Number of International Arrivals Predicts Severity of the first Global Wave of the COVID-19 Pandemic

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ABSTRACT

Background: Reported death rates from different countries during the COVID-19 pandemic vary. Lack of universal testing and death underreporting make between-country comparisons difficult. The country-level determinants of COVID-19 mortality are unknown.

Objective: Derive a measure of COVID-related death rates that is comparable across countries and identify its country-level predictors.

Methods: An ecological study design of publicly available data was employed. Countries reporting >25 COVID-related deaths until 01/05/2020 were included. The outcome was the mean mortality rate from COVID-19, an estimate of the country-level daily increase in reported deaths during the ascending phase of the epidemic curve. Potential predictors assessed were most recently published Demographic parameters (population and population density, percentage population living in urban areas, median age, average body mass index, smoking prevalence), Economic parameters (Gross Domestic Product per capita; environmental parameters: pollution levels, mean temperature (January-April)), co-morbidities (prevalence of diabetes, hypertension and cancer), health systems parameters (WHO Health Index and hospital beds per 10,000 population and international arrivals). Multivariable linear regression was used to analyse the data.

Results: Thirty-one countries were included. Of all country-level predictors included in the multivariable model, only total number of international arrivals was significantly associated with the mean death rate: Beta 0.3798 (95% Confidence Interval 0.2414, 0.5182), P <0.001.

Conclusion: International travel was directly associated with the mortality slope and thus potentially the spread of COVID-19. Stopping international travel, particularly from affected areas, may be the most effective strategy to control COVID outbreak and prevent related deaths.
INTRODUCTION

The atypical pneumonia caused by novel corona virus (SARS-CoV 2) detected in Wuhan, Hubei province, China at the end of 2019 has subsequently spread across five continents at a remarkable speed, with Europe and North America being the most affected regions of the world. The World Health Organisation (WHO) declared COVID-19 to be a pandemic of proportions similar to the Spanish Influenza of 1918. As of the 1st May 2020, there have been over 224,172 deaths related to COVID-19 infection worldwide.¹

Data collated from across the world suggest that the overall case fatality rate is around 7%, with country-level estimates ranging between 0.5-14%.² These figures however are not useful for universal comparison as testing rates also vary by country and there is a lag phase in reported deaths that occur in the community. Consequently, there is wide variation in the reported country-specific death rates which may be attributed to variation in testing rates, underreporting or real differences in environmental, sociodemographic and health system parameters.

The only previous ecological study to date assessing country-level predictors of the severity of the COVID-19 pandemic including data on 65 countries³ has found that the cumulative number of infected patients in each country was directly associated with the case fatality rate, whilst testing intensity was inversely associated with case fatality rate. This study found no association between health expenditure and case fatality rate. However, other important country-level predictors were not evaluated and thus their relationship with pandemic severity remains unknown.

Several risk factors for COVID-related mortality have been proposed, including older population,⁴ higher population co-morbid burden,⁵ smoking,⁶ obesity,⁷ pollution levels⁸ and healthcare system performance.⁹ Furthermore, countries outside China most severely hit by
the pandemic were those with a high income, high GDP per capita and well-established healthcare systems, such as Italy, Spain, France, the United Kingdom and the United States. In contrast, lower- and middle-income countries reported much lower COVID-19 incidence and mortality rates. Whilst these differences may be attributable to case under-reporting due to inadequate testing facilities in poorer countries, other factors may also be involved.

In this study, we aimed to derive a comparable measure of COVID related death rates. In addition, we aimed to assess the determinants for this measure by examining the association between potential country level determinants driven by hypothesis based on currently available evidence and this measure using country level publicly available data and an ecological study design.
METHODS

Study Design

An ecological study design was used. The chosen outcome was the steepness of the ascending curve of country specific daily reports of COVID related deaths from January to 1\textsuperscript{st} May 2020. The following predictors were used: demographic predictors (population and population density, percentage population living in urban areas, median age, average body mass index (BMI), smoking prevalence), economic predictors (gross Domestic Product (GDP) per capita), environmental predictors (pollution levels, mean temperature (January-April) [2010-2016]), prevalent co-morbidities (diabetes, hypertension and cancer), health systems predictors (WHO Health Index and hospital beds per 10,000 population) and international arrivals, as a proxy measure of the globalisation status of each country.

