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A Regional-Scale Assessment-Based SARS-CoV-2 Variants Control Modeling with Implications for Infection Risk Characterization

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Background: The emergence and progression of highly divergent SARS-CoV-2 variants have posed increased risks to global public health, triggering the significant impacts on countermeasures since 2020. However, in addition to vaccination, the effectiveness of non-pharmaceutical interventions, such as social distancing, masking, or hand washing, on different variants of concern (VOC) remains largely unknown.

Objective: This study provides a mechanistic approach by implementing a control measure model and a risk assessment framework to quantify the impacts of control measure combinations on the transmissions of five VOC (Alpha, Beta, Delta, Gamma, and Omicron), along with a different perspective of risk assessment application.

Materials and Methods: We applied uncontrollable ratios as an indicator by adopting basic reproduction number (R_0) data collected from a regional-scale survey. A risk assessment strategy was established by constructing VOC-specific dose-response profiles to implicate practical uses in risk characterization when exposure data are available.

Results: We found that social distancing alone was ineffective without vaccination in almost all countries and VOC when the median R_0 was greater than two. Our results indicated that Omicron could not be contained, even when all control measure combinations were applied, due to its low threshold of infectivity (~3×10^{-4} plague-forming unit (PFU) mL^{-1}).

Conclusion: To facilitate better decision-making in future interventions, we provide a comprehensive evaluation of how combined control measures impact on different countries and various VOC. Our findings indicate the potential application of threshold estimates of infectivity in the context of risk communication and policymaking for controlling future emerging SARS-CoV-2 variant infections.

Keywords: SARS-CoV-2, variants of concern, basic reproduction number, modeling, non-pharmaceutical interventions, infection risk

Introduction

Coronavirus disease 2019 (COVID-19) pandemic, the most severe crisis faced by human society in this decade, has caused significant loss of life and a widespread impact on social stability and economic development worldwide. With limited medications available and approved by the United States Food and Drug Administration (FDA), preventive measures are the current strategy that could best limit the spread of the virus. Three principles have been suggested for the comprehensive application of multiple prevention and control measures: controlling infection sources, cutting off infection routes, and protecting susceptible groups.[1,2]

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As no single approach is 100% effective in preventing COVID-19, prevention measures were found to work best when layering with vaccination and non-pharmacologic interventions (NPIs). In addition to ventilation, filtration, or disinfection applications that could attenuate SARS-CoV-2 concentrations, both physical distancing and community masking help reduce the likelihood of encountering or inhaling direct transfer of virus-containing respiratory droplets.[3] Other mitigation strategies, such as hand washing, could be effective in preventing direct transfer of respiratory droplets (eg, coughing, sneezing, saliva, handling mucous membranes from mouth, nose, and eyes) or indirect transfer through contaminated surfaces.[4,5]

In the absence of vaccines, four major strategies could be applied to control COVID-19: (i) identification of new cases and isolations; (ii) contact tracking and quarantining; (iii) personal protection; and (iv) travel restrictions.[6] Moreover, it is essential to understand the effectiveness of different control measures, especially for NPIs. Haug et al[7] used a multi-method approach to rank the effectiveness of worldwide COVID-19 government interventions, indicating that curfews, lockdowns, and closing or restrictions on gatherings are the most effective NPIs. However, the effectiveness of combining NPIs with vaccination, particularly in the context of different SARS-CoV-2 variants, remains underexplored. This gap is critical for optimizing public health responses as new variants emerge.

In this study, we aimed to address this gap by applying a mechanistic research framework that integrates the control measure effectiveness approach with risk assessment to provide insights into decisions for choosing different combined control measures and a better understanding of infectivity risk when effect data are available. Thus, we selected vaccinations with three different NPIs (social distancing, masking, and hand washing) to investigate the effectiveness of six combinations of control measures in different countries and SARS-CoV-2 variants. In addition, a risk assessment approach was performed to compare the dose-response relationships and infectivity thresholds among five variants of concern (VOC), namely, Alpha, Beta, Gamma, Delta, and Omicron. Therefore, the objectives of this study were threefold: (i) to evaluate the trend of SARS-CoV-2 pandemics on a regional scale and compare the effectiveness of control measure combinations in different countries; (ii) to assess how different combinations of control measure could be effectively implemented to mitigate the spread of various VOC; and (iii) to quantitatively evaluate infectivity thresholds among VOC for potential applications in assessing SARS-CoV-2 infection risk.

Materials and Methods

Study Data and Framework

To investigate the effectiveness of the control measures and conduct a risk assessment for SARS-CoV-2 transmission, we collected and collated country- and VOC-specific basic reproduction number (R_0) data from available studies based on a regional-scale survey (Tables S1 and S2). Four types of control measures (vaccination, social distancing, masking, and hand washing) were applied to assess the combined control effectiveness across different countries and five VOC (Figure 1A).

For risk assessment, dose–response relationships between the SARS-CoV-2 dose and cycle threshold (C_t) values of the five VOC were constructed based on data from previous studies (Figure 1B and Table S2).[8–10] Subsequently, thresholds of SARS-CoV-2 transmission were derived based on the cumulative distribution function (CDF) curves generated from *ED*10 from dose-response relationships (Figure 1C). For risk characterization, the transmission risks of SARS-CoV-2 could then be characterized with exceedance risk (ER) by applying the exposure data of viral transmission dosages and thresholds of the five VOC derived in this study (Figure 1D).

