta variant [23,25]. According to a meta-analysis that summarized 54 studies of secondary transmission to household contacts from October 2020 to June 2021, the factors affecting the increased SAR included the development of diagnostic tools, improvements in diagnostic procedures, and an increase in the viral transmission of variants as the COVID-19 pandemic continued [26]. Considering that only a laboratory of the KDCA could identify the Omicron variant until December 30, 2022 in Korea [27], the SAR of the Omicron variant in the community may have been much higher than indicated by our study results.

In our study, the SAR for index cases aged <19 years with the Delta or Omicron variant was approximately 33% or 51% lower, respectively, than that noted for patients aged 30 to 49 years. This is similar to a previous study's result, wherein the SAR for adults was approximately 2.2-fold higher than that for children [28]. Our study results may be related to the lower rate of vaccination among those <19 years during the time when the Delta variant became predominant in Korea [7]. Similarly, in the present study, the SAR for Delta variant-infected index cases aged ≥75 years was approximately 2.04-fold higher than that for cases aged 30 to 49 years. A previous study reported that the SAR for cases aged 70 to 79 years and ≥80 years was higher than that of the cases aged 30 to 39 years, which was similar to the result of this study [25]. As age increases, individuals tend to spend more time at home. Thus, the household contacts of index cases were more likely to be exposed to the virus for a longer period. Furthermore, these findings could support the hypothesis that exposure to a high viral load for a long period is associated with a high incidence rate [29].

Our study estimated and compared the SAR among household contacts according to the number of vaccine doses received by the index cases. The SARs of the Delta and Omicron variants were 30.2% and 36.7%, respectively, for unvaccinated index cases. A previous study reported that the SARs of the Delta and Omicron variants among household contacts were 38% and 57%, respectively, for unvaccinated index cases, which was higher than our study results [23]. The SAR of the Omicron variant was 1.51-fold higher than that of the Delta variant. In addition, another study that estimated the SAR of the Omicron variant according to the number of vaccine doses reported higher SARs for unvaccinated index cases than for vaccinated cases (second and third doses), consistent with the results of the present study [24].

In the present study, statistically significant VET was shown in the mRNA-vaccinated group compared to the unvaccinated group. Index cases with the Delta variant who received 2 doses of mRNA vaccine within ≤90 days or >90 days showed a VET of 37%, while index cases with the Omicron variant who received a dose of mRNA vaccine within ≤90 days showed a VET of 64%. A Norwegian study of the Delta variant reported that the VET in index cases who received the second vaccine dose was 37% regardless of the type of vaccine when compared to the unvaccinated group [23]. A Danish study reported a VET of 42%, which is similar to the results of the present study [15].

Furthermore, the present study confirmed the VET in index cases who had received the third dose of mRNA vaccine (within ≤90 days) compared to the unvaccinated group. The VET among index cases infected with the Delta and Omicron variants was 59% and 78%, respectively. Previous studies have reported reduced VE against the Omicron variant due to immune escape [10–12]. A study conducted in Colombia reported that the odds ratio for 3 doses of mRNA vaccines versus unvaccinated status was 0.33 for the Omicron variant and 0.065 for the Delta variant, confirming VE [13]. A Korean study reported VE in individuals aged ≥60 years who received 3 doses of mRNA vaccines [16]. VE has been reported in those who received 3 doses of mRNA vaccines, but further studies on VET should be conducted. The present study results support the findings of other

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studies that a third dose can enhance humoral immunity due to antibody boosting [30,31]. A previous study reported that the risk of infection increased beyond 90 days after receiving an mRNA vaccine [32]. Further studies on VET by the type of the vaccine and the duration post-vaccination should be conducted.

This study has some limitations. First, since tests to identify the variants were not carried out in all confirmed cases in South Korea, representativeness might be a concern. However, to ensure the representativeness of participants, we carried out tests to identify the variants using randomization. Second, despite frequent household contacts, infection risk-related factors such as the number of rooms in a house, compliance with face mask-wearing, and the degree of physical distancing were not adjusted because no information was available on these variables.

Supplementary Material

Table S1. Secondary attack rates and adjusted relative risks by sex, age and vaccination status of index cases in the South Korea; **Table S2.** Secondary attack rates and adjusted relative risks by sex, age and vaccination status of index cases with Delta variant in the South Korea; **Table S3.** Secondary attack rates and adjusted relative risks by sex, age and vaccination status of index cases with Omicron variant in the South Korea. Supplementary data are available at https://doi.org/10.24171/j.phrp.2022.0243.

Notes

Ethics Approval

This study was approved by the Institutional Review Board of Korea Disease Control and Prevention Agency (2022-05-02-PE-A) and performed in accordance with the principles of the Declaration of Helsinki.

Conflicts of Interest

The authors have no conflicts of interest to declare.

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None.

Availability of Data

The datasets are not publicly available. If you have any questions about this study, please contact the corresponding author (pahmun@korea.kr).

Authors' Contributions

Conceptualization: YJP, HP; Data curation: HP, MJL, HA; Formal analysis: HP; Methodology: YJP, HP, SEL; Project administration: HP; Visualization: YJP, HP; Writing–original draft: HP; Writing–review & editing: all authors.