Ethics Committee Approval

Given the study design and the use of publicly available data, no ethical approval was necessary.

Selection criteria

Countries reporting at least 25 daily deaths up to the 1\textsuperscript{st} of May 2020 with available data for all chose predictors were included. A total of 31 countries were included in the analysis: Algeria, Austria, Belgium, Brazil, Canada, the Dominican Republic, Ecuador, Egypt, Finland, France, Germany, Hungary, India, Indonesia, Ireland, Italy, Japan, Mexico, the Netherlands, Peru, the Philippines, Poland, Portugal, Romania, the Russian Federation, Spain, Sweden, Switzerland, Turkey, the United Kingdom and the United States.

Data Sources
Country-level parameters were obtained from freely accessible data sources. The daily reported number of COVID-19 cases and deaths between 31\textsuperscript{st} of December 2019 and 1\textsuperscript{st} of May 2020 as well as the 2018 population data were extracted from the European Centre for Disease Control.\textsuperscript{11}

The data regarding the median population age and population density were extracted from the United Nations World Population Prospects\textsuperscript{12} and United Nations Statistics Division, respectively.\textsuperscript{13} The data regarding the percentage of the population living in urban areas were extracted from the World Urbanisation Prospects, issued by the United Nations Population Division.\textsuperscript{14} Temperature data were extracted from the Climate Change Knowledge Portal from the World Bank Group.\textsuperscript{15} Prevalent diabetes, gross domestic product, international arrivals in 2018, and current health expenditure data were extracted from the World Development Indicators (WDI) database, provided by the World Bank Group.\textsuperscript{16} Prevalent cancers data were extracted from the Our World in Data and the Sustainable Development Goals (SDG) tracker,\textsuperscript{17} an open-access publication tracking global progress to the United Nations Sustainable Development Goals for global development, adopted in September 2015. Prevalent hypertension, body mass index (BMI), cigarette smoking and ambient air pollution data were obtained from the Global Health Observatory (GHO) data repository of the World Health Organization.\textsuperscript{18} The world health organisation health index was extracted from the WHO Global Partnership for Education (GPE) paper series published in 2000.\textsuperscript{19} Country-level total hospital beds per 10,000 population data were extracted from the World Bank Dataset “World Bank Indicators of Interest to the COVID-19 Outbreak”.\textsuperscript{20}

**Definition of outcome and predictors**
Outcome

Whilst previous ecological studies of other epidemics have utilised case or death counts as outcome, these variables may be prone to bias due to variations in country level control measures including different testing strategies, variations in population movement controls and differences in secondary attack rates within community cohorts. The mean mortality rate was thus chosen as outcome instead, since it is independent of these highly variable parameters and may thus represent a more reliable indicator of the country-level severity of the COVID-19 pandemic.

Mean mortality rate was defined as the slope of the mean mortality curve (Figure 1), measured from the first day when more than 2 COVID-19 deaths were reported until either the mortality curve reached a peak value or the 1st of May 2020, whichever occurred first. Before slope calculation, the mortality curve in each country was smoothed using a locally weighted (Lowess) regression using a bandwidth of 0.4. In order to ensure a good fit of the Lowess regression line, only countries having reported at least 25 daily deaths until the 1st of May 2020 were included. The mean mortality rate thus represents an estimate of the country-level daily increase in reported deaths during the ascending phase of the epidemic curve.