Key Epidemiological Parameter Estimation

The proportion of asymptomatic infections (θ) was used to describe the proportion of transmission that occurred prior to symptom onset. By definition, θ can be calculated as

$$\theta = \frac{\text{Incubation period} - \text{Latent period}}{\text{Mean duration of viral shedding}}, \quad (1)$$

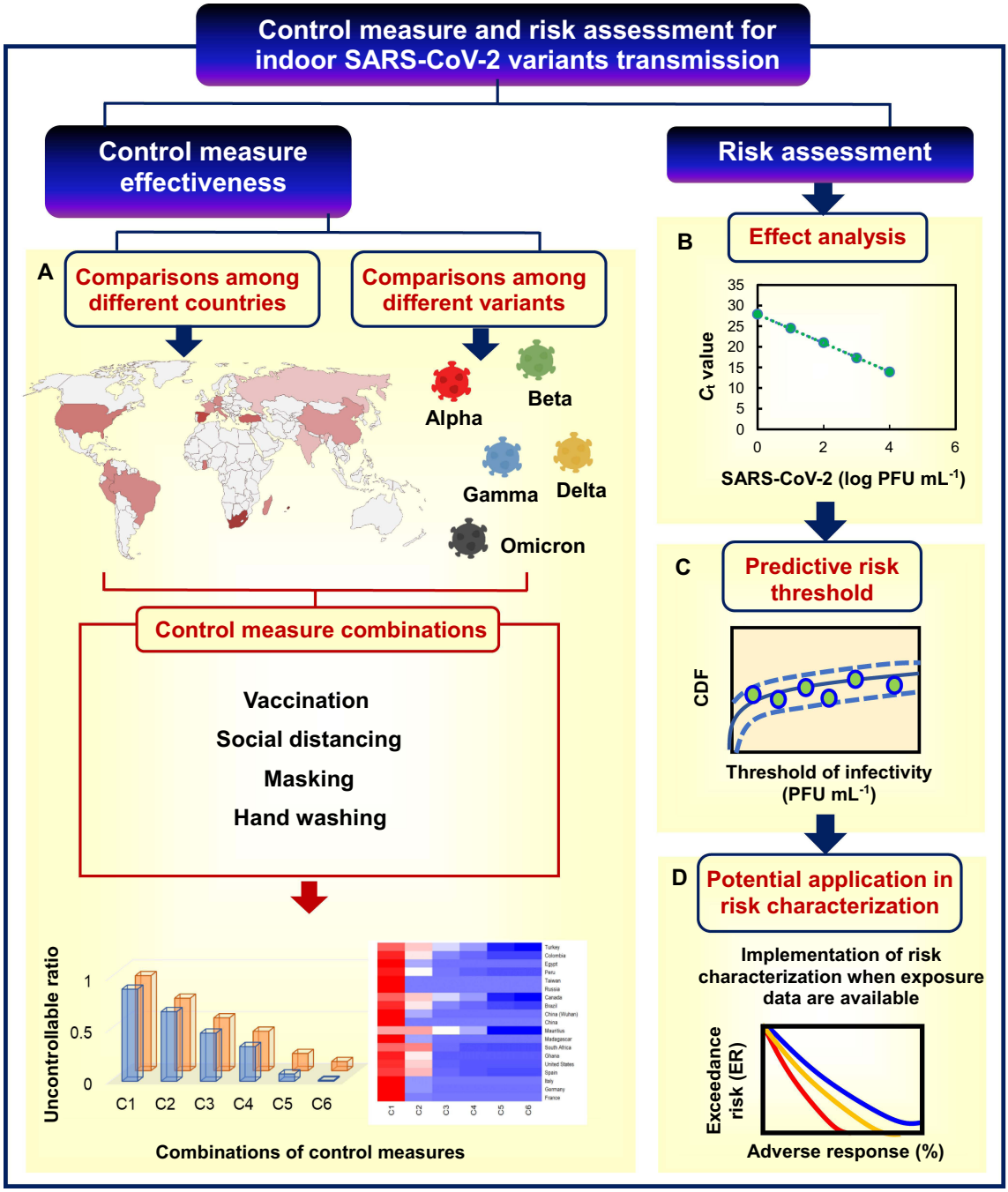

Figure 1 Overall research framework illustrating control measure and risk assessment for COVID-19 transmission: (**A**) Comparisons of control measure effectiveness among different countries and variants. Risk assessment approach of (**B**) effect analysis of relationship between SARS-CoV-2 dose and C_t values, (**C**) predictive risk threshold of infectivity, and (**D**) potential application in risk characterization for five VOC.

Abbreviations: COVID-19, coronavirus disease 2019; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; C_t, cycle threshold; VOC, variants of concern.

where the incubation period is the interval from the point of infection to the appearance of symptoms.[11] Latent period is the interval from infection to the beginning of infectious state.[11] Mean duration of viral shedding is the infectious period of upper and lower respiratory tracts.[12]

To evaluate the effectiveness of the combined control measures, we constructed an efficacy-based control measure model by adopting a two-efficacy-based mathematical model.[12] The critical control curves were constructed with two critical epidemiological determinants R_0 and θ as well as different control efficacies (ε_j), as follows:

$$R_0\left\{\left[\prod_{j=1}^{N}(1-\varepsilon_j)\right]\sum_{p=0}^{N}\left\{\frac{\theta}{p-(p-1)^{\theta}}\sum_{\sum L_j=p, L_j\in\{0,1\}}\left[\left(\frac{\varepsilon_1}{1-\varepsilon_1}\right)^{L_1}\times\left(\frac{\varepsilon_2}{1-\varepsilon_2}\right)^{L_2}\cdots\left(\frac{\varepsilon_N}{1-\varepsilon_N}\right)^{L_N}\right]\right\}\right\}=1, \quad (2)$$

where ε_j is defined as the control effectiveness of control measure j. The curve below represents the optimal control that is eventually achieved. The uncontrollable ratio (UR) can be calculated as the ratio of the area above the control curve to the total area obtained based on the confidence intervals of R_0 and θ.[13]

We developed a control measure model by applying multiple efficacy control measures.[14] In the present study, we employed a four-efficacy based equation,

