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RESEARCH

Vaccine effectiveness of COVID-19 and rebound in the real world

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Abstract

We intend to evaluate the relationship between the rates of global SARS-CoV-2 vaccination and the number of COVID-19 confirmed cases, as well as the mortality rate after the declaration of a pandemic. Of the data from 191 countries at the time of data retraction, we selected 111 countries that have SARS-CoV-2 vaccination reports. We stratified countries into high-income and non-high-income countries (HIC and non-HIC) based on World Bank income-group. We used a fixed-effects model (FEM) and performed a longitudinal analysis. The number of confirmed cases decreased as the vaccination rates increased in both non-HICs ($B = -0.027$, $T = -2.0$) and HICs ($B = -0.207$, $T = -17.5$). The number of deaths decreased as the vaccination rates increased in both non-HICs ($B = -0.151$, $T = -2.3$) and HICs ($B = -0.230$, $T = -40.9$). For full vaccination, this measure had a negative association with daily confirmed cases and daily deaths in both non-HICs and HICs. In non-HICs, daily cases and daily deaths decreased as the first vaccination and full vaccination coverages increased. However in HICs, daily cases and daily deaths decreased as the first vaccination and full vaccination coverages increased in the early phase, but after a certain period, they tended to increase again. We observed a significant association between the increase in vaccination coverage in the real world and reduced daily confirmed cases and deaths. However, as the confirmed cases and deaths have rebounded in HICs, our findings indicate that COVID-19 is not completely prevented through vaccine distribution.

Keywords COVID-19 · SARS-CoV-2 · Vaccines · Rebound · Mortality

Introduction

Prior to the development of vaccines against severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), the main response against coronavirus disease 2019 (COVID-19) worldwide relied on non-pharmacological interventions (NPI), such as minimizing personal contact. The main NPIs, including social distancing, lockdown of schools and offices, personal hygiene, and national lockdowns, are reported to be relatively effective in controlling the spread of the virus. [1] The problem with these measures, however, is that there is a significant amount of social, economic, and political costs involved. National and other lockdowns, especially, reduce financial activities and negatively impact economic growth. [2] It was reported that the total gross domestic product (GDP) during the first quarter of 2020 in Hubei, China, decreased by approximately 37% after the COVID-19 outbreak. [3] The International Monetary Fund reported that the world economy also declined by approximately -3% in 2020, [4] and this was more serious than the financial crisis in 2008–09. [5]

Fortunately, the development of vaccines against SARS-CoV-2 began worldwide, and the mass vaccination program was initiated with the first participant in the U.K. in December 2020. [6] The SARS-CoV-2 vaccine was the fastest approved vaccine after the appearance of the disease. [7] With concerns regarding insufficient vaccine quantities, the world has developed vaccination plans and quickly expanded the number of people vaccinated. The priority for most countries has been to prevent the collapse of the healthcare system and protect the elderly and minorities. [8] For example, the U.K. and South Korea categorized medical doctors, nurses, elderly, caregivers, and public health

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and social workers as the high-risk group and progressively expanded vaccination to the public. [8, 9] The vaccination program is effective in preventing the vaccinated public from SARS-CoV-2 infections directly, and it is also effective in reducing the risk of infection from those who are in contact with vaccinated individuals. [10] Vaccinated individuals also shed less viral particles, even after breakthrough infection, are less symptomatic, and have a faster recovery time, thus leading to reduced hospitalization and death. [11, 12]

Therefore, some countries have based their COVID-19 response strategies on the vaccination rate. As an example, Singapore, which had a 65% first-dose vaccination rate, announced the mitigation of the infectious disease prevention and control plan in June 2021 in favor of a return to normal life while living with COVID. [13] Following this, the U.K. announced July 19th, by which the vaccination rate had reached 68%, as the 'freedom day'. [14]· Germany, Denmark, the Netherlands, and South Korea also mitigated their infectious disease and prevention measures to allow the return to pre-COVID-19 life.

