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A global epidemiological analysis of COVID-19 vaccine types and clinical outcomes

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ARTICLE INFO

Article history:
Received 26 June 2022
Revised 30 August 2022
Accepted 9 September 2022

Keywords:
SARS-CoV-2
COVID-19 vaccine
mRNA vaccine
Adenovirus vaccine
Inactivated virus vaccine
Comparative effectiveness

ABSTRACT

Objectives: To compare messenger RNA (mRNA)–based and adenovirus-vectored vaccines (ADVVs) with inactivated virus vaccines (IVVs) using real-world aggregate data.

Methods: We performed longitudinal analyses of publicly accessible epidemiological, clinical, virological, vaccine-related, and other public health data from 41 eligible countries during the first half of 2021. The relationships between vaccination coverage and clinical outcomes were analyzed using repeated measures correlation analyses and mixed-effects modeling to adjust for potential mediating and confounding factors.

Results: Countries that used mRNA and/or ADVV (n = 31) vs IVV, among other vaccine types (n = 10), had different distributions of age (42.4 vs 33.9 years, respectively; P-value = 0.0006), gross domestic product per capita ($38,606 vs $20,422, respectively; P < 0.0001), and population sizes (6,555,541 vs 5,139,162, respectively; P-value = 0.36). After adjustment for country differences, the stringency of non-pharmaceutical interventions, and dominant SARS-CoV-2 variant types, populations that received mRNA and/or ADVV had significantly lower rates of cases and deaths over time (P < 0.001 for each analysis). Populations vaccinated with IVV, among others, had significantly higher rates of cases and deaths over time (P < 0.05 for each analysis).

Conclusion: The real-world effectiveness of IVV may be inferior to mRNA and/or ADVV, and prospective comparative studies are needed to critically evaluate the role of IVV in the context of contemporary SARS-CoV-2 variants.

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Background

SARS-CoV-2 has led to more than 275 million cases of disease and 5 million deaths worldwide. COVID-19 vaccines deployed in many parts of the world since early 2021, albeit unevenly, have been shown to protect vaccinees against disease and mortality (Al Kaabi et al., 2021; Butt et al., 2021; Cheng et al., 2021; Fadlyana et al., 2021; Jara et al., 2021; Li et al., 2021; Rotshild et al., 2021; Sadoff et al., 2021; Tanriover et al., 2021). However, at this time this study was conducted, there was conflicting evidence about the quality and potency of immune protection afforded by COVID-19 messenger RNA (mRNA)-based and adenovirus-vectored vaccines (ADVV) compared with inactivated virus vaccines (IVV) against SARS-CoV-2 pre-Omicron variants (Cheng et al., 2021; Duarte et al., 2021; Earle et al., 2021; Khoury et al., 2021; Lim et al., 2021; Mallapaty, 2021; Melo-González et al., 2021; Pan et al., 2021; Rotshild et al., 2021). The purpose of this study was to compare the clinical impact of different types of COVID-19 vaccines administered in diverse countries, after adjustment for variations in demographics, economics, public health interventions, and circulating viral strains.

https://doi.org/10.1016/j.ijid.2022.05.014
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Protection from vaccines is modulated by various microbial, biomedical, and socioeconomic factors. As the COVID-19 pandemic evolved, SARS-CoV-2 genetic variants emerged, resulting in potentially greater transmissibility and pathogenicity, as well as the propensity of viruses to escape immunity (Krause et al., 2021). Furthermore, differences in population structure and host characteristics, such as older age and high-risk comorbidities, as well as health care access and other socioeconomic determinants of health may also have played a role in influencing the pandemic.

More than 4 billion COVID-19 vaccine doses were administered worldwide during the first half of 2021. However, the types of vaccines and rates of vaccine distribution have varied substantially, and the viral spread and distribution of viral variants have changed over time. A striking contrast in COVID-19 epidemiology in two similarly sized neighboring countries is illustrated by an unexpected eruption of COVID-19 in Bahrain, despite the high rates of vaccination primarily with aluminum hydroxide-adjuvanted IV (BBIBP-CorV, Sinopharm, China), compared with the well-controlled COVID-19 rates in Qatar that relied primarily on the mRNA BNT162b2 vaccine (Pfizer, Inc. and BioNTech) during the first half of 2021 (Alhina and Eldség, 2021). This observation prompted us to question if intrinsic differences in the vaccine types may have contributed to the divergent outcomes.