$$R_0\left\{\begin{array}{l}(1-\varepsilon_1)(1-\varepsilon_2)(1-\varepsilon_3)(1-\varepsilon_4)+[\varepsilon_1(1-\varepsilon_2)(1-\varepsilon_3)](1-\varepsilon_4)\\+\varepsilon_2(1-\varepsilon_1)(1-\varepsilon_3)(1-\varepsilon_4)+\varepsilon_3(1-\varepsilon_1)(1-\varepsilon_2)(1-\varepsilon_4)+\varepsilon_4(1-\varepsilon_1)(1-\varepsilon_2)(1-\varepsilon_3)]\theta\\+\left[\begin{array}{l}\varepsilon_1\varepsilon_2(1-\varepsilon_3)(1-\varepsilon_4)+\varepsilon_1\varepsilon_3(1-\varepsilon_2)(1-\varepsilon_4)+\varepsilon_1\varepsilon_4(1-\varepsilon_2)(1-\varepsilon_3)\\+\varepsilon_2\varepsilon_3(1-\varepsilon_1)(1-\varepsilon_4)+\varepsilon_2\varepsilon_4(1-\varepsilon_1)(1-\varepsilon_3)+\varepsilon_3\varepsilon_4(1-\varepsilon_1)(1-\varepsilon_2)\end{array}\right]\left(\frac{\theta}{2-\theta}\right)\\+[\varepsilon_1\varepsilon_2\varepsilon_3(1-\varepsilon_4)+\varepsilon_1\varepsilon_2\varepsilon_4(1-\varepsilon_3)+\varepsilon_1\varepsilon_3\varepsilon_4(1-\varepsilon_2)+\varepsilon_2\varepsilon_3\varepsilon_4(1-\varepsilon_1)]\left(\frac{\theta}{3-2\theta}\right)+\varepsilon_1\varepsilon_2\varepsilon_3\varepsilon_4\left(\frac{\theta}{4-3\theta}\right)\end{array}\right\}=1, \quad (3)$$

where ε_1, ε_2, ε_3, and ε_4 represent vaccination, social distancing, masking, and handwashing, respectively. Two approaches were used to analyze the URs, which were based on the R_0 values from different countries, and the other based on values of the five VOC.

Dose-Response Model

As an effect analysis in the risk assessment framework, we constructed dose-response relationships for SARS-CoV-2 dose versus decremental proportion of C_t values compared to 0.1 plaque-forming unit (PFU) mL^{-1} by fitting the three-parameter Hill model[15] to datasets of five VOC from the published literature,[16] (Table S3). The dose-response profile of the SARS-CoV-2 dose-decremental proportion of Ct value relationships can be described as follows:

$$E(D)=\frac{E_{max}}{1+\left(\frac{ED50}{D}\right)^{n}}, \quad (4)$$

where D is the SARS-CoV-2 dose (PFU mL^{-1}), E_{max} is the maximum decremental proportion of C_t values compared to 0.1 PFU mL^{-1}, $ED50$ is the dose causing an effect equal to 50% E_{max} (PFU mL^{-1}), $ED10$ is the dose causing an effect equal to 10% E_{max} (PFU mL^{-1}), and n is the fitted Hill coefficient.

Predictive Risk Threshold

As the next step to derive thresholds of SARS-CoV-2 doses, a three-parameter Weibull threshold model was used to derive threshold of infectivity based on the 2.5-, 5-, 50-, 95-, and 97.5-percentiles of $ED10$ CDFs. The CDFs were probabilistically estimated by using the Hill-based dose-response model (Eq. (4)) based on experimental datasets.[17] The Weibull threshold model has the following form:

$$F(D)=1-exp\left[-\left(\frac{D-\gamma}{\alpha}\right)^{\beta}\right], D>\gamma>0, \alpha>0, \beta>0, \quad (5)$$

where $F(D)$ is the $ED10$ CDF data corresponding to a specific SARS-CoV-2 dose, α is the scale parameter influencing the distribution of $F(D)$ as a change in the abscissa scale, β is the shape parameter representing the slope of the line in the CDF data, and γ is the fitted threshold dose of SARS-CoV-2 (PFU mL^{-1}).

Uncertainty and Data Analysis

Mathematical model fitting was conducted using TableCurve 2D (version 5.01, AISN Software, Mapleton, OR, USA). Uncertainty analyses for estimating the incubation period, latent period, mean duration of viral shedding, and θ were implemented with 100,000 Monte Carlo (MC) simulations to obtain geometric means (gms) and geometric standard deviations (gsds) in lognormal (LN) functions (LN (gm, gsd)) using the Crystal Ball software (Version 11.1.2.4, Oracle

Corporation, Redwood Shores, CA, USA). Data visualizations, such as heatmaps, were generated using R language (version 4.1.3, The R Foundation for Statistical Computing) and Power BI.

Results

Epidemiological Parameter Estimates

The θs of the upper and lower respiratory tracts were estimated based on the epidemiological data of the incubation, latent, and infectious periods (ie, the mean duration of viral shedding), followed by Eq. (1) (Table S4). The results showed that the mean incubation and latent periods were 6.9 and 5.5 days, respectively. The mean durations of viral shedding in the upper and lower respiratory tracts were 17 and 14 days, respectively. Thus, the estimated θs values 0.08 (gm) and 0.09 in the upper and lower respiratory tracts, respectively (Table S4).

Control Measure Model

Critical control curves based on six combinations of control efficacies (ε_j), with or without vaccination, were constructed based on country- and VOC-specific R_0 (Tables S1 and S2) and θ (upper respiratory tract: 0.04–0.13; lower respiratory tract: 0.04–0.18) (Table S4) estimates (Figure 2). To achieve optimal containment of SARS-CoV-2 transmission, combinations of pandemic vaccination (ε_1=83%) with NPIs including social distancing (ε_2=72%), surgical mask (ε_3 =61%), and hand washing (ε_4=40%) were implemented. The control measure model adopted six combinations: C1 (ε_2), C2 ($\varepsilon_2+\varepsilon_3$), C3 ($\varepsilon_2+\varepsilon_3+\varepsilon_4$), C4 ($\varepsilon_1+\varepsilon_2$), C5 ($\varepsilon_1+\varepsilon_2+\varepsilon_3$), and C6 ($\varepsilon_1+\varepsilon_2+\varepsilon_3+\varepsilon_4$) (Table S5). The URs of the six combinations of control measures were calculated for different countries and five VOC based on the constructed control measure model.