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Brief Report

The effectiveness of Paxlovid treatment in long-term care facilities in South Korea during the outbreak of the Omicron variant of SARS-CoV-2

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ABSTRACT

Objectives: On November 5, 2021, Pfizer Inc. announced Paxlovid (nirmatrelvir + ritonavir) as a treatment method that could reduce the risk of hospitalization or death for patients with confirmed coronavirus disease 2019 (COVID-19).
Methods: From February 6, 2022 to April 2, 2022, the incidence of COVID-19 and the effects of treatment with Paxlovid were analyzed in 2,241 patients and workers at 5 long-term care facilities during the outbreak of the Omicron variant of severe acute respiratory syndrome coronavirus 2 in South Korea.
Results: The rate of severe illness or death in the group given Paxlovid was 51% lower than that of the non-Paxlovid group (adjusted risk ratio [aRR], 0.49; 95% confidence interval [CI], 0.24–0.98). Compared to unvaccinated patients, patients who had completed 3 doses of the vaccine had a 71% reduced rate of severe illness or death (aRR, 0.29; 95% CI, 0.13–0.64) and a 65% reduced death rate (aRR, 0.35; 95% CI, 0.15–0.79).
Conclusion: Patients given Paxlovid showed a lower rate of severe illness or death and a lower fatality rate than those who did not receive Paxlovid. Patients who received 3 doses of the vaccine had a lower rate of severe illness or death and a lower fatality rate than the unvaccinated group.

Keywords: COVID-19; Effectiveness of vaccine; Omicron variant; Paxlovid

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Introduction

In November 2021, the World Health Organization reported the Omicron variant of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), which had the characteristics of immune

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evasion potential and fast transmission. Among other known variants of coronavirus disease 2019 (COVID-19), Omicron was classified as a major variant of concern [1,2]. Accordingly, to prepare for the spread of COVID-19 in Korea and other countries, epidemiological studies were actively conducted to identify the time required for diagnosis of the Omicron variant [3], explore the characteristics of its transmission in the community [4], and analyze the effects of the vaccine on the Omicron variant [5].

By December 30, 2021, after the appearance of the Omicron variant in Korea, the vaccination rate increased along with the number of confirmed COVID-19 cases, as 82.7% of the general population had completed a second dose of the vaccine [6]. However, because the Omicron variant was easily transmitted, the cumulative number of confirmed cases in Korea as of April 25, 2022 reached 16,929,564, and the number of deaths per 100,000 population was 1.05 in the fourth week of February 2022. This rate increased to 1.74 in the first week of March 2022, to 2.61 in the second week of March 2022, and to 3.79 in the third week of March 2022 [7].

Although the Omicron variant had a low severity rate in confirmed patients, those admitted to long-term care facilities (LTCFs) were more likely to have severe illness and death than those in the community, since most of them had underlying diseases. Therefore, treatment was necessary to prevent infections in this high-risk group. Early studies had recommended the development of a medication that could be administered orally and conveniently, along with the development of a vaccine to prevent COVID-19 [8].

In November 2021, Pfizer Inc. announced Paxlovid (nirmatrelvir+ritonavir) as a medication that could reduce hospitalizations and deaths in patients with COVID-19. This medication was developed to inhibit the action of the SARS-CoV-2 proteolytic enzyme and was formulated as an oral treatment [9]. In addition, Pfizer reported that using Paxlovid could reduce the risk of hospitalization or death in confirmed patients by 89% [10].

In Korea, the use of Paxlovid, was started on January 14, 2022 [11]. The target population for treatment included those over 60 years old, the immunocompromised, and those with underlying diseases in their 50s. Since the number of confirmed cases and deaths increased due to the prevalence of the Omicron variant, on February 21, 2022, the scope of treatment targets was expanded to include those with underlying diseases in their 40s [12]. As of March 3, 2022, the cumulative use of Paxlovid in Korea was 25,342 courses; specifically, 20,827 courses for those treated at home, 785 courses for people in community treatment centers, and 3,730 courses for people in hospitals specializing in infectious diseases [13]. Long-term care hospitals and facilities were at high risk for severe cases when confirmed cases of COVID-19 occurred among their patients.

A systematic analysis to assess the effectiveness of major government measures, such as continuous monitoring of outbreaks and the use of vaccines and treatments, was needed. Therefore, this study investigated the incidence of COVID-19 in 5 LTCFs during the peak of the Omicron variant outbreak from February 6, 2022 to April 2, 2022. The preventive effect of the COVID-19 vaccine and the effect of treatment with Paxlovid on the development of severe illness were evaluated in the residents of these LTCFs.

Materials and Methods

Participants

The analysis targeted 2,241 residents and workers from 5 LTCFs in Korea where COVID-19 occurred from February 6, 2022 to April 2, 2022. The observation period was 52 days from the start of the Omicron outbreak to April 2, 2022, and the data for analysis were collected directly from each LTCF. The type of drug administered was determined by the medical staff, taking into consideration the patient's medical condition and current medications.

Statistical Analysis

This study used a retrospective cohort design, and the participants' general characteristics were presented as categorical variables using descriptive statistics. To compare severity and mortality according to the treatments and vaccines used, the relative risk was estimated and logistic regression analysis was applied. The term “severe cases” referred to patients with critical, life-threatening illness and those who died. The analysis model was adjusted for sex, age, vaccination history, and treatment history. All analyses were performed using R ver. 4.1.2 (R Foundation for Statistical Computing, Vienna, Austria), and the results were presented with 95% confidence intervals (95% CIs).

Ethics Statement

The study collected data in accordance with Article 76-2 of the Infectious Diseases Control and Prevention Act and was approved by the Institutional Review Board of the Korea Disease Control and Prevention Agency (IRB No: 2012-12-02-PE-A) of the Korea Disease Control and Prevention Agency.

Results

The average incidence rate of COVID-19 in the LTCF groups was 71.9% (95% CI, 58.6%–86.2%). Among the confirmed

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cases, 44.7% (95% CI, 26.9%–63.0%) of residents and 0.2% (95% CI, 0%–1.80%) of workers received oral drug treatment, of which 86.8% (95% CI, 72.9%–100%) was Paxlovid, and 13.2% (95% CI, 12.4%–27.1%) was remdesivir (Veklury; Gilead Sciences Inc., Foster City, CA, USA) or Regkirona (regdanvimab; Celtrion Healthcare, Incheon, Korea). The number of severe cases ranged from 2 to 19, and the number of deaths from 0 to 18 in the 5 LTCFs. The detailed status of each LTCF is shown in Table S1–S4.