However, despite ongoing vaccinations, the COVID-19 burden remained significant. Vaccine distribution rates ranged from 1 to 70%, based on the economic level of the respective country, and the inequality was significant. [15] As a result, SARS-CoV-2 variants continued to emerge, which had caused a rise in the disease burden and delays the return to pre-COVID social and economic conditions. As of December 2021, COVID-19 infection cases due to the Delta variant drastically increased, especially in Europe, and lockdown plans was imposed due to the emergence of the Omicron variant, which had shown greater transmissibility. As a result, more countries mandated vaccinations and enforcing the 'vaccine pass,' which allows border entrance to only those who are vaccinated. [16]

The preventative effects of vaccines against SARS-CoV-2 have been proven in clinical trials, [17] and some countries that started vaccinations early have reported positive effects as the vaccination rates increased. [18, 19] Vaccination is still the best defense against COVID-19 even with the release of antiviral treatment such as Nirmatrelvir with Ritonavir (Paxlovid) and Molnupiravir (Lagevrio) in November and December 2021, respectively[20, 21]. While medications can be used to treat patients who have already contracted the disease, vaccine prevent people from getting infected with the virus in the first place. Moreover, vaccination is critical to reduce the likelihood of the emergence of new variants emerging. However, it remains unclear whether vaccines can completely eradicate the disease. [22] As the vaccines are being distributed worldwide and the vaccination rates increase, the effects are being reported both at an individual level as well as community and population levels. However, it is difficult to confirm whether vaccines are effective against the COVID-19 pandemic considering the individualistic fallacy in certain studies. Additionally, because the local and national statuses of COVID-19, cultures, laws, and regulations differ, even when the effects of vaccination are reported per country, this does not indicate a reduction or slowing down of the COVID-19 pandemic. There are still few studies on whether mass vaccination has a positive effect at the global level.

Thus, it is necessary to scientifically evaluate the effects of vaccine distribution on the COVID-19 pandemic in the real world. The purpose of this study was to evaluate the introduction of COVID-19 vaccines in 111 countries. To do this, we intend to evaluate the relationship between the rates of global SARS-CoV-2 vaccination and the number of COVID-19 confirmed cases, as well as the mortality rate after the declaration of a pandemic.

Materials and methods

Data and study population

For this study, we used data from 'Our World in Data.' This institution provides various statistics from the world, and these data are used for educational purposes as well as academic research. This site provides a COVID-19 Data Repository from Johns Hopkins University as well as various data related to COVID-19 based on the reports collected from each country. These data are considered academically reliable. [23] Of the data from 191 countries at the time of data retraction, we selected 111 countries that have SARS-CoV-2 vaccination reports. The study was conducted from the date COVID-19 was declared a pandemic by the World Health Organization (WHO), March 11, 2020–November 15, 2021. Given the low bivalent booster vaccination coverage at the time [24], only the period before the identification of Omicron (first reported after November 24, 2021) was used as the study period.

Variables

Vaccination

Vaccination rate indicates the proportion of people vaccinated against COVID-19 in a country. To maximize the comparison between countries, we did not differentiate vaccine manufacturers per country. Based on reports that the effectiveness of vaccines differs based on the number of doses, [25] both having received one or more doses and attaining the 'fully vaccinated' status (≥ 2 vaccine shots) were considered.

Incidence and mortality rate of COVID-19

We selected the number of people confirmed with COVID-19 and the mortality rate as the variables that reflected the outcome in evaluating vaccine effectiveness. Confirmed cases and deaths are figures sourced from the official reports of each country, with deaths representing the case fatality rate. Consequently, we utilized daily deaths per 1,000,000 people and daily confirmed cases per 1,000,000 people as the dependent variables.