Country-Specific Control Measure Effectiveness

Country-specific URs based on the available R_0s, when implemented with combinations of control measure efficacies, were investigated (Figure 3 and Table S1). When control measure C1 was implemented, only pandemics in India (median R_0: 1.64 (95% confidence interval (CI): 1.20−2.21)) (Figure 3A) and Australia (R_0: 2.07 (1.79–2.37)) were fully contained (Figure 3B). If C2 is implemented, countries including China (Wuhan) (R_0: 4.47 (3.10−6.44), India (R_0: 1.64 (1.20−2.21)), Russia (R_0: 2.17 (1.32−3.41)), Australia (R_0: 2.07 (1.79−2.37)), and Canada (R_0: 2.74 (2.51–2.98)) can

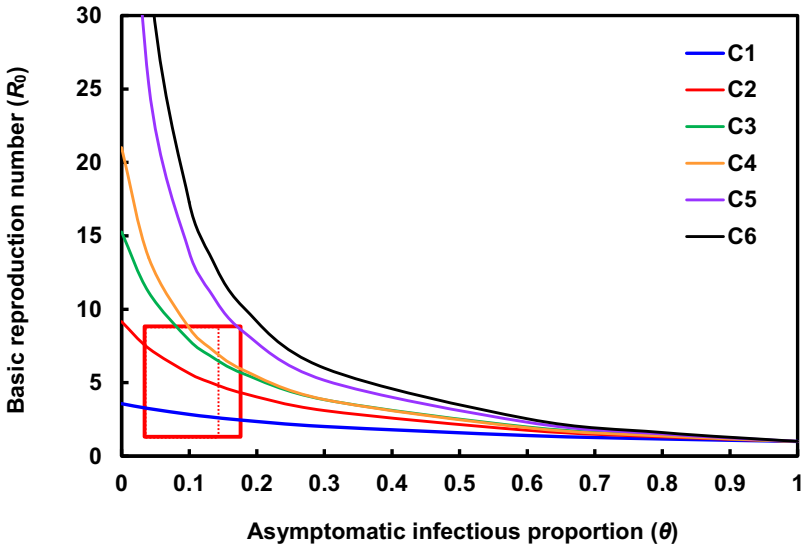

Figure 2 R_0–θ control curves constructed based on combinations of control measures (C1 – C6), together with the rectangle indicated the impacts of control measures. Upper respiratory tract: θ = 0.04–0.13 (dash line) and lower respiratory tract: θ = 0.04–0.18 (solid line).

Abbreviations: R_0, basic reproduction number; θ, asymptomatic infectious proportion; C1, social distancing; C2, social distancing + masking; C3, social distancing + masking + hand washing; C4, vaccination + social distancing; C5, vaccination + social distancing + masking; C6, vaccination + social distancing + masking + hand washing.

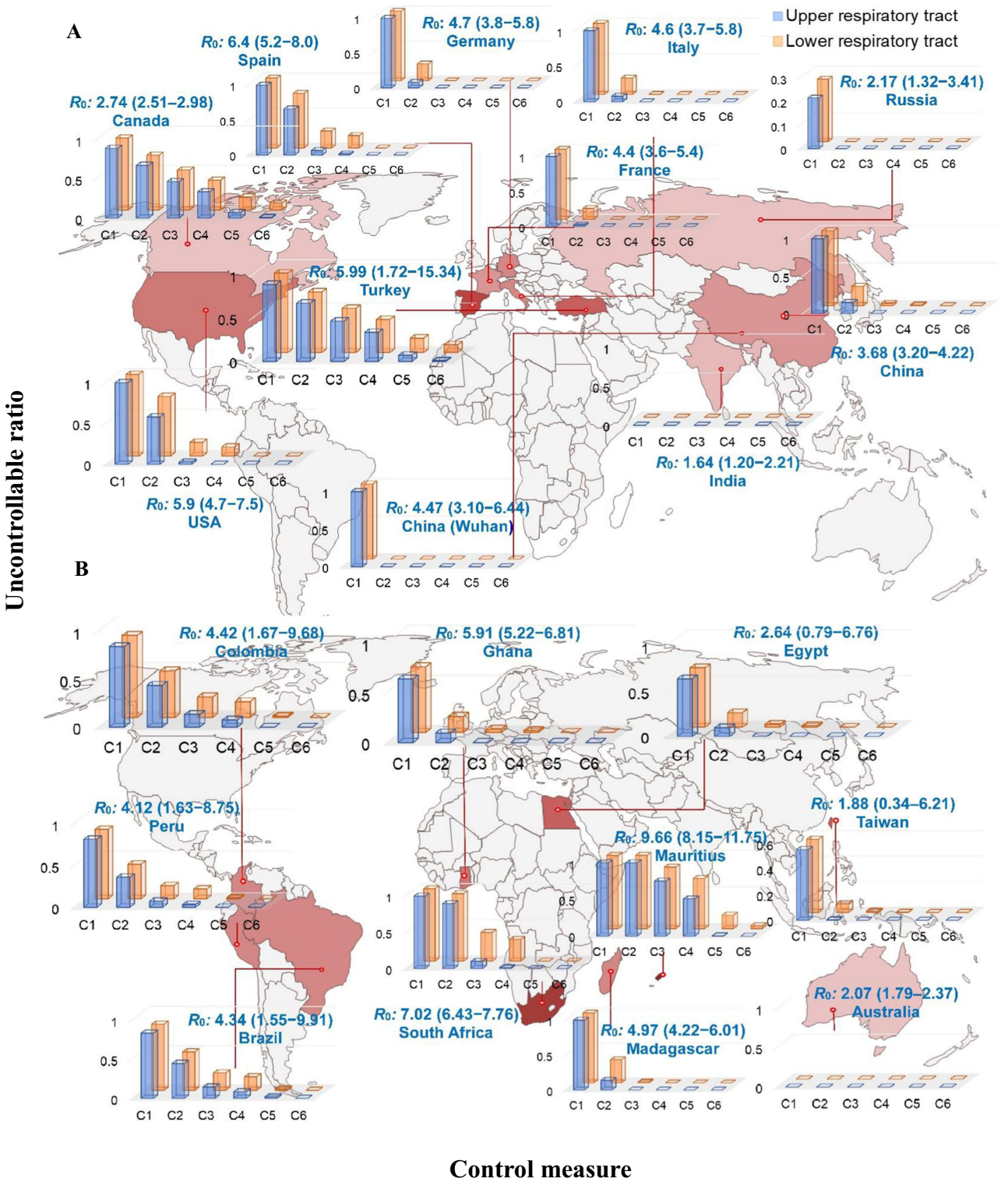

Figure 3 Estimated uncontrollable ratios of SARS-CoV-2 in the upper and lower respiratory tracts, respectively, in (**A**) Canada, USA, Spain, Germany, Turkey, France, Italy, Russia, China, China (Wuhan), and India and (**B**) Colombia, Peru, Brazil, Ghana, South Africa, Egypt, Mauritius, Madagascar, Taiwan, and Australia with application of control measures combinations (C1 – C6).

