Effectiveness of International Travel Controls for Delaying Local Outbreaks of COVID-19

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During the coronavirus disease pandemic, international travel controls have been widely adopted. To determine the effectiveness of these measures, we analyzed data from 165 countries and found that early implementation of international travel controls led to a mean delay of 5 weeks in the first epidemic peak of cases.

International travel control (e.g., screening of inbound travelers, requiring quarantines, and even closing borders) has been a key strategy implemented by many countries to limit importations of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). However, early in the coronavirus disease (COVID-19) pandemic, the World Health Organization (WHO) did not recommend restricting travel (*1*), and travel controls have not been widely used in previous pandemics (e.g., the 2009–10 influenza pandemic) (*2*,*3*). Limiting international movement has enormous social and economic costs, and the benefits of this strategy (i.e., delaying or averting an epidemic) lack real-world evidence. Previous studies, most of which were simulation studies, suggest that travel restrictions can delay but not prevent local epidemics (*2*–*4*).

To examine the association between implementation of international travel controls and local outbreak progress of COVID-19, we used publicly available data (*5*–*7*; T. Wu et al., unpub. data, https://www.medrxiv.org/content/10.1101/2020.02.25.2002743 3v1) for January 1–July 31, 2020. Only 14 (8.5%) of the 165 countries studied enacted international travel controls coincident with the lockdown in Wuhan, China (January 23); all controls involved screening inbound travelers (Figure). Enactment of international travel controls peaked ≈3 weeks after WHO declared the pandemic (March 11, 2020), by which time 112 (67.8%) countries completely closed their borders, 44 (26.6%)

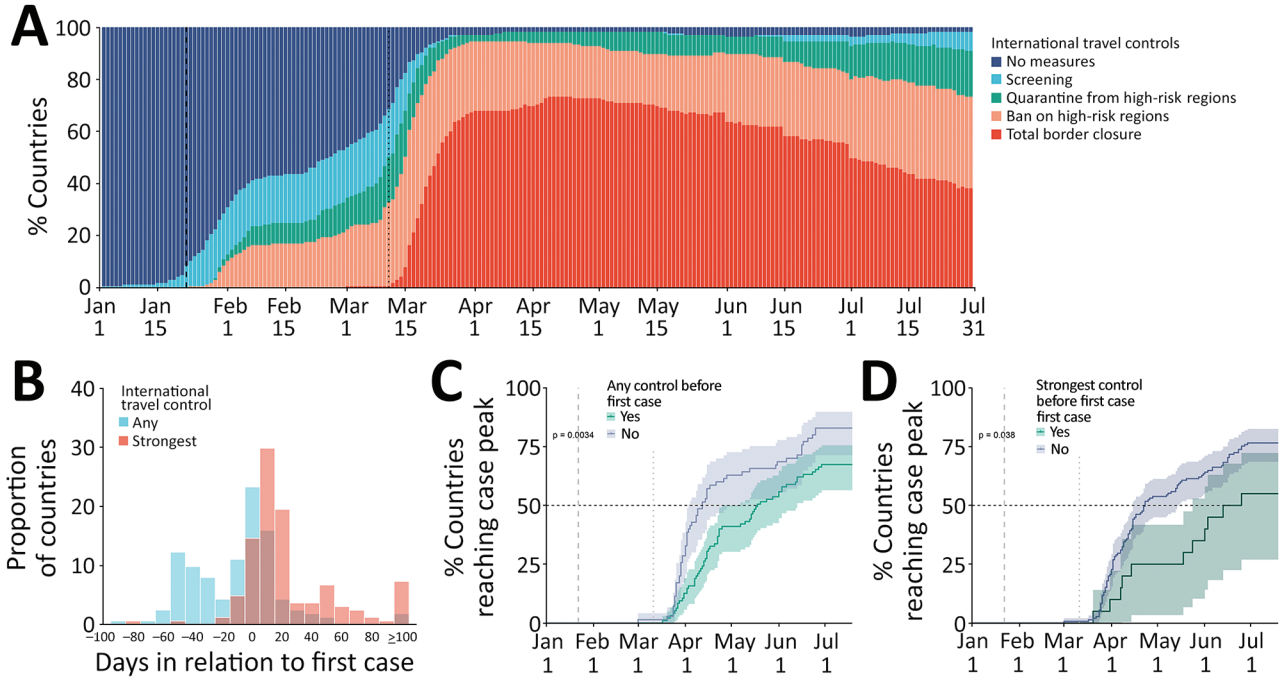

Figure. Association between international travel controls and local coronavirus disease (COVID-19) outbreaks in 165 countries, January 1–July 31, 2020. A) Temporal distribution of the international travel controls enacted by the studied countries. Data from (*7*). B) Distribution of the time between a country's first COVID-19 case and its enactment of any or of the strongest international travel controls. C, D) Probability of reaching first local peak of COVID-19 cases by the time of implementing any (C) or the strongest (D) international travel controls, estimated by using the Kaplan-Meier survival function. Vertical dashed lines in panels B, C, and D indicate the date that Wuhan, China, underwent lockdown; vertical dotted lines indicate the date that the pandemic was declared.