Control variables

The national response for preventing the spread of infectious diseases such as COVID-19 affects COVID-19 incidence and mortality rates. [26] Therefore, we chose a stringency index as the adjustable variable, and this variable is based on nine measurable items, including school closures, workplace closures, public transport closure, and international travel restrictions, among others. These measures have points that range from 0 to 100, and points closer to 100 indicate stricter government control. [27]

The number of confirmed COVID-19 cases and deaths may change significantly depending on the capacity of each country's COVID-19 testing and data collection methods. [28, 29] Of these, the number of tests can directly affect the number of confirmed cases, and some countries test both suspected individuals and those who were in contact with individuals confirmed to have the disease to prevent the spread of infection. Asymptomatic patients are identified through proactive testing. However, it is thought that developing countries and some countries with a large number of confirmed cases might have a significant number of individuals who are not tested due to limited medical resources. It is known that the rate of testing relates to both the number of confirmed cases and the mortality rate. [30]

Sub-group analysis

The World Bank classifies countries into low, lower-middle, upper-middle, and high-income countries (HIC) according to gross national income (GNI) per capita. In the sub-group analysis, we divided the countries into the HIC and non-HIC groups.

Statistical analysis

All variables are in the form of panel data, and the unit for the time variable is 'day.' Demographic characteristics, such as population density per country, [31] population ≥ 65 years of age, [32] and GDP per capita, [33], can affect COVID-19 outcomes. However, these variables are presented as current status data through descriptive analyses, as they do not change in a short amount of time. Furthermore, because collinearity occurs in study models that are analyzed daily, in the assessment of the relationship between each variable, these items were not included.

To analyze the relationship between major factors, we used a fixed-effects model (FEM) and performed a longitudinal analysis. The FEM is a commonly used method for longitudinal analyses at the national level. This method can control the effects of variables that can affect the relationship between dependent and independent variables, especially factors that do not change over time or factors that the investigator did not observe.

Certain effects of vaccines can have a delayed impact on COVID-19 outcomes, while others may be more immediate. It has been reported that SARS-CoV-2 has a 14 day incubation period. [34] Therefore, to evaluate delayed effects, we used lags of 0 and 14 days as variables.

Lastly, the relationship between each variable and the coefficients for COVID-19 can change with time and vaccination rates. In other words, there is a high likelihood that the linear regression may not be a straight line. Therefore, we created a spline curve using cubic fixed-effect regression and assessed the relationship between daily mortality, daily confirmed cases, and vaccination rates. This graph will aid in understanding the relationship between the dependent and independent variables more intuitively. All variables in all the models, except for the technical analysis, were converted to natural logs and analyzed.

Results

Descriptive analysis by income groups

The average number of daily deaths per million was higher in HICs than in non-HICs (1.32 in non-HIC; 2.08 in HIC), and the daily number of cases per million was approximately 2.5 times higher in HICs (60.24 in Non-HIC; 148.21 in HIC) (Table 1). In the non-HICs, 19.72% of the total population had received the first dose of vaccine, and 14.72% were fully vaccinated. First and second dose vaccination rates of HICs were 38.27% and 30.63%, respectively. The stringency indices for non-HICs and HICs were 57.69 and 57.30, respectively, and these were statistically similar. Lastly, demographic characteristics showed that population density (133.70 in non-HIC; 781.02 in HIC, inhabitants per km^2), older population (5.91% in non-HIC, 14.79% in HIC), and GDP per capita (8154.02 in non-HIC, 41,479.16 in HIC, US dollar) were higher in HICs (Table 1). The incidence rate comparison between the two groups was established over time using time series line plots. Throughout the designated period, the incidence rate was higher in HIC, as was the mortality rate. However, the increasing trend was more