Abbreviations: SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; C1, social distancing; C2, social distancing + masking; C3, social distancing + masking + hand washing; C4, vaccination + social distancing; C5, vaccination + social distancing + masking; C6, vaccination + social distancing + masking + hand washing.

be fully contained in both lower and upper respiratory tracts; Taiwan (R_0:1.88 (0.34–6.21)) and Egypt (R_0: 2.64 (0.79–6.76)) have relatively lower URs of 0.003–0.07 and 0.100–0.160 in lower and upper respiratory tracts, respectively, among all countries in north hemisphere (Figure 3A and B).

When C3 was implemented, relatively higher URs were observed in South Africa (lower respiratory tract: 0.400), Mauritius (upper respiratory tract: 0.750; lower respiratory tract: 0.839) (Figure 3B), and Turkey (upper respiratory tract: 0.464; lower respiratory tract: 0.510) (Figure 3A). If C4 was applied as a control measure strategy, Turkey (upper respiratory tract, 0.335; lower respiratory tract, 0.381) (Figure 3A), South Africa (lower respiratory tract, 0.301), and Mauritius (upper respiratory tract, 0.509; lower respiratory tract, 0.684) had relatively higher URs (Figure 3B). When C5 and C6 were enforced, pandemics in almost all countries were contained, except in Turkey (C5: lower respiratory tract: 0.166; C6: upper respiratory tract: 0.010, lower respiratory tract: 0.089) (Figure 3A) and Mauritius (C5: lower respiratory tract: 0.184; C6: lower respiratory tract: 0.041) (Figure 3B).

Taken together, with the implementation of control measures of C1 or C2, the pandemic can be fully contained in both the lower and upper respiratory tracts when R_0 estimates range from 1 to 3. For C3 or C4, containment can be achieved in both the lower and upper respiratory tracts when R_0 estimates range from 4 to 5. If applied C5 or C6, the pandemic can be contained in both the lower and upper respiratory tracts for all countries except Mauritius. Among all six control measure combinations, Mauritius (R_0: 9.66 (8.15−11.75)) had the highest UR, followed by South Africa (R_0: 7.02 (6.43−7.76)) and Spain (R_0: 6.4 (95% CI: 5.2−8.0)) (Figure 3B).

To assess the trend in URs among all countries, a heatmap was also created to observe the implementation of different combinations of control measures. The results showed that Mauritius had higher URs when either C1 or C2 was implemented compared to other countries. The URs in Canada, Turkey, Brazil, Colombia, Egypt, Ghana, Peru, and Spain were in the medium range (Figure 4A). Notably, if only C1 were implemented, the European region would have the highest URs, followed by Mauritius and China (Figure 4B).

VOC-Specific Control Measure Effectiveness

The URs in the upper and lower respiratory tracts of the five VOC were evaluated when six combinations of control measure efficacies were implemented (Figure 5 and Table S2). The results indicated that none of the five VOC could be contained when C1 was implemented in both the upper and lower respiratory tract. However, the URs for Beta and Gamma variants decreased to 0.764 and 0.527 in the upper respiratory tract and to 0.848 and 0.684 in the lower respiratory tract, respectively (Figure 5). If C2 were applied, only the gamma variant in the upper respiratory tract would be fully contained (Figure 5A).

When C3 was used, higher URs of Omicron were still observable in both the upper (0.810) and lower (0.844) respiratory tracts, while another VOC (Beta, Gamma, and upper respiratory tract for Alpha and Delta) could be fully contained or had slightly higher URs (0.03 and 0.112 in lower respiratory tract for Alpha and Delta, respectively) (Figure 5). The application of C4 showed similar trends among the five VOC to those of C3 in both the upper and lower respiratory tracts. When C5 or C6 was performed, all VOC in both the upper and lower respiratory tracts could be contained, except for Omicron, in which URs in the upper (0.329) and lower (0.408) respiratory tracts for C5 and 0.197 (upper) and 0.305 (lower) respiratory tracts for C6 were still observed (Figure 5B).

Overall, no VOC can be contained with the implementation of C1. For C2, none of the VOC can be contained, except for the upper respiratory tract when infected with the Gamma variant. Both Beta and Gamma variants can be contained in upper and lower respiratory tracts when C3 or C4 are applied. However, Omicron cannot be fully contained even when C4 or C5 measures are implemented.

Effect Analyses

To construct the dose-response profiles for the five VOC, the relationships between log-transformed viral dosage (PFU mL^{-1}) and C_t values were described in a linear fashion. Results showed that Among the five VOC, Gamma had the highest (absolute) slope value (–3.63), followed by Delta (–3.53), Alpha (–3.48), Beta (–3.44), and Omicron (–3.26) (Figure S1).