Table. Estimated time ratios and hazard ratios for comparing selected outcomes in countries that did and did not implement international controls before identifying their first cases of COVID-19, January–July 2020*

	Adjusted time ratio (95% CI)†		Adjusted hazard ratio (95% CI)‡	
Endpoint	Any international controls	The strongest international controls	Any international controls	The strongest international controls
Case peak	1.22 (1.06–1.41)	1.31 (1.02–1.68)	0.66 (0.46–0.93)	0.65 (0.39–1.08)
Death peak	1.23 (1.01–1.51)	0.98 (0.71–1.37)	0.74 (0.53–1.04)	0.90 (0.53–1.55)
Cumulative incidence, no. cases/10,000 population				
0.2	1.20 (1.10–1.31)	1.23 (1.05–1.44)	0.55 (0.38–0.78)	0.61 (0.35–1.04)
1.0	1.26 (1.13–1.42)	1.27 (1.04–1.55)	0.49 (0.35–0.71)	0.90 (0.53–1.51)
5.0	1.25 (1.05–1.49)	1.34 (0.99–1.82)	0.59 (0.41–0.85)	0.90 (0.54–1.51)

*AFT, accelerated failure time; COVID-19, coronavirus disease.
†Estimates were obtained from accelerated failure time models with log-logistic distribution, adjusted for population density and the strictest level of each nonpharmaceutical intervention used during the study period for each country. The 2 columns show time ratio of implementing international controls before the country's first COVID-19 case to that after the country's first case.
‡Estimates were obtained from Cox proportional hazard models, which adjusted for population density and time-varying nonpharmaceutical interventions during the study period for each country. The 2 columns show hazard ratio of implementing international controls before the country's first COVID-19 case to that after the country's first case.

banned travelers from high-risk regions, and 4 (2.4%) required quarantine for travelers from high-risk regions (Figure; Appendix Figure 1, https://wwwnc.cdc.gov/EID/article/28/1/21-1944-App1.pdf). Of the 165 countries, 90 (54.5%) had imposed at least some restriction before reporting their first COVID-19 case, and 20 (12%) had imposed their strictest restrictions before reporting their first case (Figure; Appendix Figures 1–3).

We determined the progress of outbreaks in each country to be the time from January 1, 2020, to the first epidemic peak, which was identified from the modal daily case counts within any 53-day sliding window (i.e., a quarter of the length of the study period) and needed to comprise ≥10% of the cumulative incidence during the study period (Appendix Figure 2). By July 31, 2020, the first epidemic peak had been reached in 122 (74%) of the studied countries (Appendix Figure 4). In countries that had enacted any international travel controls before their first COVID-19 case, the first peak was reached an average of 36 days (95% CI 10–61 days) later than it was in countries that did not enact controls until after their first case was reported ($p<0.01$ by log-rank test; Figure). Countries that implemented their strictest international travel controls before detecting any COVID-19 cases reported their first case a median of 57 days (95% CI 14–70 days) later than countries that imposed their strongest controls after the first case was reported ($p = 0.04$ by log-rank test; Figure).

After adjusting for population density and implementing nonpharmaceutical interventions by using the accelerated failure time model (Appendix), we estimated that the average time to detection of the first case occurred 1.22 (95% CI 1.06–1.41) times later in countries that implemented any restrictions than in countries that implemented no travel restrictions. This time ratio was extended to 1.31 (95% CI 1.02–1.68) if countries implemented their strongest travel restrictions (Table). Such associations still held when adjusting for time-varying nonpharmaceutical interventions by using the Cox model.

To confirm that these observations were maintained according to alternative measures of epidemic activity, we used the following as outcomes in the models: the time by which COVID-19 deaths first peaked, and attainment of a cumulative incidence of 0.2, 1.0, or 5.0 cases/10,000 persons (by which time peaks had been reached in ≈10%, 30%, and 60% of the countries; Appendix Figure 5). These outcomes may better indicate community spread in countries in which most cases were imported and identified during quarantine (e.g., Fiji), information that was not available from public data. Moreover, outcomes may be better when the epidemic was multimodal (e.g., Guyana) or the country did not experience its main epidemic until later in the study period (e.g., Argentina) (Appendix Figure 2). Both accelerated failure time and Cox models supported earlier observations that enactment of any international travel controls delayed the time in which cumulative incidence rates or deaths peaked. However, enactment of the strongest control was not associated with a reduced time to peak death or cumulative incidence of 5 cases/100,000 persons (Table).

Our work may be influenced by other unmeasured confounders, such as the stringency of international travel controls. We repeated our analyses by removing countries in Asia, in which implementation tended to be more strict, and found that our earlier observations largely held (Appendix Table). In addition, we examined the broader association between international travel controls and local epidemic progression, but we did not examine the roles of specific measures (e.g., quarantine and risk-dependent triage management).

Our findings suggest that implementing international travel controls earlier delayed the initial epidemic peak by ≈5 weeks. Although travel restrictions did not prevent the virus from entering most countries, delaying its introduction bought valuable time for local health systems and governments to prepare to respond to local transmission.