Table 1 Descriptive statistics on the averages of 111 countries

Statistics	Non-HIC (Mean, SD)	HIC (Mean, SD)
Daily deaths per million	1.32(3.69)	2.08(5.07)
Daily cases per million	60.24(160.78)	148.21(258.03)
Vaccination (%)	19.72(20.70)	38.27(26.60)
Full vaccination (%)	14.72(16.81)	30.63(25.55)
Stringency index	57.69(20.96)	57.30(17.24)
Test per thousand	0.723(1.24)	4.79(9.39)
Population density (per km^2)	133.70(204.70)	781.02(2766.94)
65 + population (%)	5.91(3.82)	14.79(6.12)
GDP per capita (US dollar)	8154.02(6280.16)	41,479.16(19,271.54)

Vaccination is the proportion of those who have received more than one dose, and full vaccination is the percentage of those who have received two or more doses. The stringency index ranges from 0 to 100, and the closer to 100, the stronger the government's control

pronounced in the non-HIC group. In terms of vaccination and full vaccination, HIC consistently outperformed non-HIC throughout the period, with the vaccination rate experiencing a more rapid increase (Fig. 1).

Relationship between daily mortality, daily confirmed cases, and vaccine coverage using the fixed-effects model

The relationship between vaccination and daily confirmed cases and daily deaths is presented in Table 2. The number of confirmed cases decreased as the vaccination rates increased in both non-HICs ($B = -0.027$, $T = -2.0$) and HICs ($B = -0.207$, $T = -17.5$). However, in the 14-day lag model, non-HICs ($B = 0.071$, $T = 5.0$) showed a positive association. The number of deaths decreased as the vaccination rates increased in both non-HICs ($B = -0.151$, $T = -2.3$) and HICs ($B = -0.230$, $T = -40.9$).

For full vaccination, this measure had a negative association with daily confirmed cases ($B = -0.144$, $T = -9.8$ in non-HIC; $B = -0.166$, $T = -14.4$ in HIC) and daily deaths ($B = -0.042$, $T = -5.7$ in non-HIC; $B = -0.218$, $- = -40.3$ in HIC) in both non-HICs and HICs. However, in the 14-day lag model, only HIC had a negative