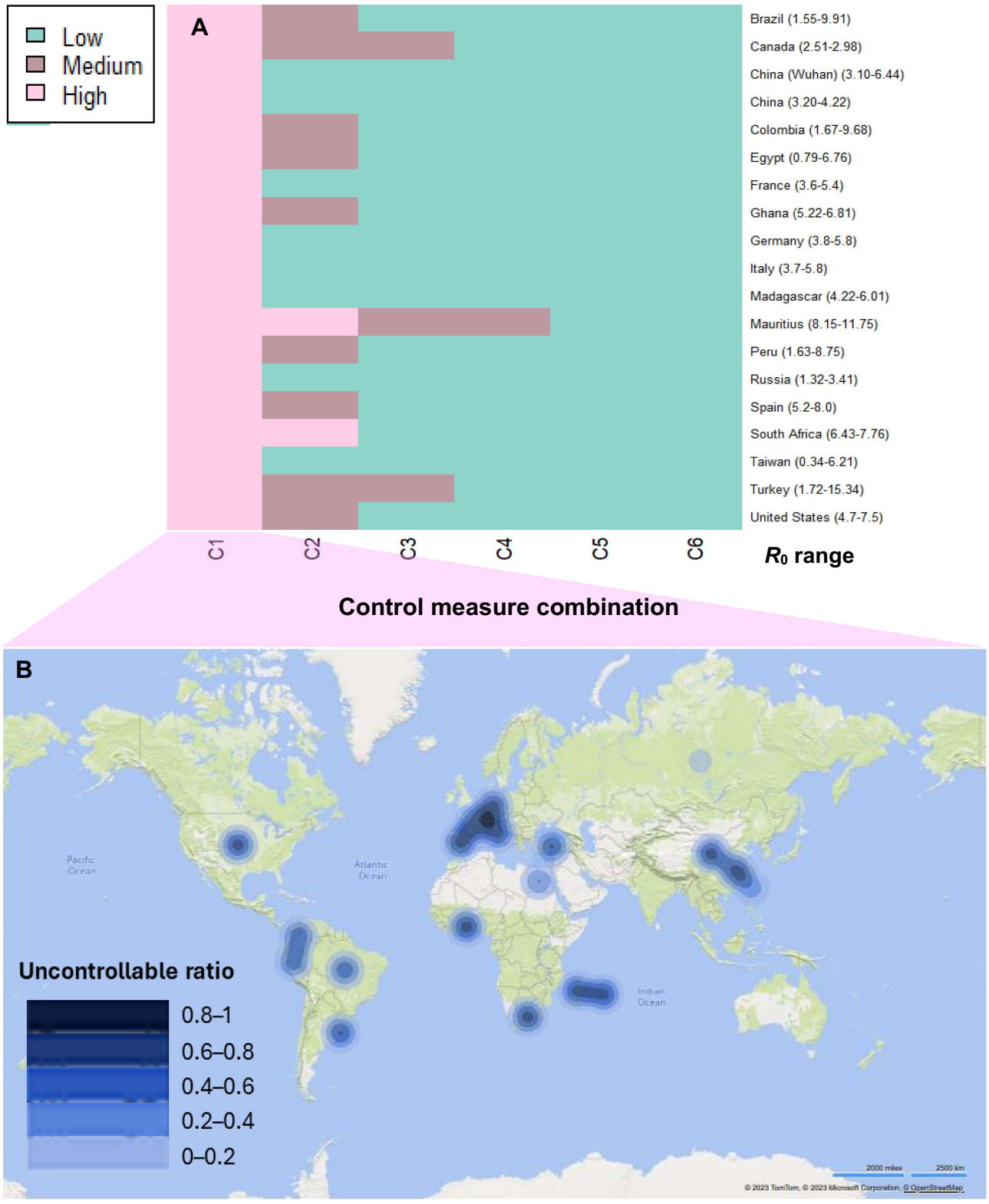

Figure 4 Heatmaps illustrating uncontrollable ratios in (**A**) low, medium, and high with application of combinations of control measures (C1 – C6) and (**B**) contour representations in different geographic regions in the world if only C1 is implemented.

Abbreviations: C1, social distancing; C2, social distancing + masking; C3, social distancing + masking + hand washing; C4, vaccination + social distancing; C5, vaccination + social distancing + masking; C6, vaccination + social distancing + masking + hand washing.

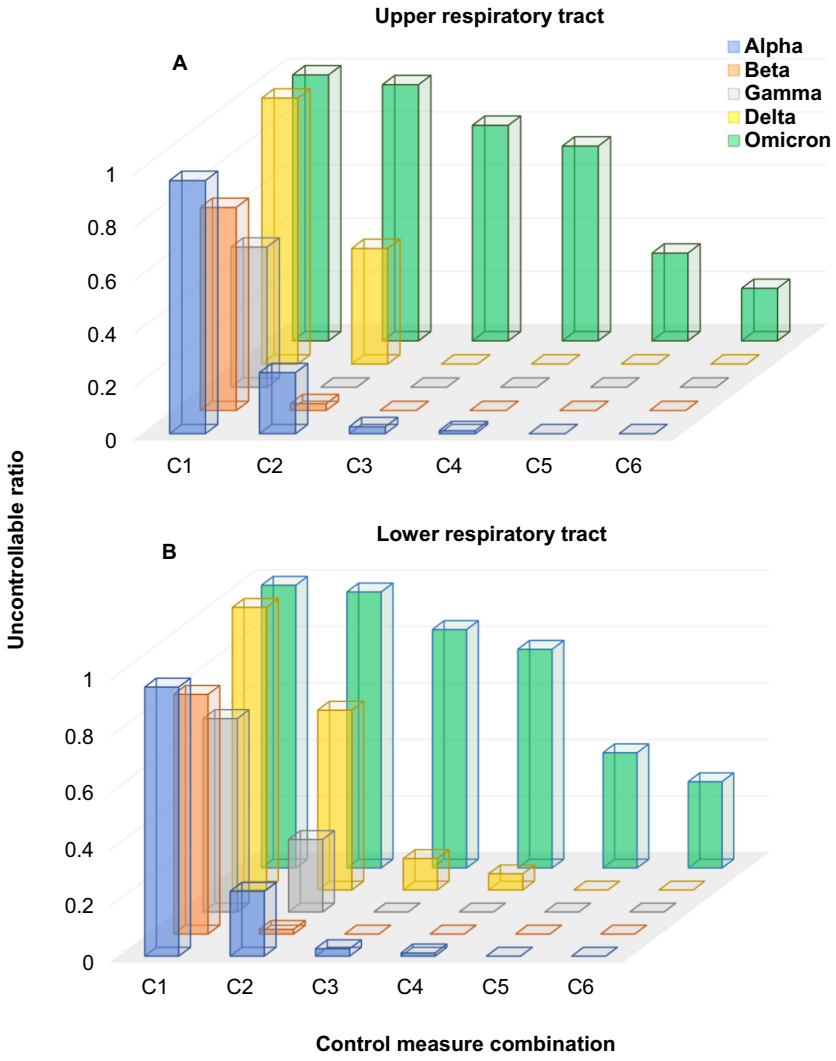

Figure 5 Estimated uncontrollable ratios for five VOC in (**A**) upper and (**B**) lower respiratory tracts, respectively, with application of combinations of control measures (C1 – C6).
Abbreviations: VOC, variants of concern; C1, social distancing; C2, social distancing + masking; C3, social distancing + masking + hand washing; C4, vaccination + social distancing; C5, vaccination + social distancing + masking; C6, vaccination + social distancing + masking + hand washing.