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All authors are affiliated with WHO collaborating centers. The objective technical analysis and results reported here were not part of official WHO work, and opinions contained herein do not necessarily represent the views of WHO.

About the Author

Dr. Yang is a postdoctoral fellow at the School of Public Health, University of Hong Kong. Her research interests are quantifying transmission dynamics and control of infectious diseases.

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Atezolizumab Treatment for Progressive Multifocal Leukoencephalopathy

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Atezolizumab successfully reinvigorated JC virus immunity in a patient in Belgium with progressive multifocal leukoencephalopathy, as demonstrated by clinical, virologic, and radiologic response to treatment. However, the treatment also resulted in immune reconstitution inflammatory syndrome and life-threatening immune-related adverse events. These conditions were treated with corticosteroids, leading to treatment resistance.

Progressive multifocal leukoencephalopathy (PML) is a devastating infectious disease of the brain that is caused by JC virus (JCV) in the context of cellular immunodeficiency. To date, no effective antiviral treatment for PML exists, and survival depends on the person's ability to achieve timely immune

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Appendix

Data sources

Data on the country-specific time series of reported COVID-19 cases and deaths were obtained from Johns Hopkins Coronavirus Resource Center between Jan 22 to Jul 31, 2020 (*1*). As some countries reported their first COVID-19 case before Jan 22, 2020 (e.g., Thailand and Japan), we obtained the date of first reported COVID-19 case for those countries from T. Wu et al. (unpub. data, https://www.medrxiv.org/content/10.1101/2020.02.25.20027433v1). We only used data before Jul 31, 2020, as many countries started to experience their second wave during or after that time, to which controls targeting local communities would contribute more than that targeting international travels.

We obtained time series of non-pharmaceutical interventions (NPIs) that were implemented by countries from a publicly available database (*2*,*3*), which included international travel restrictions, testing, contact tracing, facial covering, restrictions internal movements, cancel public events, restriction gatherings, close public transport, school closures, stay home requirements and workplace closures. International travel restrictions were classified into five categories with increasing stringency, i.e., no measures, screening, quarantine from high-risk regions, ban on high-risk regions and total border controls (*2*). We characterized the time of any international travel controls as the first date when any international travel controls other than no measures was implemented. We characterized the time of the strongest international travel controls as the first date when the strictest international travel controls during the study period was implemented.

We included countries where have data available for both time series of reported cases and NPIs. We excluded China where the first COVID-19 case was detected.

Methods

We examined the associations between the time of implementing international travel controls and the local outbreak progress of COVID-19 across the studies countries.

Exposure. Binary variable was modelled for the exposure to measure if the international travel control was implemented before or after the country reported its first COVID-19 case. We looked at the time for implementing both any or the strongest international travel control.

Endpoint event. To characterize the local COVID-19 outbreaks progression, we first fit cubic smooth spline to the time series of each country, to avoid the impact of short-term noise caused by reporting. We then used the following five endpoint measurements to characterize the local outbreak progress (Appendix Figure 4):

1) *the first epidemic peak for confirmed COVID-19 cases*, which was the primary outcome used in the main analysis and was defined as the first appeared maxima of cases within any 53-days sliding window (i.e., a quarter of the length of the study period). We also excluded peak with value less than 10% of the cumulative incidence during the study period, to avoid false identification due to sparse cases reported in early phases in some countries. Countries could have multiple peaks during our study period (e.g., United States) and we recorded the first appeared peak. By 31 July 2020, 74% (n = 122) of the countries had experienced their first peak of COVID-19 cases (Appendix Figure 4A).

2) *the first epidemic peak for confirmed COVID-19 death*, which was defined as the same to that of the confirmed cases but using time series of confirmed COVID-19 related deaths. By 31 July 2020, 59% (n = 97) of the countries had experienced their first peak of COVID-19 cases (Appendix Figure 4B).

3) *the cumulative incidence reached 0.2 case per 10,000 persons*, by which 13% of the studied countries had peaked. By 31 July 2020, 87% (n = 143) of the countries had experienced their first peak of COVID-19 cases (Appendix Figure 4C).

4) *the cumulative incidence reached 1 case per 10,000 persons*, by which 30% of the studied countries had peaked. By 31 July 2020, 87% (n = 143) of the countries had experienced their first peak of COVID-19 cases (Appendix Figure 4D).

5) *the cumulative incidence reached 5 cases per 10,000 persons*, by which 57% of the studied countries had peaked. By 31 July 2020, 62% (n = 102) of the countries had experienced their first peak of COVID-19 cases (Appendix Figure 4E).