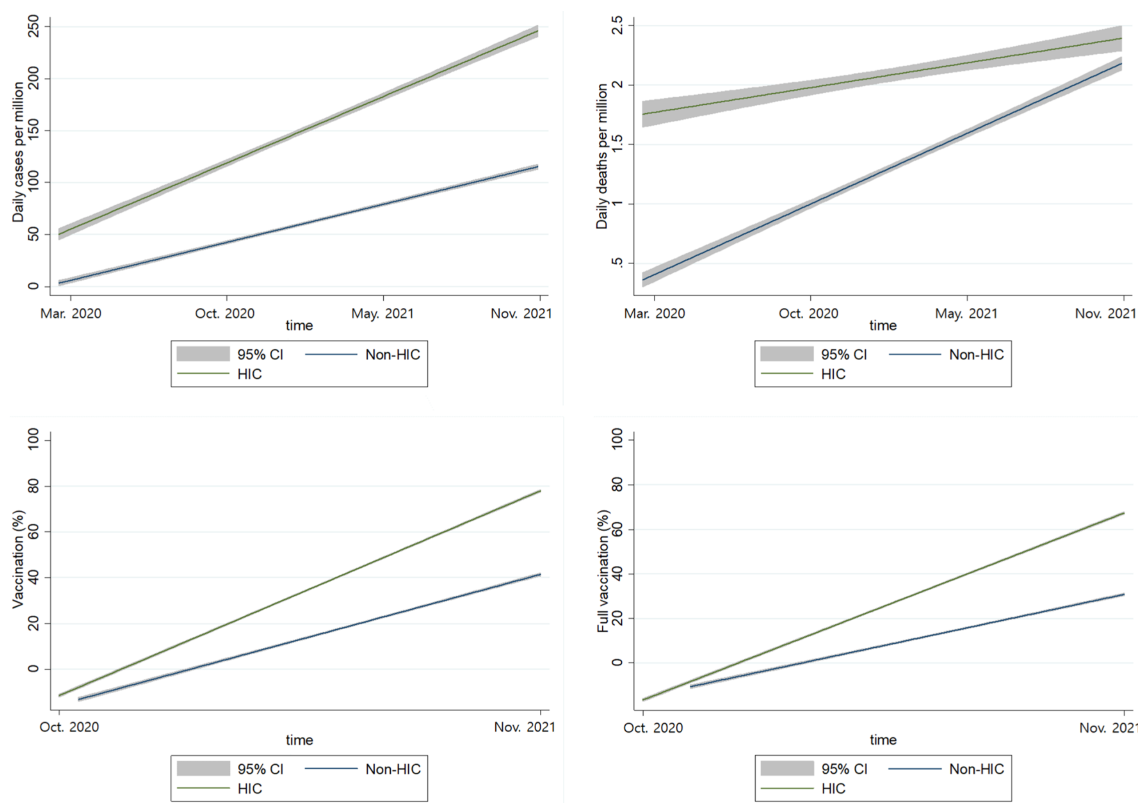

Fig. 1 Daily cases, daily deaths, vaccination coverage and full vaccination coverage of COVID-19 during the study period (March 11, 2020–November 15, 2021)

Table 2 Relationship between daily cases per million, daily deaths per million, and vaccination by a fixed-effects model

	Daily cases per day, B (T) value				Daily deaths per day, B (T) value			
	Non-HIC		HIC		Non-HIC		HIC	
	Non	Lag 14	Non	Lag 14	Non	Lag 14	Non	Lag 14
Cons	− 2.902†	− 3.790†	− .489*	− 2.075†	− 2.976†	− 2.622†	− 2.290†	− 3.090†
	(− 9.5)	(− 11.9)	(− 2.11)	(− 9.1)	(− 19.98)	(− 16.8)	(− 20.9)	(− 27.6)
Vaccination	− .027*	0.071†	− 0.207†	− 0.136†	− 0.151*	− 0.060†	− 0.230†	− 0.205†
	(− 2.0)	(5.0)	(− 17.5)	(− 11.6)	(− 2.3)	(− 8.6)	(− 40.9)	(− 35.9)
R^2	.235	0.190	0.228	0.237	0.231	0.140	0.399	0.401
Observation	6758	6758	10,024	10,025	6755	6755	10,032	10,032
Number of countries	67	67	44	44	67	67	44	44

Stringency index and daily number of tests per thousand were adjusted. Vaccination is the proportion of those who have received more than one dose. All variables were natural log-transformed. * $P<.05$, † $P<.001$

association with daily cases ($B = -0.136$, $T = -12.1$) and daily death ($B = -0.209$, $T = -38.3$), while the associations were not statistically significant in non-HICs (Table 3).

Relationship between daily mortality, daily cases, and vaccine coverage using cubic fixed-effect regression splines

Figure 2 describes the changes in the daily mortality and daily cases according to the changes in the cumulative vaccination coverage through a cubic regression spline. In non-HICs, daily cases and daily deaths decreased as the first vaccination and full vaccination coverages increased. However in HICs, daily cases and daily deaths decreased as the first vaccination and full vaccination coverages increased in the early phase, but after a certain period, they tended to increase again.

Discussion

Vaccination is still the most effective way to prevent COVID-19 and remains critically important in controlling the spread of the disease. While medications are available to treat COVID-19, they are not a substitute for vaccination. Thus, staying up to date with COVID-19 vaccination is highly recommended and demonstrating the effectiveness of COVID-19 vaccines is an important step in persuading people to get vaccinated.

This study shows that there is a significant association between vaccination and decreased numbers of confirmed cases and deaths in both HICs and non-HICs. This finding is in agreement with those of prior studies that evaluated the effectiveness of vaccination in the US and certain European countries. [11, 12, 35, 36] This indicates that the effectiveness of vaccines in clinical studies and within particular populations are globally applicable in the real world.