A three-parameter Hill-based model was also applied to assess the relationship between SARS-CoV-2 dose of five VOC and decremental proportion of C_t when compared to 0.1 PFU mL^{-1} of the variant (Table S6). The results showed that the Hill-based model could appropriately describe the relationships (R^2 = 0.64–0.73, $0.01 < p < 0.05$) with a similar mean E_{max} of 0.55–0.61 among five VOC. Delta variant has the lowest $ED50$ of 183.20 PFU mL^{-1}, followed by Beta (189.00), Gamma (193.90), Omicron (272.65), and Alpha (274.90) (Table S6).

VOC-Specific Predictive Risk Threshold

The three-parameter Weibull threshold model was adopted to best fit to CDFs of $ED10$ (R^2 = 0.99, $p < 0.001$) derived from the constructed profiles of dose of five VOC and decremental proportion of C_t when compared to 0.1 PFU mL^{-1} of the variant (Figure S2 and Table S7). The fitted mean threshold estimates (γ) for Alpha, Beta, Gamma, Delta, and Omicron were 0.001, 0.001, 0.002, 0.001, 0.0003 PFU mL^{-1}, respectively, with Omicron having the lowest threshold of infectivity (Table S7).

Discussion

Implementation of Risk Assessment Tool for COVID-19

Quantitative microbial risk assessment (QMRA) is an effective methodology for estimating human health risks associated with exposure to pathogens.[18] In this approach, after the pathogen is identified, dose–response and exposure assessments can be performed and integrated into risk characterization to estimate the risk. The QMRA method has recently been applied to assess SARS-CoV-2 risk in different environmental settings, such as wastewater treatment plants,[19,20] healthcare facilities,[21,22] public transportation and shared rooms,[23] and food market and manufacturing facilities.[24–26] However, pathogen dose–response models are not readily accessible when new pathogens emerge. In light of this, establishing the dose-response profiles of SARS-CoV-2 based on previous studies could be beneficial for the risk characterization of different VOC.

Moreover, as the COVID-19 pandemic continues from 2019 to the present, various variants of SARS-CoV-2 have emerged, such as Alpha, Beta, Gamma, Delta, and Omicron, suggesting that developing appropriate dose–response models for these variants could be challenging. Such lags have led to the use of the classical Wells-Riley model. The Wells-Riley model takes a similar approach to QMRA, but does not include pathogen-specific dose-response models. The Wells-Riley model is based on the concept of quantum of infection, defined as the number of infectious droplet nuclei or infectious dose required to infect 1–1/e (~63.2%) of susceptible people.[27,28]

Our study has the potential to be applied to COVID-19 risk assessments. The cumulative Weibull threshold model was used to estimate the exposure thresholds of infection for different variants, based on human epidemiological data. Exposure thresholds can be applied to risk assessments once the exposure doses are available. Exposure doses can be calculated using various methods including direct measurements, biomarker monitoring, and model calculations. Exposure doses were then compared to thresholds using methods such as hazard quotient or risk quotient to characterize the potential risk of SARS-CoV-2 infection for individuals or populations.

Global Progression of SARS-CoV-2 Variants

The emergence of SARS-CoV-2 variants from 2020 to 2021 witnessed globally has raised concerns for their increased transmissibility, risk of reinfection, and reduced vaccine efficacy despite rising population immunity through interventions of multiple control measures.[29] Due to the distinctiveness and intricacy in the development of viral genes, it is hard to redisplay the evolutionary trends among variants into a unified conclusion based on the present evolutionary models. However, the transmissibility, infectivity, and virulence among variants can be interpreted based on their genetic aspects.[30]

The D61G mutation on the spike protein gene existed broadly among VOC and variants of interest (VOI), which gave them considerable transmissibility in human populations.[31–35] Moreover, in VOC such as Alpha, Beta, and Gamma variants, the N501Y mutation probably increased the affinity between viral spike protein receptor-binding domain and human ACE2 receptor, and possibly interrupt the neutralization capability of antibodies to virus.[33,36,37] Conversely, though there was no evidence of increased virulence and disease severity associated with the Beta variant, the carried E484K and K417N mutations can decrease the susceptibility to monoclonal antibodies and partially alleviate the neutralizing antibodies derived from vaccination or recovery from previous infection.[38–41] The E484K and K417N mutations carried in Gamma variant may also impair the antibody neutralizing capacity in plasma from convalescent or vaccinated persons.[42] For Delta variant, the L452R mutation may not only impair the neutralization capability of antibodies but also increase the replication ability inside human cells.[43,44] Compared to other variants, more mutations on both spike protein and non-spike protein genes provided Omicron variant with additional entry pathways (endocytic and receptor-mediated endocytosis) to increase transmissibility and infectivity, as well as to evade vaccinations and antibodies.[30]

Vaccination potency can also be affected by distinct traits of different variants. Among the variants, the Moderna and Pfizer vaccines were the most effective against the Alpha variant and its mutant strain.[45,46] In the Beta variant dominating region (eg, South Africa), the protective efficacy of the vaccines decreased significantly. The neutralization capacity was reduced to 9 and 7.6 folds for AstraZeneca and Pfizer vaccinations against the Beta variant, respectively, whereas the

Novavax vaccine showed ~96% efficacy against the Alpha variant but only 60% efficacy in South Africa where Beta variant was prevalent at ~93%.[33,37] Moderna mRNA-1273 vaccine-induced antibody production was reduced to 5–10 folds when exposed to the Beta variant.[33,45] Compared to the Alpha variant, only a slight reduction in vaccine efficacy was found in the Delta variant.[33,39]

Limitations and Implications

During the COVID-19 pandemic, governments worldwide implemented various control measures including NPIs and vaccinations to reduce disease transmission from 2021 to 2022.[47] Ge et al[47] revealed that China invested significant efforts in strict zero-COVID measures to contain outbreaks of varying scales caused by different SARS-CoV-2 variants. Based on the analysis of R_0 reduction resulting from relative intervention effectiveness, social distancing (38% reduction), face masks (30%), and close contact tracing (28%) were the most effective. We evaluated the effectiveness of individuals and combinations of common control measures for COVID-19 at the national scale. Here, social distancing was included in all six control measure combinations. Aquino et al[48] reviewed that maintaining and strengthening social distancing strategies is vital to avoid overwhelming the healthcare systems. Reducing social contact by at least 60% could mitigate COVID-19 transmission. Furthermore, a recent study demonstrated that face mask use was associated with a 62–85% reduced risk of COVID-19 infection, which is consistent with our assumption.[49]

Our results showed that the combination of social distancing and vaccination (C4) can reduce the risk from high to low levels compared to the application of social control only (C1). A previous study using epidemiological modeling also found that vaccination against COVID-19 is crucial while with additional social distancing measures can significantly strengthen the overall effectiveness by both lowering the number of infected individuals and delaying the epidemic peak timing.[50] Chu et al[51] also concluded that physical distancing $\geq$ 1 m, optimum use of face masks and eye protection are effective with more than 10% reduced risk.