The crude rate of severe cases was 3.7% for the residents who received Paxlovid and 7.1% for those who did not, and the crude mortality rate was 3.5% for those who received Paxlovid and 5.6% for those who did not. To compare the preventive effects of Paxlovid in residents who received the treatment compared to those who did not, the relative risk was estimated using logistic regression analysis and was adjusted for sex, age, and vaccination history. The adjusted rate of severe illness among residents who received Paxlovid was 51% lower than the rate among residents who did not receive Paxlovid (adjusted risk ratio [aRR], 0.49; 95% CI, 0.24–0.98) (Table 1; Figures 1, 2).

Among the residents, the crude rate of severe disease was 9.84% for those who were not vaccinated and 3.27% for those who had completed 3 doses of the vaccine.

Table 1. Severity of COVID-19 (Omicron variant) according to Paxlovid use among all patients at 5 Korean long-term care facilities

Variable	Total	Severe illness or death			Death		
		Total (%)	cRR (95% CI)	aRR (95% CI)	Total (%)	cRR (95% CI)	aRR (95% CI)
Total	819	37 (4.5)			33 (4.0)		
No treatment	196	14 (7.1)	1.00 (ref.)	1.00 (ref.)	11 (5.6)	1.00 (ref.)	1.00 (ref.)
Treated with Paxlovid	623	23 (3.7)	0.50 (0.25–0.99)	0.49 (0.24–0.98)	22 (3.5)	0.62 (0.29–1.29)	0.62 (0.29–1.32)

Adjusted for sex, age, and vaccination status.
COVID-19, coronavirus disease 2019; cRR, crude relative risk; CI, confidence interval; aRR, adjusted relative risk; ref., reference.

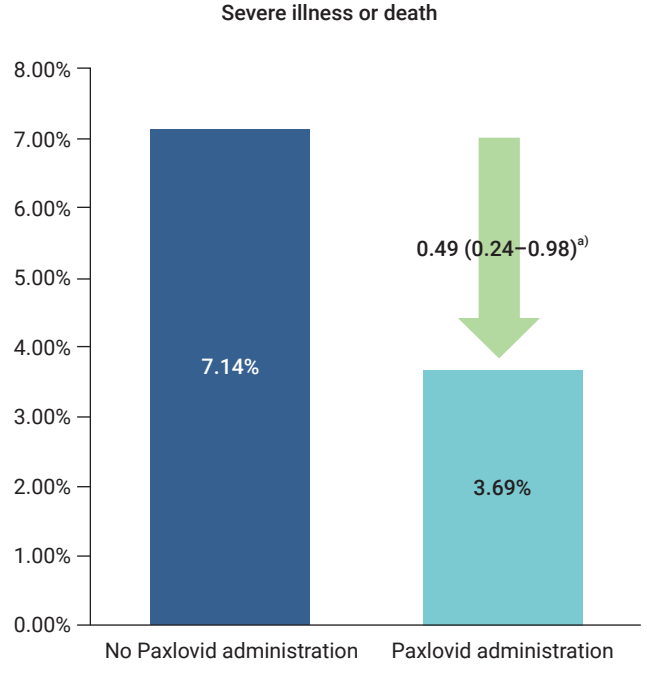

Figure 1. Comparison of severe illness or death according to the Paxlovid administration history in patients at 5 Korean long-term care facilities during the Omicron variant outbreak, from February 6, 2022 to April 2, 2022. a)When non-treatment was set as reference, adjusted relative risk (95% confidence interval).

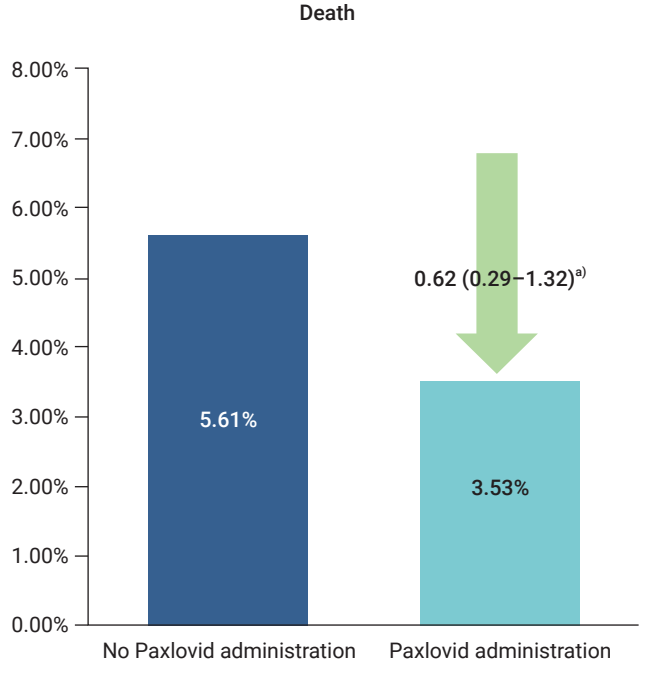

Figure 2. Comparison of death according to the Paxlovid administration history in patients at 5 Korean long-term care facilities during the Omicron variant outbreak, from February 6, 2022 to April 2, 2022. a)When non-treatment was set as reference, adjusted relative risk (95% confidence interval).