In previous studies, it had been reported that vaccines reduce COVID-19 severity or death. [37] In this study, we

Table 3 Relationship between daily cases per million, daily deaths per million, and full vaccination by a fixed-effects model

	Daily cases, B (T) value				Daily deaths, B (T) value			
	Non-HIC		HIC		Non-HIC		HIC	
	Non	Lag 14	Non	Lag 14	Non	Lag 14	Non	Lag 14
Cons	− 2.398†	− 3.850†	0.627*	− 1.579†	− 3.040†	− 2.85†	− 1.724†	− 2.409†
	(− 6.9)	(− 10.6)	(2.6)	(− 6.6)	(− 17.5)	(− 15.5)	(− 14.9)	(− 20.7)
Full vaccination	− 0.144†	− 0.015	− 0.166†	− 0.136†	− 0.042†	0.015	− 0.218†	− .0209†
	(− 9.8)	(− 1.0)	(− 14.4)	(− 12.1)	(− 5.7)	(1.9)	(− 40.3)	(− 38.3)
R^2	0.260	0.207	0.228	0.248	0.271	0.162	0.399	0.416
Observation	5747	5747	9400	9401	5744	5744	9408	9408
Number of countries	66	66	44	44	66	66	44	44

Stringency index and daily number of tests per thousand were adjusted. Full vaccination is the percentage of those who have received two or more doses. All variables were natural log-transformed. * $P<.05$, † $P<.001$