We noted that the first epidemic peak of COVID-19 cases that we used for our main analysis have many caveats (Appendix Figure 6). For example, some countries (e.g., Fiji) may find most of their cases in quarantine facilities, and therefore the reported cases in these countries may not to be the locally transmitted cases, which could result in misclassification of the first epidemic peak. For some countries had many fluctuations over the study period (e.g., Guyana) or experienced a much larger outbreak during the later of our study period (e.g., Argentina), which could result in right-censoring for the first epidemic peak (i.e., no epidemic peak was observed according to the peak measurement). To validate if our results would be greatly affected by these issues, we used the reaching a certain threshold for cumulative incidence. We believe using the alternative outcome measurements could overcome the abovementioned misclassifications or right-censoring issues, although for some countries with low COVID-19 circulation it could introduce right-censoring as well (e.g., Vietnam, Appendix Figure 6). Nevertheless, results suggested that these measurements were less likely to affect our main conclusion (Table in the main text).

Time-to-event. We calculate the time-to-event as the time between January 1 2020 (the day after the Wuhan cluster was first reported) and the time when the country reached the abovementioned outcome.

Statistical analyses

We plotted the Kaplan–Meier survival curve for the above-mentioned measurements for local COVID-19 outbreaks as endpoint and stratified by whether the country implemented their international travel controls before reporting their first case (Figure panels C, D in the main text and Appendix Figure 4).

We fitted accelerated failure time (AFT) model (Table in the main text) to examine the time ratio of countries which implemented their international travel controls before or after their first case. We adjusted for the country's population density and the strictest level of each NPI that was implemented by the country during the study period. Other NPIs include testing, contact tracing, facial covering, restrictions internal movements, cancel public events, restriction

gatherings, close public transport, school closures, stay home requirements and workplace closures (*2*). We fitted the AFT with four distributions, i.e., exponential, Weibull, lognormal and loglogistic. We presented the results from the AFT model with loglogistic distribution as the Akaike information criterion (AIC) suggested it provided the best model fit.

Country adjusted their NPIs along with the progress of local COVID-19 outbreak. So, we also fitted a Cox proportional hazard model (Appendix Table), to allow for modelling individual NPIs as time-varying variables. We reported the hazard ratio of reaching the outcome measurements between countries that implemented their international travel controls before or after their first case, after adjusting for population density and time-varying NPIs.

There may be other unmeasured confounders that could lead the observed associations between earlier enactment of international travel controls and delayed local epidemic progressions. For instance, countries where implemented travel controls before their first COVID-19 case may also be more precautious and adherent when implanting other non-pharmaceutical interventions. We performed a sensitivity analysis by fitting the AFT and Cox models with data that excluding Asian countries, where tended to have stricter enactment, higher adherence and more precautious when implementing these control measures (Appendix Table). In total 42 Asian countries were excluded in the sensitivity analyses, which are Afghanistan, Azerbaijan, Bahrain, Bangladesh, Bhutan, Cambodia, Cyprus, Georgia, India, Indonesia, Iran, Iraq, Israel, Japan, Jordan, Kazakhstan, Kuwait, Kyrgyzstan, Laos, Lebanon, Malaysia, Mongolia, Myanmar, Nepal, Oman, Pakistan, Philippines, Qatar, Saudi Arabia, Singapore, South Korea, Sri Lanka, Syria, Tajikistan, Thailand, Timor-Leste, Turkey, United Arab Emirates, Uzbekistan, Vietnam and Yemen.