The spike protein of SARS-CoV-2 is delivered to the host’s immune system by mRNA-based vaccines and IVVs in different ways. The mRNA platform is a genetically engineered vaccine that encodes the expression of spike proteins in a highly immunogenic and stable prefusion conformation. On the other hand, IVV are protein-based vaccines purified from chemically inactivated whole viruses that contain spike proteins in both pre- and postfusion conformations that may impact effectiveness (Heinze and Stiasny, 2021). Antibodies against IVV may wane rapidly (Azak et al., 2021; Sauré et al., 2022), especially in the elderly with immune senescence (Karamese and Tutuncu, 2022), and may have significantly reduced neutralization potency against specific SARS-CoV-2 variants of concern (Chen et al., 2021; de Souza et al., 2021; Fernandez et al., 2022).

Based on these observations and in vitro data, we hypothesized that IVV (BBIBP-CorV and CoronaVac, Sinovac Biotech, China) are associated with less clinical protection than mRNA and/or ADVV. To test our hypothesis, we performed longitudinal analyses of publicly accessible data from 41 eligible countries with the highest vaccination rates, using a multivariable statistical model and adjusting for potential mediating and confounding factors during the first 6 months of 2021.

Methods

Study design

This is a retrospective epidemiological study that analyzed longitudinal data to determine the potential associations between COVID-19 vaccine types and clinical outcomes (disease or death per million population). The study was conducted over a 6-month period from epidemiological week 1 (January 3) to week 25 (June 26) of 2021. Countries with a population size of >500,000 individuals that deployed >50 doses per 100 population of IVV, mRNA, and/or ADVV and had sufficient information about vaccine types and relevant outcomes were eligible for inclusion. Countries were excluded if COVID-19 cases were <5/million population due to successful mitigation measures (China and Hong Kong), or data were insufficient for analysis (Kuwait and Saudi Arabia).

The use of IVV alone or with other vaccine types was classified as the IVV category for that country. Data for countries that administered mRNA and/or ADVV but not IVV were combined for meaningful statistical analysis because there were too few countries that used mRNA vaccines alone (n = 3).

Data sources

Available data for (i) potential predictors and confounders, including vaccine types, percentage vaccination coverage, population size, age distribution, gross domestic product (GDP) per capita, nonpharmaceutical interventions, and dominant circulating SARS-CoV-2 variants, and (ii) outcomes (cases and deaths) were systematically extracted from the COVID-19 Data Explorer - Our World in Data (Mathieu et al., 2020) and other online sources (Supplementary Table 1). Nonpharmaceutical interventions were quantified using the stringency index, a previously published composite measure of nine mitigation actions, rescaled to a value from 0 to 100, where 100 is the strictest response indicator (Hale et al., 2021). If governmental responses varied at the subnational level, the reported index indicated the level of response in the strictest subregion. Nine metrics were used to calculate the stringency index: school closures, workplace closures, cancellation of public events, restrictions on public gatherings, closures of public transport, stay-at-home requirements, public information campaigns, restrictions on internal movements, and international travel controls (Hale et al., 2021).

Statistical methods

Differences in population size, age, and GDP per capita between vaccine types were compared statistically with Mann-Whitney tests. The percentages of individuals who were partially or fully vaccinated, stringency index scores, and the dominant circulating SARS-CoV-2 variants were collated every 4 weeks by country to ensure we captured accurate time-varying data for these potential predictors and confounders over a 6-month period. The frequencies of COVID-19 cases and deaths in each country were also aggregated every 4 weeks by calculating the average daily counts per million population over the previous 4 weeks. In this manner, we sought to analyze the associations between predictors and outcomes during cycles of surges and declines in COVID-19 incidence while taking potential confounding and secular trends into account.

To measure the strength of correlations between vaccination rates and clinical outcomes stratified by vaccine type (mRNA/ADV or IVV), we applied a technique designed specifically for repeated measures correlation analysis (rmcorr) using R 4.1.0 (R Foundation for Statistical Computing). This statistical method uses a concordance correlation coefficient to determine the common within-country associations for paired measures of continuous data assessed on two or more occasions for multiple countries. Rmcorr estimates the common regression slope, which reflects the association shared among individual countries, without violating independence assumptions (Bakdash and Marusich, 2017; King et al., 2007).