Furthermore, the crude rate of mortality was 8.20% for the unvaccinated and 3.27% for those who had completed 3 doses of the vaccine. To compare the preventive effects of vaccination, the relative risks were estimated using logistic regression, adjusted for sex, age, and treatment history. For residents who received 3 doses of the vaccine, the adjusted rate of severe cases was 71% lower than in residents who were unvaccinated (aRR, 0.29; 95% CI, 0.13–0.64), and the rate of mortality was 65% lower than in the unvaccinated (aRR, 0.35; 95% CI, 0.15–0.79) (Figures S1, S2).

Discussion

Our study analyzed the effect of treatments and vaccines on residents of LTCFs, where a cluster of Omicron variant outbreaks occurred from February 6 to April 2, 2022. Our results confirmed that patients treated with Paxlovid had a 51% lower rate of severe cases than those who did not receive Paxlovid treatment. In addition, residents who had received 3 doses of the vaccine had a 71% lower rate of severe cases and a 65% lower rate of mortality than those who were not vaccinated.

Studies by Pfizer that targeted adults at risk of severe illness and death among non-hospitalized COVID-19 patients reported that the risk of hospitalization or death in these patients was reduced by 89% when they received Paxlovid within 3 to 5 days of symptom onset [9,10]. The monitoring period for hospitalization and mortality in the Pfizer study was 28 days. Furthermore, a study in Hong Kong reported that nirmatrelvir/ritonavir prevented hospitalization in 20% of confirmed COVID-19 patients [14]. Our study targeted patients hospitalized for confirmed COVID-19, and although there was a difference in that our dependent variables were critical disease and death, the effects of Paxlovid were confirmed.

As of March 4, 2022, the quarantine authorities in Korea reported that the BA.2 variant, a subclassification of the Omicron variant, had become dominant [15]. The authorities promptly conducted risk assessments for the new variant as well as response effect analyses, with the intention of minimizing the negative impact of new variants on public health. They have periodically analyzed outbreaks, deaths, and vaccination effects in long-term care hospitals and facilities to identify the epidemiological characteristics and treatment effects in cluster outbreaks.

Compared to the Delta variant, the Omicron variant had a lower fatality rate but a higher incidence rate [16], resulting in an increased number of severe cases and deaths along with an explosion of confirmed cases. Even though the effectiveness of the vaccine against the Omicron variant has been confirmed for Omicron mutations [5], to minimize severe illness and death, the intensive management and analysis of high-risk groups in vulnerable facilities should continue. In addition, the Central Quarantine Countermeasures Headquarters has distributed a guide for the correct use of COVID-19 treatments. Notably, medical staff administering Paxlovid must carefully consider underlying diseases and current medications when deciding whether to administer the drug [17].

The main limitation of this study was that deaths due to other causes, which are characteristic of patients in LTCFs, could not be excluded. We did not adjust for the underlying diseases and conditions that could have affected the death rate among those being treated for COVID-19. However, we did consider that most of the subjects had comorbidities because they were patients in LTCFs. It is suggested that an extended sample of study subjects and a longer monitoring period be used in future studies to supplement the limitations of this study. This study is significant, however, because it is the first study on this topic to adjust for major factors related to death in residents of LTCFs in Korea, which have similar environments. Our findings confirm that the COVID-19 vaccine and Paxlovid effectively reduced the severity and fatality rates of the COVID-19 Omicron variant. In the future, it is expected that adverse reactions and treatment side effects will be investigated and that information will be used to help establish policies for COVID-19 treatment and prevention.

Supplementary Material

Table S1. Details of LTCF, from February 6, 2022 to April 2; **Table S2.** General characteristic and incidence in subjects; **Table S3.** General characteristics of all patients at long-term care facilities according to therapeutic agent used; **Table S4.** Severity according to vaccination status among patients at five long-term care facilities; **Figure S1.** Comparison of severity according to vaccination history of patients of long-term care facilities with an outbreak of the Omicron variant, from February 6, 2022 to April 2, 2022; **Figure S2.** Comparison of death according to vaccination history of patients of long-term care facilities with an outbreak of the Omicron variant, from February 6, 2022 to April 2, 2022. Supplementary data are available at https://doi.org/10.24171/j.phrp.2022.0262.

Notes

Ethics Approval

This study was approved by the Institutional Review Board of the Korea Disease Control and Prevention Agency (IRB No: 2012-12-02-PE-A) and conducted in accordance with the principles of the Declaration of Helsinki.

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

Funding
None.

Availability of Data
The datasets are not publicly available. If you have any question about this study, contact the corresponding author (pahmun@korea.kr)

Authors' Contributions
Conceptualization: YJP; Data curation: HP, HYL, MY, JJL, ESL, YK; Formal analysis: HP, HYL, MY; Methodology: YJP, HP, SEL, HYL, MY, YJS; Project administration: HP; Visualization: YJP, HP; Writing-original draft: HP; Writing-review & editing: all authors.

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Brief Report

A low risk of nosocomial transmission of subclinical tuberculosis to neonates in a postpartum care center under COVID-19 control measures

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ABSTRACT

We report the results of investigating and managing a tuberculosis (TB) exposure in a postpartum care center. Among the contacts exposed to a nursing assistant with subclinical TB, 5 of 44 neonates (11.4%) had positive tuberculin skin tests (TSTs) at 3 months of age, and all the TST-positive neonates received the Bacille Calmette-Guérin vaccination. Seven of 28 healthcare workers (25.0%) and 1 of 3 household contacts (33.3%) were positive in the initial or repeated interferon-gamma release assay. None of the contacts developed TB disease during the study period. Annual TB examinations of healthcare personnel at a postpartum care center under the Tuberculosis Prevention Act in South Korea enabled the early detection of subclinical TB, which reduced the risk of transmission to neonates under strict coronavirus disease 2019 prevention measures.