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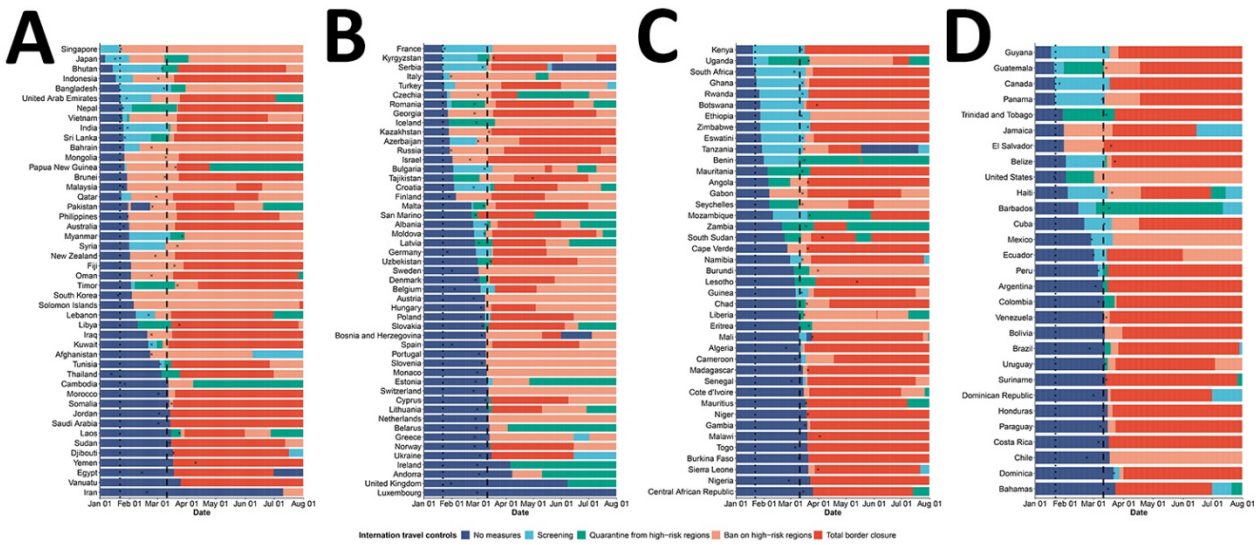
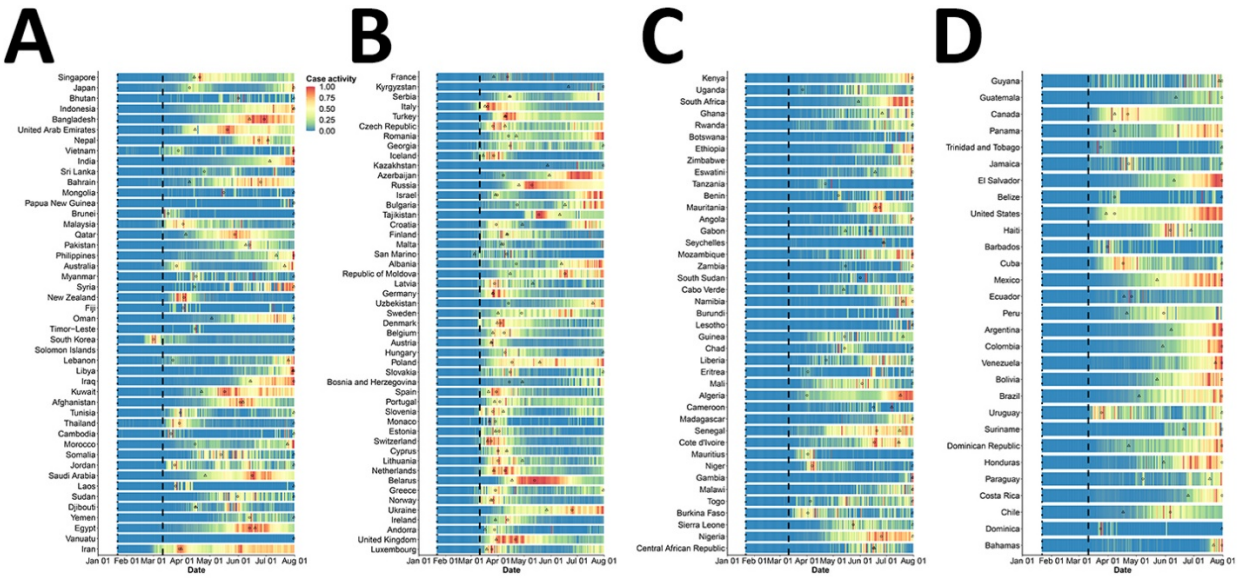
Appendix Table. Estimated time ratios and hazard ratios for selected outcomes comparing countries which implemented international controls before identification of their first cases versus those that did not, after removing Asian countries*

	Adjusted time ratio (from AFT model)†		Adjusted hazard ratio (from Cox model)‡	
Endpoint	Any international controls	The strongest international controls	Any international controls	The strongest international controls
Case peak	1.27 (1.08, 1.51)	1.31 (0.95, 1.79)	0.67 (0.44, 1.02)	0.70 (0.37, 1.30)
Death peak	1.30 (1.05, 1.60)	1.01 (0.72, 1.42)	0.71 (0.47, 1.07)	0.93 (0.49, 1.78)
Cumulative incidence				
0.2 per 10,000	1.25 (1.14, 1.37)	1.34 (1.14, 1.58)	0.42 (0.27, 0.67)	0.42 (0.20, 0.88)
1 per 10,000	1.35 (1.20, 1.53)	1.40 (1.13, 1.74)	0.34 (0.22, 0.53)	0.79 (0.42, 1.48)
5 per 10,000	1.43 (1.17, 1.76)	1.69 (1.17, 2.44)	0.45 (0.29, 0.69)	0.73 (0.40, 1.35)