We then performed mixed-effects modeling using SAS 9.4 (SAS Institute, Cary, NC) to examine the effect modification of vaccine types on the relationship between percentage immunization coverage and frequencies of cases or deaths with or without adjustment for country-specific population size, median age, GDP per capita, stringency index, and the dominant circulating SARS-CoV-2 variants.

The frequencies of COVID-19 cases and deaths were log-transformed for statistical analysis. For the analyses that showed significant effect modification, we carried out separate analyses for...
mRNA and/or ADVV versus IVV. A two-sided $P < 0.05$ was considered statistically significant.

**Ethics statement**

The data included in this study are in the public domain obtained from Our World in Data under a CC-BY license (Hale et al., 2021; Mathieu et al., 2020) and other publicly available resources. No protected health information was used.

**Role of the funding source**

The funders of the study had no role in study design; data collection, analysis, or interpretation; writing of the report; or the decision to submit for publication.

**Results**

A total of 41 geographically dispersed countries met the inclusion criteria for the study. The countries that used mRNA and/or ADVV (n = 31) versus IVV, among other vaccine types (n = 10), had different distributions of median ages (42.4 vs 33.9 years, respectively; $P$-value = 0.0006) and GDP per capita ($\$ 38,606 vs $\$ 20,422, respectively; $P < 0.0001$). The population sizes were not statistically different (8,655,541 vs 5,139,162, respectively; $P$-value = 0.36). IVV constituted $\geq 50\%$ of all vaccines used in 8 of 10 countries (range 21 to $\sim\%95$; Table 1 and Supplementary Table 1).

Figure 1 shows the country-level repeated measurement correlations between the percentages of partially (Figure 1a and 1b) or fully (Figure 1c and 1d) vaccinated populations and outcomes (COVID-19 cases in Figure 1a and 1c and deaths in Figure 1b and 1d), stratified by vaccine type (mRNA/ADV vs IVV), without adjustment for potential confounding. During the 6-month time frame of the study, countries with increasing use of mRNA and/or ADVV had significantly lower frequencies of COVID-19 cases ($r = -0.58$, $P < 0.001$ for partial vaccination; $r = -0.68$, $P < 0.001$ for complete vaccination) as well as lower frequencies of COVID-19-related deaths ($r = -0.74$, $P < 0.001$ for partial vaccination; $r = -0.78$, $P < 0.001$ for complete vaccination). On the other hand,

**Table 1**

| Countries included in the study and vaccine utilization. |
|----------------------------------------------------------|
| **Country** | mRNA-based vaccines | Adenovirus-vectored vaccines | Inactivated virus vaccines |
|-------------|---------------------|-------------------------------|---------------------------|
| Austria     |ustria               |                               |                           |
| Bahrain     |                                |                               |                           |
| Belgium     |                                |                               |                           |
| Bhutan      |                                |                               |                           |
| Canada      |                                |                               |                           |
| Chile       |                                |                               |                           |
| Croatia     |                                |                               |                           |
| Cyprus      |                                |                               |                           |
| Czechia     |                                |                               |                           |
| Denmark     |                                |                               |                           |
| Dominican Republic |                   |                               |                           |
| Estonia     |                                |                               |                           |
| Finland     |                                |                               |                           |
| France      |                                |                               |                           |
| Germany     |                                |                               |                           |
| Greece      |                                |                               |                           |
| Hungary     |                                |                               |                           |
| Ireland     |                                |                               |                           |
| Israel      |                                |                               |                           |
| Italy       |                                |                               |                           |
| Latvia      |                                |                               |                           |
| Lithuania   |                                |                               |                           |
| Madagascar |                                |                               |                           |
| Maldives    |                                |                               |                           |
| Mauritania  |                                |                               |                           |
| Mongolia    |                                |                               |                           |
| Netherlands |                                |                               |                           |
| Norway      |                                |                               |                           |
| Poland      |                                |                               |                           |
| Portugal    |                                |                               |                           |
| Qatar       |                                |                               |                           |
| Serbia      |                                |                               |                           |
| Singapore   |                                |                               |                           |
| Slovakia    |                                |                               |                           |
| Slovenia    |                                |                               |                           |
| Spain       |                                |                               |                           |
| Sweden      |                                |                               |                           |
| Switzerland |                                |                               |                           |
| Turkey      |                                |                               |                           |
| United Kingdom |                       |                               |                           |
| Uruguay     |                                |                               |                           |
| USA         |                                |                               |                           |