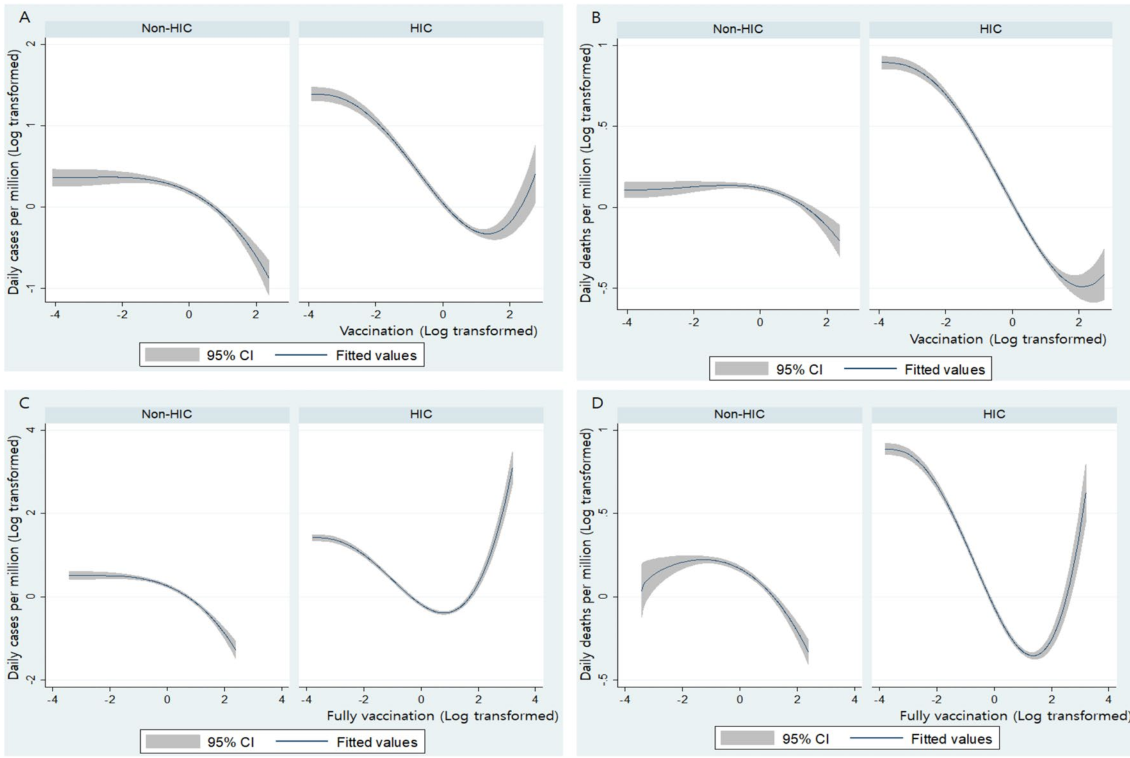

Fig. 2 Relationship between daily mortality, daily cases, and vaccine coverage using cubic fixed-effects regression splines: (**A**) between daily cases and vaccination; (**B**) between daily deaths and vaccination; (**C**) between daily cases and full vaccination; and (**D**) between daily deaths and full vaccination

confirmed that vaccine distribution is effective in reducing COVID-19 incidence and death rate at a national level. Additionally, this study demonstrates that '*B*' and '*T*' values were higher in daily deaths than in daily confirmed cases, which suggests greater effectiveness in reducing the death rates than the incidence rates. The '*B*' value signifies the slope or regression coefficient and fluctuates based on the unit of the variable. '*T*' represents the value derived from dividing '*B*' by the standard error. A substantial 'T' value indicates a small standard error and a high correlation between the independent and dependent variables concurrently. Therefore, in this study, the collective '*T*' value exhibited notably greater in the HIC, implying a more robust relationship between the vaccine, incidence, and mortality within the HIC.

While the association of vaccination with reduced COVID-19 incidence and death was present to a certain point, as vaccination continued to increase in both non-HICs and HICs, we observed increased COVID-19 incidence and death in HICs as the vaccination rate increased. It is difficult to quantitatively conclude the rationale behind this observation in this study. However, it is possible that the effects of vaccination reduce over time, as the national vaccination program started early in HICs than in non-HICs. Reports from the U.K., Israel, and other countries showed limited reduction in vaccination effects over time. [38, 39] This could be due to reduced humoral response over time. Another explanation could be the diminished effects of vaccines due to the variants. Lastly, as the self-quarantine and social distancing strategies have been mitigated as a result of vaccination, a return to the pre-pandemic lifestyle could have an impact on COVID-19 resurgence. [40] In major HICs, including the US, Europe, Israel, and South Korea, it was thought that the risk of COVID-19 severity and death would be minimized as the vaccination rate reached a certain point, and therefore, infectious disease prevention and control measures were mitigated. It is possible that this intervention may have led to an increased number of confirmed cases.

Taken together, vaccination is significantly associated with COVID-19 infection and the risk of death at the global level, and, therefore, a continued vaccination strategy is needed. However, despite the increased vaccination rates in HICs, the number of confirmed cases and deaths has rebounded. This poses many implications to non-HICs and suggests that vaccine distribution does not completely prevent COVID-19 throughout the real world. Even if vaccination rates reach a certain desirable point, infectious disease control and prevention strategies should not be mitigated prematurely.

Similarly, there is a need to consider the fair distribution and delivery of vaccines. According to the data form the WHO, as of March 7th 2023, total number of vaccine doses administered globally was over 11 billion; however, the distribution of vaccines has been uneven. The average vaccination coverage rate in African region as 13.8%, while in the Americas region it was 56.5%, and in the European region it was 62.7% [41]. During the study period, vaccine distribution was also confirmed to be more slowly disseminated in non-HIC than in HIC. This is because HICs can access vaccines preferentially, leading to vaccine monopoly due to their large economic scale and sufficient medical resources. Thus, in HICs, a large-scale vaccination policy can be realistically implemented for the entire population. [42] On the other hand, it is difficult for developing countries to obtain vaccines in large quantities, and the citizens living in areas without medical facilities cannot benefit from vaccinations due to limited medical resources. The Global Alliance for Vaccines and Immunisation (Gavi) and several non-governmental organizations (NGOs) have supported the distribution of COVID-19 vaccination in low-income countries (LICs). Specifically, Gavi, in partnership with the WHO and the Coalition for Epidemic Preparedness Innovations (CEPI), launched the COVAX Facility, which aims to provide equitable access to COVID-19 vaccines for all countries. The COVAX is pooling the purchasing power of participating countries to negotiate vaccine prices and secure vaccine supplies[43]. As of March 2022, COVAX has delivered over 570 million vaccine doses to 146 countries. However, the vaccination distribution alone is not enough to control the COVID-19 pandemic. Encouraging booster shot is also important part of the strategy to combat the virus. The administration of booster shots was initiated in the US and other developed countries. However, in the developing country where COVID-19 vaccination rates are very low, it may difficult to prioritize a booster shot. Therefore, international organizations, including the WHO, should strive to provide efficient vaccine distribution and technical advice, such as methods for infectious disease control and measures for maximizing the effects of vaccination at national and international levels, to prevent the spread of COVID-19.