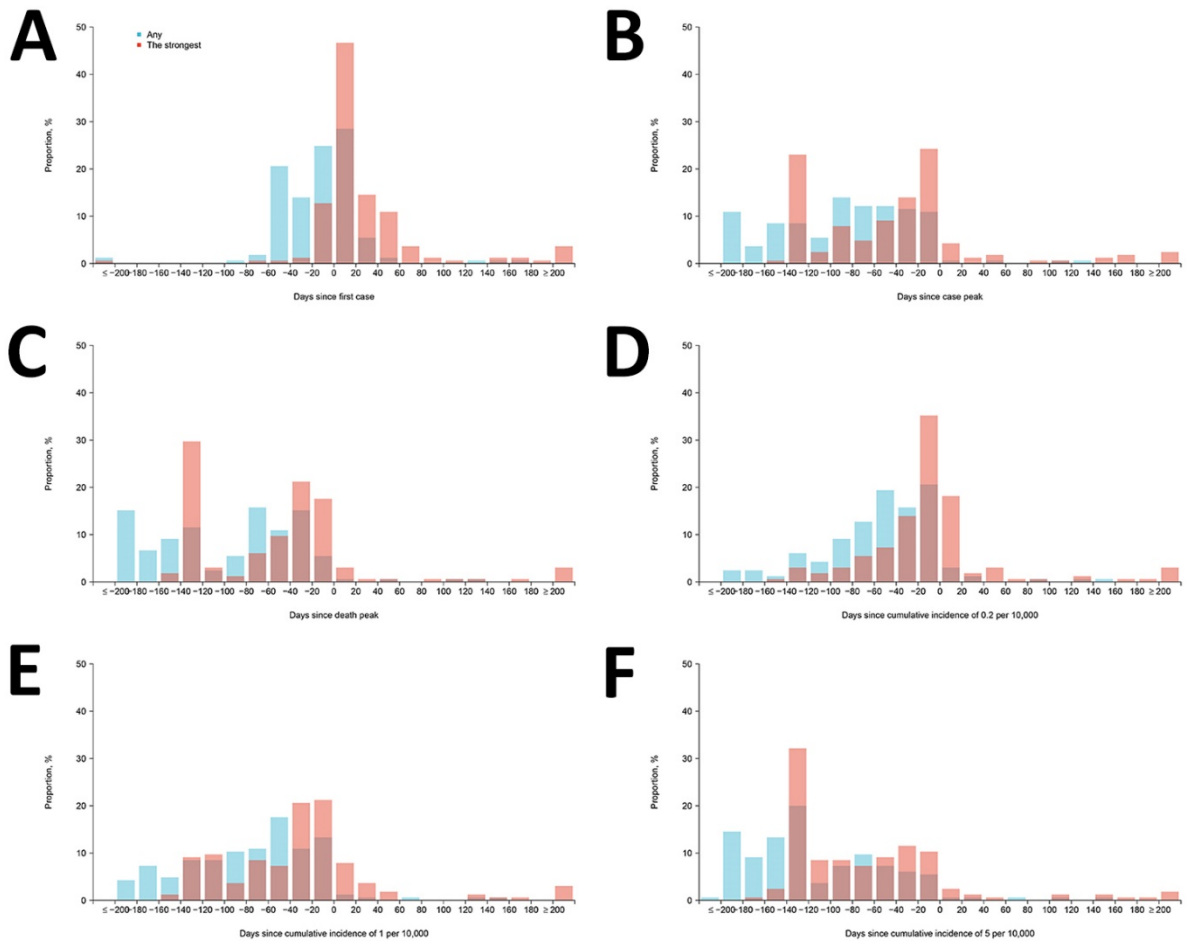
*A total of 42 Asian countries were excluded in the analyses.
†Estimates were obtained from accelerated failure time (AFT) models with loglogistic distribution, adjusted for population density and the strictest level of each NPI used during the study period for each country. The two columns show time ratio of implementing international controls before the country's first COVID-19 case to that after the country's first case.
‡Estimates were obtained from Cox proportional hazard models, which adjusted for population density and time-varying NPIs during the study period for each country. The table shows hazard ratio of implementing international controls before the country's first COVID-19 case to that after the country's first case.