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\*McGill Covid-19 Vaccine Tracker Team, June 26, 2021; country-specific approved vaccines: [https://covid19.trackvaccines.org/trials-vaccines-by-country/#approvals](https://covid19.trackvaccines.org/trials-vaccines-by-country/#approvals)

\*Wall Street Journal, June 2, 2021; [https://www.wsj.com/articles/bahrain-facing-a-covid-surge-starts-giving pfizer boosters to recipients-of-chinese-vaccine-11622648737](https://www.wsj.com/articles/bahrain-facing-a-covid-surge-starts-giving pfizer boosters to recipients-of-chinese-vaccine-11622648737)

\*Our World in Data, June 26, 2021; [https://ourworldindata.org/covid-vaccinations](https://ourworldindata.org/covid-vaccinations)

\*Dominican Today, May 16, 2021; [https://domicantoday.com/dr/local/2021/05/16/more-than-95-of-the-vaccines-contracted-by-the-country-come-from-the-chinese-company-sinovac/](https://domicantoday.com/dr/local/2021/05/16/more-than-95-of-the-vaccines-contracted-by-the-country-come-from-the-chinese-company-sinovac/)

\*The Times of India, June 2, 2021; [https://timesofindia.indiatimes.com/india/sii-unable-to-supply-covishield-vaccine-maldives-looks-elsewhere/articleshow/83132944.cms](https://timesofindia.indiatimes.com/india/sii-unable-to-supply-covishield-vaccine-maldives-looks-elsewhere/articleshow/83132944.cms)

\*LeMatinal, July 5, 2021; [https://english.lematinal.media/mauritius-receives-500000-doses-of-sinopharm-vaccine/](https://english.lematinal.media/mauritius-receives-500000-doses-of-sinopharm-vaccine/) also used Covaxin (Bharat Biotech; inactivated whole virus Vaccine)

\*CNBC, May 1, 2021; [https://www.cnbc.com/2021/07/08/five-vaccinated-countries-with-high-covid-rates-rely-on-china-vaccines.html](https://www.cnbc.com/2021/07/08/five-vaccinated-countries-with-high-covid-rates-rely-on-china-vaccines.html)

\*Republic of Serbia, May 27, 2021; [https://www.srbija.gov.rs/vest/en/173298/42-million-sinopharm-vaccines-delivered-to-serbia-to-date.php](https://www.srbija.gov.rs/vest/en/173298/42-million-sinopharm-vaccines-delivered-to-serbia-to-date.php)

\*NikkeiAsia, April 13, 2021; [https://asia.nikkei.com/Spotlight/Coronavirus/COVID-vaccines/Turkey-says-China-s-Sinovac-vaccine-is-significantly-effective](https://asia.nikkei.com/Spotlight/Coronavirus/COVID-vaccines/Turkey-says-China-s-Sinovac-vaccine-is-significantly-effective)
countries with increasing use of IVV, among others, experienced significantly higher frequencies of COVID-19 deaths \( (r = 0.37, P\text{-value} = 0.019) \) and a trend in increased frequency of cases \( (r = 0.27, P\text{-value} = 0.094) \). The rates of cases and deaths among populations who were fully vaccinated with IVV, among others, did not change significantly \( (r = -0.05; P\text{-value} = 0.800 \text{ and } r = 0.23; P\text{-value} = 0.194, \text{respectively}) \).