Keywords: Latent tuberculosis; Neonates; Postpartum period; Pulmonary tuberculosis

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Introduction

The nosocomial transmission of tuberculosis (TB) to neonates is a recognized risk factor with a high mortality rate [1]. The growth in the number of private postpartum care centers in South Korea, which provide customized services for mothers and their newborns during the postpartum period, has contributed to increased TB exposure to neonates, causing serious public concerns [2]. However, uncertainty about the risk of TB transmission to neonates makes it challenging to determine the appropriate level of TB exposure management. This

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study evaluated the risk of TB transmission among the contacts exposed to a nursing assistant with subclinical TB at a postpartum care center.

Materials and Methods

Index Case

A 58-year-old nursing assistant working at a postpartum care center was referred to a tertiary university-affiliated hospital following abnormal findings on chest radiography (CXR), performed as part of an annual TB screening program on August 9, 2021. Subsequently, computed tomography and repeated CXR showed a nodule in the right upper lung, but no cavities. Bronchoalveolar lavage fluid analysis revealed smears for acid-fast bacilli (AFB), and cultures in liquid and solid media for *Mycobacterium tuberculosis* were negative; however, polymerase chain reaction for *M. tuberculosis* was positive. Additionally, the Xpert MTB/RIF (Cepheid, Sunnyvale, CA, USA) assay was positive for *M. tuberculosis* complex without rifampin resistance. The patient had no symptoms such as fever, cough, or sputum production. In 2017, an interferon-gamma release assay (IGRA) was negative, and a CXR during a 2020 recruitment check-up was normal. The index case worked 8 hours per day, 4 to 5 days a week, at the facility. She spent around 6 hours caring for newborns, such as feeding, soothing, and changing diapers in a neonate care room, while always using a facial mask. On average, she cared for 3.5 neonates per day. Casual contacts or conversations between the index case and other nursing staff may have occurred in a dressing room or during 30 minutes of duty handover.

Setting

The postpartum care center was a 4-story structure with a total area of 657 m^2. The mothers resided in 19 separate rooms on the first and second floors. The neonatal care unit was located on the third floor, which measured 59.2 m^2, and was divided into 3 sections: a nursing room (10.3 m^2), an intensive care room (15.9 m^2), and a neonate care room with 19 newborn cribs (33.0 m^2). The building was served by a mechanical ventilation system, and each room was equipped with a portable air cleaner appliance. In accordance with the national coronavirus disease 2019 (COVID-19) response protocol, mandatory face mask-wearing and respiratory hygiene were strictly followed in the entire facility, and visitors were not allowed except for the mother's spouse.

Contact Investigation

According to the Korea Disease Control and Prevention Agency guidelines [3], the beginning of the infectious period was determined to be 4 weeks before the date of suspected diagnosis, given that the index case had no TB symptoms and was sputum smear-negative in AFB without lung cavities on CXR. Given the index case's work schedule and absence in the facility, the infectious period was estimated as July 13 to August 7, 2021. All contacts, including neonates, healthcare workers (HCWs), and household contacts, were examined and followed. The exposed neonates underwent CXRs and were recommended to receive isoniazid prophylaxis (10 mg/kg/day) until 3 months. Tuberculin skin tests (TSTs) using 2 Tuberculin Unit (TU) of Purified Protein Derivative (PPD) RT23 (Statens Serum Institut, Copenhagen, Denmark) were performed using the Mantoux method at the end of preventive TB treatment. A positive TST was defined as an induration of ≥5 mm in neonates without Bacille Calmette-Guérin (BCG) vaccination and ≥10 mm in those with BCG vaccination. HCWs and household contacts were initially offered CXRs and IGRAs. After 8 weeks, they underwent second CXRs, and those with negative results at the initial IGRA were offered repeat IGRAs. Along with the findings of the epidemiological investigation, the Korean National TB Surveillance System (KNTSS) database was used to verify previous TB history, latent tuberculosis infection (LTBI) test results, and treatment outcomes. All contacts were followed up for around a year after the last exposure to the index case, until August 13, 2022 (Table 1).

Results

The staff, patient, and visitor records were reviewed, and a total of 76 contacts were identified, comprising 44 infants, 29 HCWs or administrative staff, and 3 family members; of these, 75 contacts, except for an accountant who had been working from home, were identified as having potential exposure to the index case and were included in this investigation.

The median (interquartile range) chronological and corrected ages of neonates at the start of the investigation were 30.0 days (20.8–38.3 days) and 19.5 days (7.5–32.3 days), respectively. Thirty-one neonates had received the BCG vaccination, while 13 had not. None had abnormal findings suggesting active TB on their CXRs. During TST screening at 3-months of age, 5 neonates, including 4 males and 1 female, tested positive and continued to receive LTBI treatment with 3-month rifampicin and isoniazid or 9-month isoniazid at the physician's discretion. There was no significant difference between intradermal and subcutaneous BCG vaccination in regard to the induration diameters. Notably all neonates with positive TSTs had received the BCG vaccine (Table 2), resulting in a TST positivity rate of 16.1% (5/31 neonates) among the

Table 1. TB diagnostic work-up for an index case and the process of TB investigation and treatment

Date	Progress detail
August 9, 2021	Detection of abnormal findings on CXR through an annual TB screening
August 10, 2021	A nodule in the right upper lung but no cavities in CT
August 13, 2021	Xpert MTB/RIF assay of bronchoalveolar lavage fluid samples is positive for *Mycobacterium tuberculosis*
	Notified the index case to public health authorities through KNTSS
August 14, 2021	On-site epidemiological investigation
	CXRs and IGRAs for HCWs
	Positive TB-PCR in sputum
August 16, 2021	Information session for exposed infants' parents
August 17, 2021	Started screening of CXRs for infants
September 27, 2021	Started TSTs for Infants
October 11, 2021	Repeated IGRAs for HCWs
December 28, 2021	Treatment completion of the last HCW with LTBI
June 30, 2022	Treatment completion of the last infant with positive TST
August 13, 2022	End of study with complete follow-up of contacts

TB, tuberculosis; CXR, chest radiography; CT, computed tomography; KNTSS, Korean National TB Surveillance System; IGRA, interferon-gamma release assay; HCW, healthcare worker; PCR, polymerase chain reaction; TST, tuberculin skin test; LTBI, latent tuberculosis infection.