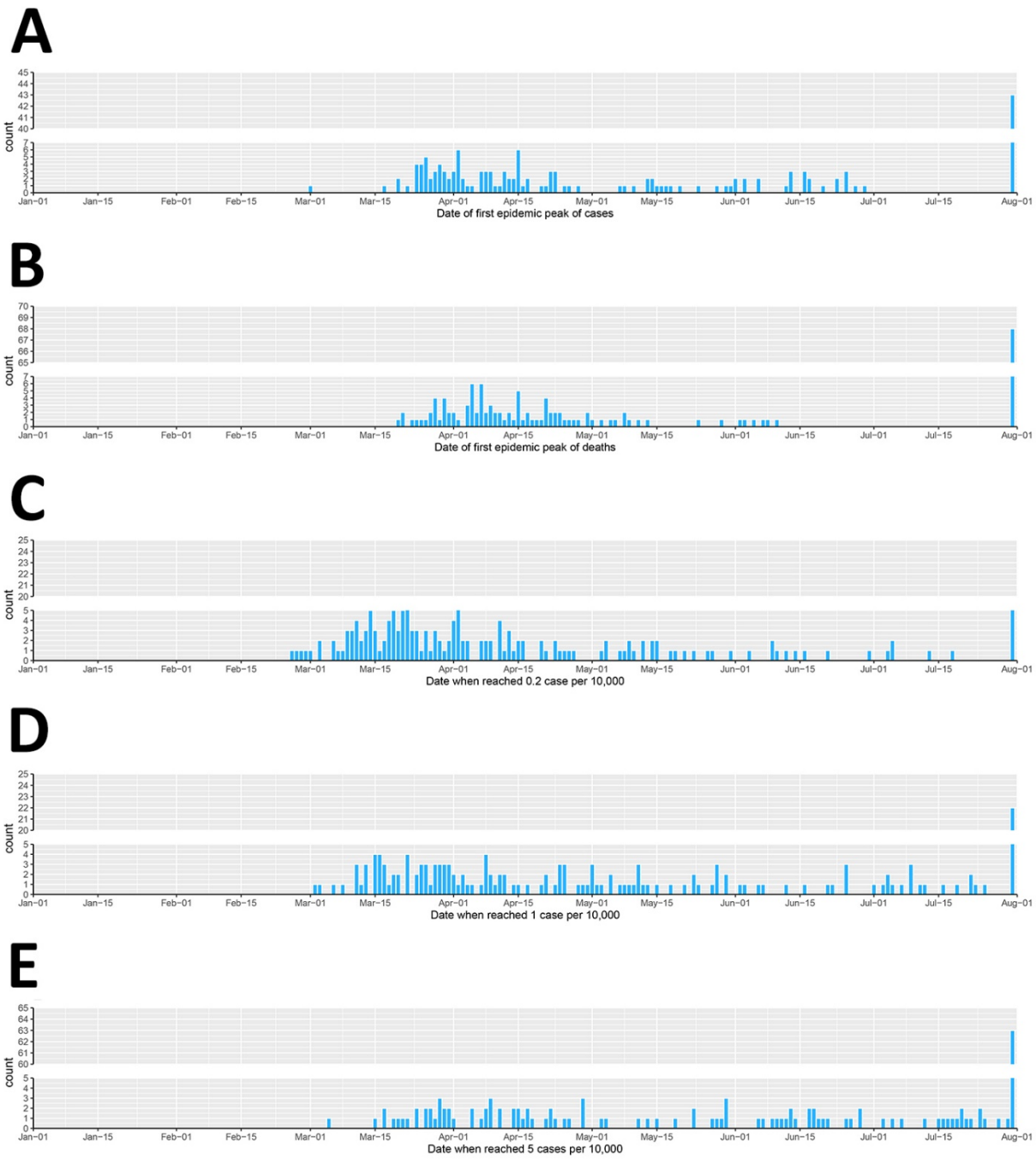
Appendix Figure 1. Temporal distribution of international travel control implementation in 165 countries, 1 January to 31 July 2020. Data were derived from https://ourworldindata.org/policy-responses-covid. Cross indicates the time when country reported its first case.



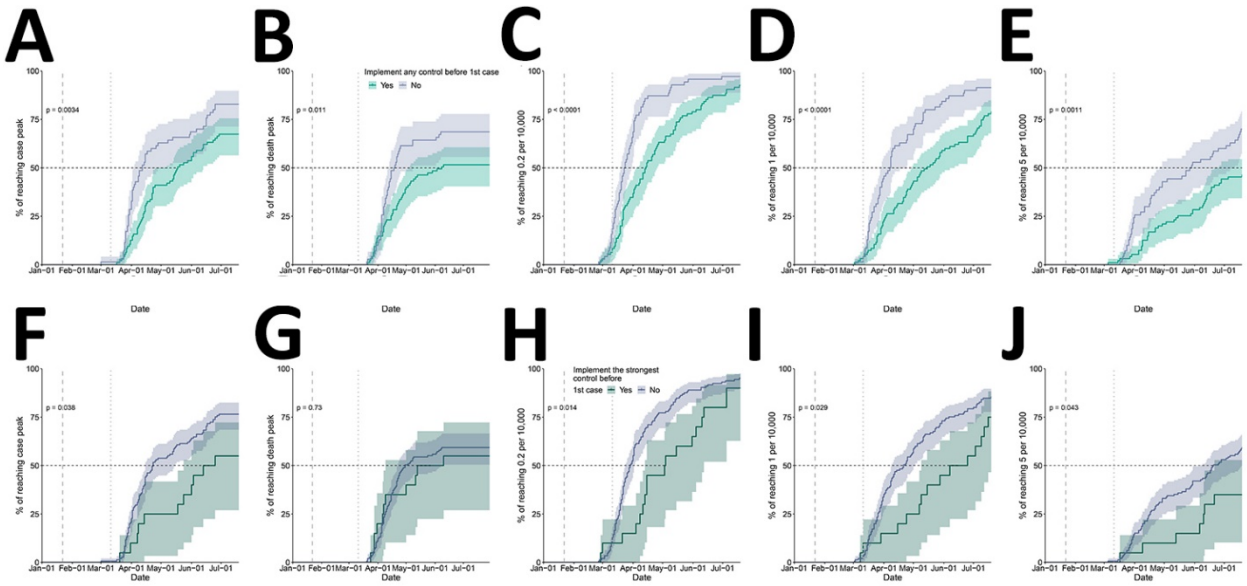
Appendix Figure 2. Temporal distribution of confirmed COVID-19 cases in 165 countries, 1 January to 31 July 2020. Data were derived from (*1*). Circle and triangle indicate the time when the country reached its first epidemic peak of cases and 5 cases per 10,000, respectively.