In the stratified analyses of mixed-effects models, there was a significant effect modification by the type of vaccine for the respective relationships between rates of vaccination (partial or complete, in separate models) and frequencies of cases and deaths, with or without adjustment for country-specific population size, median age, and GDP per capita, as well as the time-varying confounders: stringency index, and dominant circulating SARS-CoV-
Discussion

The findings from our longitudinal analyses of publicly available demographic, epidemiological, and vaccination data from 41 countries with the highest COVID-19 immunization rates indicated that populations that received IVV (BBIBP-CorV or CoronaVac) among other vaccine types, experienced significantly higher rates of COVID-19 cases and deaths during the first 6 months of 2021 than those who received mRNA and/or ADVV. These observations persisted after adjustment for country-specific population size, age structure, and GDP distributions, as well as time-varying nonpharmaceutical interventions measured with the stringency index and the dominant circulating SARS-CoV-2 variants. These large-scale epidemiological observations from geographically diverse countries place the existing data from clinical trials and ex vivo functional assays into a real-world context, which suggest that IVV does not confer as robust and durable clinical protection against SARS-CoV-2 as genetic vaccines, particularly mRNA-based COVID-19 vaccines (Chen et al., 2021; Cheng et al., 2021; de Souza et al., 2021; Earle et al., 2021; Fernandez et al., 2022; Rotshild et al., 2021).

Effective COVID-19 vaccine-induced immunity is primarily mediated by antigen-specific neutralizing antibodies (Krause et al., 2021). It is also possible that other vaccine-induced effector functions, such as antibody-dependent cellular phagocytosis or cytotoxicity and complement-dependent cytotoxicity, play a role in clinical immunity. On the other hand, previous observations of antibody-dependent enhancement of respiratory syncytial virus infections that complicated a formalin-inactivated respiratory syncytial virus vaccine (Delgado et al., 2009) raise similar concerns about COVID-19 IVV that could potentially explain higher rates of infection after vaccination in some individuals. The specific mechanisms leading to poorer effectiveness of IVV are not known but could be related to suboptimal functional antibody responses (Earle et al., 2021; Khoury et al., 2021; Lim et al., 2021), differences in cellular effector responses, differences in presentation of antigen conformation, or lower efficacy against certain SARS-CoV-2 variants that may have escaped vaccine immunity (Krause et al., 2021).

The limitations of this report include the fact that data for circulating genetic variants were either partially missing in eight (19.5%) countries or entirely missing in one (2.5%) country (Mauritius) during the study period. However, we included all eligible countries in an attempt to minimize selection bias. Owing to the ecological design of the study, we were not able to evaluate patient-level data for high-risk comorbidities, associations between types of vaccines or timing of vaccination and individual clinical outcomes, use of antiviral and immunomodulatory agents, or other potential confounders, such as rates of COVID-19 testing or within-country region-specific stringency measures. We attempted to address some of these limitations by adjusting our statistical models for country-specific population size, age, and GDP distributions, time-varying nonpharmaceutical interventions using the stringency index, and variations in circulation of dominant SARS-CoV-2 variants, assuming that these factors may partly account for certain biomedical variations and socioeconomic disparities. To address these limitations adequately in future, randomized trials or causal inference models will be needed.

In conclusion, we demonstrated significantly poorer clinical outcomes in countries that used COVID-19 IVV, among other vaccines, than those that used mRNA and/or ADVV but not IVV during the first 6 months of 2021 when the Alpha, Gamma, and Delta variants, among others (except Omicron), were circulating. Therefore, future prospective trials are urgently needed to directly compare and critically appraise the real-world effectiveness of IVV adjuvanted with alum or other immunostimulants versus other vaccine technologies to guide public health policies, particularly as new SARS-CoV-2 variants are emerging. Internationally coordinated public health interventions are essential to ensure that the most effective COVID-19 vaccines are disseminated equitably and expeditiously to all eligible individuals worldwide (United Nations Development Program, 2021).

Funding

This work was supported by the National Institutes of Health/Institute of Allergy and Infectious Diseases at the National Institutes of Health to ICM (grant number R25AI140490 to ICM).

Author contributions

All authors were responsible for aspects of study design, data collection, data analysis, and manuscript writing. ZA and ICM conceived the study and designed the analysis plan with SP and YJC. ZA and ICM collected the data, which were verified by SP and YJC. SP performed the data analysis. ZA, YJC, and ICM conducted the literature review. All authors contributed to and reviewed the final submitted manuscript. All authors had full access to all the data in the study and accept responsibility for the decision to submit for publication.

Declaration of competing interest

The authors have no competing interests to declare.

Acknowledgments

None.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.ijid.2022.09.014.

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