Table 2. Characteristics and TST results of the exposed neonates

Characteristic	Neonate (*n* = 44)
Age at start of the investigation (d)	
Chronological[a]	30.0 (20.8–38.3)
Corrected[b]	19.5 (7.5–32.3)
Gestational age (wk)	38.5 (38.1–39.3)
Sex	
Male	22 (50.0)
Female	22 (50.0)
BCG vaccination	
Vaccinated	31 (70.5)
Intradermal	19 (61.3)
Subcutaneous	12 (38.7)
Unvaccinated	13 (29.5)
TST	
Positive	5 (11.4)[c]
Negative	39 (88.6)

Data are presented as median (interquartile range) or *n* (%).
TST, tuberculin skin test; BCG, Bacille Calmette-Guérin.
[a]Chronological age refers to the number of weeks since the date of birth. [b]Corrected age refers to the number of weeks since the expected due date. [c]Two of the 5 infants had an induration diameter of 10 mm and 3 had induration diameters of 12 mm. All 5 had been BCG-vaccinated: 2 with intradermal injections and 3 with subcutaneous injections. Three of them were treated with 3 months of rifampicin and isoniazid and 2 infants with 9 months of isoniazid.

vaccinated. Positive TST findings were not associated with the duration of exposure to the index case (median 5.0 days among the 5 TST-positive neonates vs. 7.0 days among the 39 TST-negative neonates). In a year after exposure, no neonates, including the 5 with a positive TST, developed TB disease.

The mean age of the 28 HCWs was 57.0 ± 5.0 years, and 78.6% of HCWs were nursing staff. Twenty-two had previous IGRA results from 2015 to 2019, and 6 had no results recorded in the KNTSS. None of the 28 HCWs had abnormalities on the baseline or second CXRs. Six of the 21 HCWs, including 4 with negative results and 2 with no records from previous IGRAs, were positive on the first IGRA. One of the 15 HCWs who were negative at the first IGRA tested positive during repeated IGRA. At the physician's discretion, 6 of the 7 HCWs with LTBI were treated with 4-month rifampin or 3-month rifampin and isoniazid (Figure 1). None of the 3 family members had any abnormalities suggestive of TB on either CXR. They tested negative on the first IGRAs, but 1 tested positive on repeated IGRA and received a 4-month rifampin regimen. During the study period, there were no cases of TB illness among the exposed HCWs.

Discussion

Our study revealed that after an exposure investigation using TSTs/IGRAs, 13 contacts, including 5 neonates, 7 HCWs, and 1 household contact, were presumed to have LTBI with 12 contacts completing treatment for LTBI. Of the 44 neonates exposed to the index case, 5 (11.4%) had positive TST results at 3 months, significantly lower than the average 21.5% skin test-positive rate with 2 TU of PPD RT23 using a 10-mm cutoff point among those who had previous BCG vaccination without a TB exposure history [4]. None of the infants who had not received a BCG vaccination showed positive TST results. The estimated duration of exposure to

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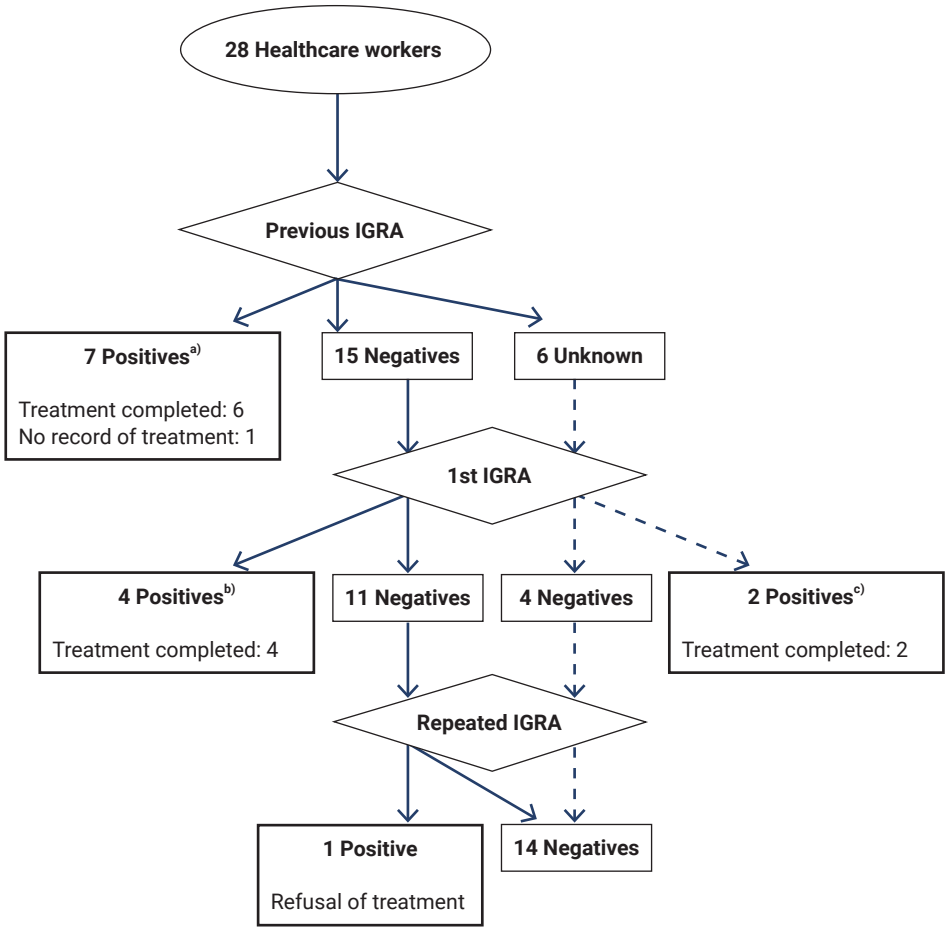