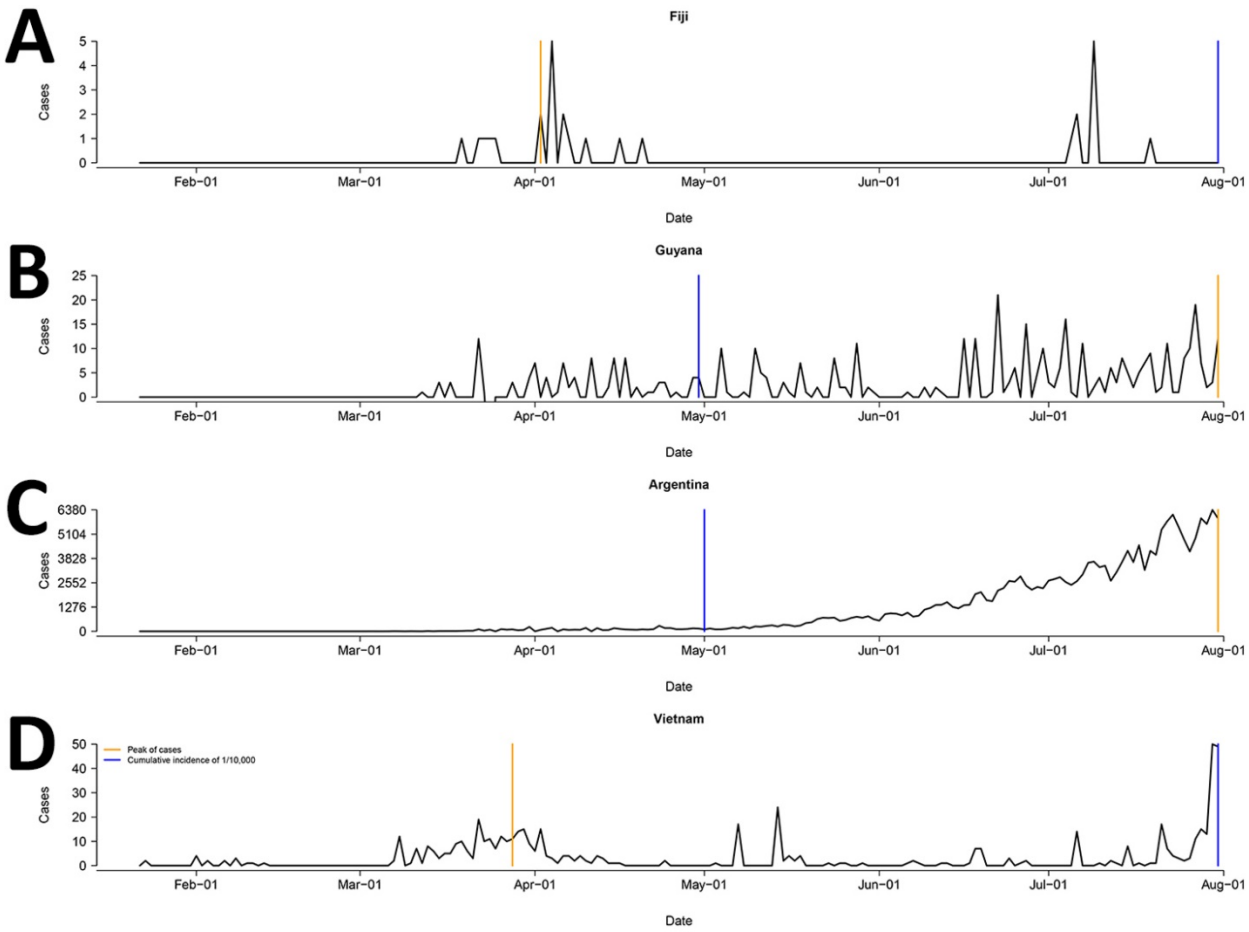
Appendix Figure 3. Distribution of times from enactment of international travel controls to local COVID-19 epidemic progression, as measured by the time of the first reported case (A), first epidemic peak of cases (B), first epidemic peak of deaths (C), reached 0.2 case per 10,000 (D), reached 1 case per 10,000 (E) and reached 5 cases per 10,000 (F).



Appendix Figure 4. COVID-19 epidemic milestones for 165 countries: first epidemic peak of cases (A); first epidemic peak of deaths (B); cumulative incidence reached 0.2 COVID-19 case per 10,000 persons (C); cumulative incidence reached 1 COVID-19 case per 10,000 persons (D); and cumulative incidence reached 5 COVID-19 cases per 10,000 persons (E). Count of countries is shown on the y-axis.



Appendix Figure 5. Association between international travel restrictions and local COVID-19 outbreaks in 165 countries, 1 January to 31 July, 2020. Countries were stratified by the start time of any (A-E) or the strongest (F-J) international travel controls. Columns from left to right were results from analyses that used endpoint of the peak of COVID-19 cases (A, F), the peak of COVID-19 deaths (B, G), reaching cumulative incidence of 0.2 per 10,000 (C, H), reaching cumulative incidence of 1 per 10,000 (D, I) and reaching cumulative incidence of 5 per 10,000 (E, J). Vertical dashed and dotted lines represent the time of Wuhan lockdown and the declaration of pandemic, respectively.



Appendix Figure 6. Representative countries for measuring local COVID-19 outbreak progression.