Strengths and limitations

This is one of the first studies to evaluate the effectiveness of vaccines against SARS-CoV-2 at clinical and individual levels at a national level throughout the world thus far. Additionally, this study assessed 111 countries that have vaccinated the public in a longitudinal analysis. However, there are a few limitations. First, we did not consider the differences in each country's vaccination policy. The effectiveness of vaccines can change depending on the type of vaccines used in the country and vaccination eligibility criteria. The type of vaccines administered can differ, especially between HICs and non-HICs. Second, we did not consider the level of acquired immunity naturally obtained from COVID-19 in each country. Countries that have experienced a mass infection at the early phase of COVID-19 may have a high level of acquired immunity even after the vaccination. Third, we included data until November 15, 2021, and did not reflect an evolved COVID-19 situations after that; the emergence of the Omicron variant, which was first reported after November 24, 2021, and the approval of new antiviral treatment for COVID-19 in November and December 2021. Since the COVID-19 situation has changed rapidly, there is a possibility that it will show a different pattern in the subsequent period. In fact, we briefly conducted additional analyses for subsequent periods (16 November, 2021–31 December, 2022) (see also supplementary tables). Surprisingly, contrary to this study's main findings, which indicates negative association between vaccination rates and the confirmed cases and mortality, the results of supplementary analyses show rather an increase in the confirmed cases and mortality, and deaths. There can be many reasons for this results. One of them could be the policy to the vaccine booster shot, which have recommended from the second half of 2021. When the booster shot is adjusted in the model, in non-HIC, the vaccination rates again show a negative associations with the confirmed cases and mortality. Therefore, to comprehend the enduring impacts of vaccines, further studies that incorporate crucial variables like booster shots and return to normal life policy are needed. Moreover, accounting for altered vaccination policies is essential in gaining a comprehensive understanding of vaccine effects.

Conclusions

In this study, we observed a significant association between the increase in vaccination coverage in the real world and reduced daily confirmed cases and deaths. However, as the confirmed cases and deaths have rebounded in HICs, our findings indicate that COVID-19 is not completely prevented through vaccine distribution. As a result, we propose the following interventional policies. First, vaccination is effective in mitigating the COVID-19 pandemic in the real world globally and in reducing both incidence and death rates, with a greater impact on death rates. Second, developing countries should learn from the COVID-19 rebound effects in HICs. It is very likely that if infectious disease prevention and control measures are mitigated prematurely as the vaccines are increasingly distributed, the number of confirmed cases and deaths will increase.

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Author contributions MBP and BS initiated the idea and led the formal analysis, reviewed and edited the final draft of the article.

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Data availability The data are available from Our World in Data. If you need the processed data, please contact the author to request the data.

Declarations

Competing interests The authors declare no competing interests.

Ethical approval This study was conducted in accordance with the Declaration of Helsinki, and all of the materials used in the article were only publicly available data. Moreover, all of those data are non-identifying data, and anyone can use it.

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