Figure 1. Flowchart of the research protocol and interferon-gamma release assay (IGRA) results from exposed healthcare workers. The solid line and dotted line indicate the flows of positive/negative cases and unknown cases from previous IGRAs, respectively.
[a)]Seven cases had records of latent tuberculosis infection in the Korean National Tuberculosis Surveillance System, but 1 of them had no record of treatment. [b)]A case was treated with 4 months of rifampin and 3 cases with 3 months of rifampin and isoniazid. [c)]A case was treated with 4 months of rifampin and 1 case with 3 months of rifampin and isoniazid.

the index case was not associated with positive TST results, and the induration diameters observed in neonates with positive results were barely over the cutoff value of 10 mm (range, 10–12 mm). Taken together, the risk of nosocomial TB transmission to newborns was estimated to be modest in this study, which is in line with previous research conducted in Canada, Australia, the United States, and South Korea [5–8].

The index case had a minimal risk of transmission, as predicted by the negative sputum smear results and a lack of respiratory symptoms and cavities. It is noteworthy that LTBI screening and annual TB examinations for HCWs in postpartum care centers under South Korea's amended Tuberculosis Prevention Act played a critical role in early detection and control of onward TB transmission [9]. Furthermore, the enhanced infection prevention and control measures implemented in the facility in response to COVID-19, such as physical distancing, wearing surgical masks or other types of masks with greater filtration efficiency, adherence to respiratory hygiene and cough etiquette, environmental disinfection, and mechanical ventilation, may have also substantially contributed to reducing the transmission of *M. tuberculosis*. In fact, a recent systematic review [10] found that the use of surgical masks in conjunction with cough etiquette training reduced TB infection by 14.8%, and mechanical ventilation was related to 2.9% to 14.8% less infection. Additionally, HCWs' use of personal respirators reduced infection by 0% to 14.8%, all suggesting that infection control measures in healthcare settings are likely to reduce TB transmission.

Six of the 28 HCWs (21.4%) exposed to the index case had positive results on the initial IGRA, and 1 (3.6%) had a positive conversion at 8 weeks on a repeated IGRA test. Although the prevalence of LTBI among HCWs in this study was substantially high, implying that the intensity of exposure to HCWs was high compared with that of neonates, the result should be interpreted with caution. The possibility that some HCWs with positive IGRA results could have been infected before the current exposure should be considered, given that the positivity rate of IGRA among HCWs was 24.1% overall and, notably, around 50% in HCWs in their 50s in another study [11], which is comparable to

the average age of 57.0 years among the 7 LTBI-positive HCWs in our study. Nonetheless, our finding that the transmission rate among exposed HCWs was higher than that among exposed neonates is consistent with previous studies [5–8]. It is likely that neonates are better protected against exposure to airborne pathogens than HCWs and that neonates were cared for in baby cribs with minimal exposure with the index case.

This study has several limitations. Indurations were measured by multiple individuals at 3 referral hospitals, which might have led to inter-observer variation. However, because they were all experienced healthcare personnel in TB management under the supervision of infectious disease specialists, this variation is expected to be modest. Second, the exposed neonates, HCWs, and household contacts could not be tracked for an extended period to ascertain whether they had developed TB. Finally, caution is warranted when extrapolating the findings of our study's risk estimate of TB transmission to different healthcare settings since the transmission risk can vary depending on the intensity and duration of exposure, the infectiousness of an index case, and environmental factors.

In summary, although 5 neonates were treated with prophylactic TB medication for fear of severe outcomes, this study demonstrated that transmission to neonates exposed to active pulmonary TB at a postpartum care center was minimal, especially under enhanced infection prevention and control measures. Our findings highlight the importance of early detection of subclinical TB through annual TB examinations, which is conducive to reducing the intensity and duration of TB exposure in healthcare settings in a country with an intermediate TB burden.

Notes

Ethics Approval

The requirement for written informed consent from participants was waived according to the Korean Infectious Disease Control and Prevention Act (No. 4). The present study protocol was reviewed and approved by the Institutional Review Board of the Korea Diseases Control and Prevention Agency (2022-04-08-PE-A).

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: IKK, YAK, JSS; Data curation: IKK, SJK, KHB; Data interpretation: IKK, YAK, JSS; Investigation: SJK, KHB, JEO, MGL, MYK, JSS; Supervision: MYK, JSS; Writing-original draft: IKK; Writing-review & editing: all authors.

Additional Contributions

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

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

Peer Review Process

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

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

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

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

MANUSCRIPT PREPARATION

General Requirements

All manuscripts must be in grammatically correct English and should be created using MS Word. The manuscript must be double-spaced and written in an A4 page format. Do not leave a space between paragraphs. Only a single font (preferably Times New Roman) should be used in 11 point with margins of 2.5 cm.