There are several limitations in the approaches applied in this study. The control measure model developed in this study assumes that people are homogeneously distributed in a community or an indoor environment. Additionally, the distribution of the time to symptoms was assumed to be exponential. Despite these assumptions, the present control measure model could provide a visual overview of the impacts of different control measure combinations on URs in the upper or lower respiratory tract, based on different R_0 estimate ranges. However, it is important to note that R_0 estimates have been obtained from various studies using either modeling results or empirical data, and the timing of these R_0 estimates and the occurrence of COVID-19 variants may not be comparable across countries. Even if the R_0 value in a population is low, the likelihood of transmission in subgroups of the population could still be high. The country-specific R_0 estimates should be more accurately derived through meta-analysis to attenuate heterogeneity among studies. Another limitation is that we did not consider the sociodemographic and cultural practice differences in real-world control measure implementations, which may lead to country-specific variations in intervention coverage.[52] However, the mechanistic approach developed in this study can be practically applied to assess URs of different combinations of control measures in various country contexts when R_0 estimates are available. Our analysis observed a trend of relatively higher URs in Europe and several regions in Africa, based on the heterogeneous R_0 estimates collected from different studies.

To explore more of differences in URs among different VOC, six control measure combinations were also used for comparison in the upper and lower respiratory tracts. In accordance with its highest transmissibility, the Omicron variant elicited the highest URs among all VOC with all control measure combinations in both the upper and lower respiratory tract. The fact that Omicron could not be fully contained, even with all the control measures applied (C6), indicating that additional control measure strategies are necessary to achieve full containment. Hoffmann et al[53] also found that most therapeutic antibodies were ineffective against Omicron, and even double immunization with BNT152b2 was not adequately protective against severe disease induced by this variant, revealing that vaccination alone may no longer a potent strategy to combat the rapid and high number of mutations of SARS-CoV-2. The biological properties of Omicron, including strong infectivity, rapid and surreptitious transmission, a high proportion of asymptomatic infections, and its ability to escape the immune response generated by previous infections or vaccines, greatly increase the difficulty in implementing effective control measures.[54,55] Therefore, in

addition to the control measures proposed in this study, more intensive measures, such as up-to-date vaccination, isolation of infected persons, mask use at home, and avoiding crowds, should be implemented to effectively cope with the evolution of SARS-COV-2.[56] Symptom-based surveillance, close contact tracing, occupation-based screening, or a set of social distancing measures (such as travel restrictions, stringent border control policies, and community confinement) can also play a complementary role in fighting the emergence of novel SARS-CoV-2 variants.[54]

Moreover, we attempted to mechanistically interpret SARS-CoV-2 infectivity by analyzing the relationship between the SARS-CoV-2 dose and decremental proportions of the C_t values compared to the lowest SARS-CoV-2 dose (0.1 PFU mL^{-1}). Since previous studies have suggested that the threshold of the C_t values causing COVID-19 infection is approximately 33.7, we adopted a more conservative approach to derive threshold values based on the *ED*10 of different variants. However, the threshold values derived from the C_t values may not reflect the epidemiological characteristics and clinical features of these VOC by simply comparing the C_t values of the variants.[57]

Mutations in SARS-CoV-2 due to errors in the genetic code during replication could raise public concerns. New SARS-CoV-2 VOC are expected to emerge as the COVID-19 pandemic continues. The emergence of variants could also exacerbate outbreaks, reduce vaccine efficacy, lead to increased rates of reinfection, and prolong pandemics. Consequently, variant surveillance is needed to track variant emergence for a more robust pandemic response plan and to make timely public health decisions and recommendations for future vaccines. Grubaugh et al[58] suggested that random subsets of positive tests should be sequenced to monitor mutations and VOC. However, because genomic surveillance is not available in most countries owing to a lack of infrastructure or technical expertise, they also suggested that the international community should provide financial or technical support to facilitate genomic surveillance in regions with fewer resources.

In addition, to prevent a variant rise in the community, it is essential to increase the level of urgency and frequency of messaging. Ideally, messaging should work with community groups to ensure that the information is widely disseminated and understood by the public. Local actions, including reducing social contact, effective testing/tracing, effective outbreak identification and control, supporting efficient isolation and quarantine, and population vaccination, should also be considered. Moreover, multilateral cooperation among countries and guidance on swift actions to control local transmission and limits of travel restrictions are appropriate for addressing the rapid progression of SARS-CoV-2 variants.[59]

Conclusion

We provide a mechanistic approach by implementing a control measure model and a risk assessment framework to provide insights into the impacts of control measure combinations on SARS-CoV-2 variant transmission control, along with a different application perspective of risk assessment. We found that the implementation of social distancing alone is not sufficient for almost all countries and VOC if R_0 estimate is higher than 2 based on the highly derived URs. However, if the control measures of both social distancing and wearing masks are practiced, only the Gamma variant in the upper respiratory tract can be contained. For Omicron, even the application of control measures (vaccination, social distancing, wearing masks, and hand washing) could not fully control the pandemic, indicating greater intensity of control measures will need to be implemented to fight the emergence of new variant. The approach to derive threshold estimate of infectivity in risk assessment framework can be further applied to risk characterization and inform public health authorities for decision-makings when SARS-CoV-2 exposure data are available. Taken together, our study has profound implications for future emerging SARS-CoV-2 variant infection control in the context of risk communication and policymaking.

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Author Contributions

All authors contributed to data analysis, drafting or revising the article, have agreed on the journal to which the article will be submitted, gave final approval of the version to be published, and agree to be accountable for all aspects of the work.

Disclosure

The authors report no conflicts of interest in this work.

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