- All pages including the title page should be paginated consecutively. All numbers should be written in Arabic numerals throughout the manuscript except for the first word of the sentence. Texts should be justified on both sides and not hyphenated and headings should be in bold letters, aligned in the center. If possible, avoid using abbreviated words at the beginning of sentences.
- Abbreviations: Where a term/definition is repeatedly referred to (i.e., 3 times in the text), it is written in full when it first appears, followed by the subsequent abbreviation in parentheses (even if it was previously defined in the abstract); thereafter, the abbreviation is used.
- Gene nomenclature: Current standard international nomenclature for genes should be adhered to. Genes should be typed in italic font and include the accession number. For human genes, use the genetic notation and symbols approved by the HUGO Gene Nomenclature Committee (http://www.genenames.org/) or refer to PubMed (http://www.ncbi.nlm.nih.gov/sites/entrez).
- Units: Système International (SI) units must be used, with the exception of blood pressure values, which are to be reported in mmHg. Please use the metric system for expressions of length, area, mass, and volume. There should be a space between the numerals and the unit symbol. When indicating time, the 24-hour system is to be used.
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Reporting Guidelines for Specific Study Designs

For specific study designs, such as randomized control studies, studies of diagnostic accuracy, meta-analyses, observational studies, and non-randomized studies, authors 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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PHPR publishes editorials, original articles, review articles, guidelines, data profiles (including cohort profiles), special articles, short communications, viewpoints, commentaries, editorials, commentaries, and correspondence, and book reviews.

- **Original articles** are papers containing results of basic and clinical investigations, which are sufficiently well documented to be acceptable to critical readers. These articles should be written in the following format: title page; abstract and keywords; main body (introduction, materials and methods, results, discussion, conclusion [if any]); references; and tables and figure legends. Manuscript limitations are 5,000 words, excluding the abstract, references, and tables and figure legends.
- **Review articles** provide concise reviews of subjects important to medical researchers, and can be written by an invited medical expert. These have the same format as original articles, but the details may be more flexible depending on the content. Manuscript limitations are 6,500 words from introduction to conclusion, 100 references, 10 figures and 10 tables. The abstract should not exceed 200 words, and must be written as one unstructured paragraph.
- **Guidelines** are similar to original articles, but provide evidence-based recommendations expected to impact

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- **Data Profiles (including Cohort Profiles)** present large data sets from specific populations that could be analyzed in epidemiological studies. Data Profiles should be structured with the following headings in the main text: Introduction, Collection, Data Resource Use, Strengths and Weaknesses, and Access. Cohort Profiles present up-to-date information about large population-based cohorts for which long-term data collection is planned. Data Profiles should be structured with the following headings in the main text: Introduction, Study Participants, Measurements, Key Findings, Strengths and Weaknesses, and Access. The main text of Data and Cohort Profiles is limited to 4,000 words, with an unstructured abstract of up to 200 words, a maximum of 7 tables and figures, and no more than 40 references.
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Title Page

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

Abstract and Keywords

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

www.ncbi.nlm.nih.gov/mesh).

Main Body

- **Introduction** should provide concise yet sufficient background information about the study to provide the readers with a better understanding of the study, avoiding a detailed literature survey or a summary of the results.
- **Materials and methods** should contain detailed procedures of the study or experiment including investigation period, methods of subject selection, and information on subjects such as age, sex or gender, and other significant features, in order to enable the experiment to be repeated. A procedure that has been already published or standardized should be described only briefly using literature citations. Clinical trials or experiments involving laboratory animals or pathogens must elaborate on the animal care and use and experimental protocols, in addition to mentioning approval from the relevant committees. The sources of special equipment and chemicals must be stated with the name and location of the manufacturer (city and country). All statistical procedures used in the study and criteria for determining significance levels must be described. Ensure correct use of the terms "sex" (when reporting biological factors) and "gender" (identity, psychosocial or cultural factors). Unless inappropriate, report the sex and/or gender of study participants, the sex of animals or cells, and describe the methods used to determine sex or gender. If the study involved an exclusive population (only one sex, for example), authors should justify why, except in obvious cases (e.g., prostate cancer). Authors should define how they determined race or ethnicity, and justify its relevance. Institutional Review Board approval and informed consent procedures can be described as follows: The study protocol was approved by the Institutional Review Board of OOO (IRB No: OO-OO-OO). Informed consent was confirmed (or waived) by the IRB.
- **Results** should be presented in logical sequence. Only the most important observations should be emphasized or summarized, and the main or the most important findings should be mentioned first. Tables and figures must be numbered in the order they are cited in the text, kept to a minimum, and should not be repeated. Supplementary materials and other details can be separately presented in an appendix. The authors should state the statistical method used to analyze the results (statistical significance of differences) with the probability values given in parentheses.
- **Discussion** should contain an interpretation and explanation of the results and important aspects of the study, followed by the conclusions drawn from them. Information already mentioned in the Introduction or Results sections should not be repeated and the main conclusions of the study may be presented in the discussion.
- **Conclusion** (if any) must be linked with the purpose of the study stated in the abstract, and clearly supported by the data produced in the study. New hypotheses may be stated when warranted, but must be clearly labeled.

References

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

- References are presented with [ ] following a surname in the main text, such as Kim [1] and Kim et al. [2]. When a reference is cited within the content, it is shown as [3] or [4,5] at the end. References should be searchable online.
- The last names and initials of all the authors (up to 3) should be included. For articles with more than 3 authors, list the first 3 authors only followed by "et al."
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- Use of DOI is highly encouraged. Note that missing data will be highlighted at the proof stage for the author to correct.
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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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When tables and figures are mentioned together in the text, they should be presented in parentheses as follows: (Table 1; Figure 1), (Tables 1, 2; Figures 1–3).

Appendix and Supplemental Data

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

FINAL PREPARATION FOR PUBLICATION

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

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- ▫ All manuscripts should be written in English.
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- ▫ Manuscripts should be double-spaced in A4-size pages.
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- ▫ The title page and the rest of the manuscript text are prepared separately in two files (not combined together).
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Abstract

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

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- ▫ Tables are included at the end of the manuscript as editable text and not as images.
- ▫ Figures are as separate files, in jpg, ppt, tiff, or pdf format.

References

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

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