Predictors

Data on population density were extracted as the country-level population per square kilometre in 2019. Data on ambient air pollution were extracted as the country-level mean concentration of fine particulate matter (PM2.5) measured in 2016. Temperature data were extracted as the mean temperature recorded in each country between January and April between 2010 and 2016. Data on International Arrivals were extracted as the total number of country-level international arrivals in 2018.
Data on prevalent diabetes were extracted as the percentage of the population aged 20 to 79 years in 2019. Data on prevalent cancers were extracted as the age-standardized cancer prevalence among both sexes in 2017, expressed as percentages. Data on prevalent hypertension were extracted as the age-standardised percentage of the population over 18 years of age with systolic blood pressure ≥140 mmHg or diastolic blood pressure ≥90 mmHg in 2015. Data on BMI were extracted as the age-standardised mean body mass index trend estimates for both sexes amongst adults (≥18 years) in 2016. Data on daily cigarette smoking were extracted as the age-standardised rate on both sexes amongst adults (≥18 years) in 2013. Whilst the definition of “daily cigarette smoking” varies across surveys, it habitually refers to current smoking of cigarettes at least once a day.

Data on GDP were extracted as GDP per capita by Purchasing Power Parity (PPP) in current international dollars in 2018. The percentage of population living in urban areas was defined as the percentage of de facto population living in areas classified as urban according to the criteria used by each area or country. The World Health Organisation (WHO) health index is a composite index that aims to evaluate a given countries healthcare system performance relative to the maximum it could achieve given its level of resources and non-healthcare system determinants. It was calculated in the year 2000. The index uses five weighted parameters: overall or average disability-adjusted life expectancy (25%), distribution or equality of disability-adjusted life expectancy (25%), overall or average healthcare system responsiveness (including speed of provision and quality of amenities; 12.5%), distribution or equality of healthcare system responsiveness (12.5%) and healthcare expenditure (25%). Data on hospital beds per 10,000 population were defined by the World Bank as including “inpatient beds available in public, private, general, and specialized
hospitals and rehabilitation centers. The published data for countries included was from 2000 to 2017. In most cases beds for both acute and chronic care are included.\textsuperscript{20}

**Statistical analysis**

All analyses were performed in Stata 15.1SE, Stata Statistical Software. A 5% threshold of statistical significance was utilised for all analyses ($P < 0.05$). Linear regression was performed to assess the univariable relationship between each country-level predictor and the calculated mean mortality rate for each country. The following predictors were included in the univariable analyses: population in 2018, median age, pollution levels, mean temperature (January-April), international arrivals, population density, prevalent diabetes, prevalent neoplasms, median BMI, prevalent hypertension, smoking prevalence, hospital beds (per 10,000 population), WHO health index, percentage population living in urban areas and GDP per capita (PPP). Predictors reaching a $P$-value <0.3 at univariable level were then included in a multivariable logistic regression model to predict the mean mortality rate outcome: median age, pollution levels, international arrivals, prevalent neoplasms, median BMI, prevalent hypertension, WHO health index, percentage of population living in urban areas and GDP per capita.

**RESULTS**

Table 1 and Supplementary File 1 detail the analysed data for the 31 included countries, including the calculated mean mortality rates. The mean mortality rates ranged between 0.01 (Japan) and 52.26 (the United States). Most included countries had a mean mortality rate <10 new daily deaths. Only five included countries had a mean mortality rate >20: the United States (52.26), Spain (34.90), the United Kingdom (27.64), France (25.61) and Italy (21.67).
Table 2 details the results of the linear regression analyses. The following country-level predictors showed a statistically significant relationship with mean mortality rate at univariable level: international arrivals in 2018 (beta (95% confidence interval) = 0.4060 (0.2956, 0.5163), $P <0.001$), prevalent neoplasms (5.6603 (2.4890, 8.8315), $P = 0.002$) and prevalent hypertension (-1.1013 (-1.9963, -0.2064), $P = 0.022$). The multivariable model included the following predictors, which were selected from univariable models: median age, pollution levels, international arrivals, prevalent neoplasms, median BMI, prevalent hypertension, WHO health index, percentage of population living in urban areas and GDP per capita. International arrivals in 2018 was the only statistically significant predictor of mean mortality rate (0.3798 (0.2414, 0.5182) for 1 million increase in international arrivals, $P <0.001$) out of the nine country-level predictors included in the multivariable model. The multivariable linear regression model accounted for 75.7% of the variability in mean mortality rate ($R^2 = 0.7565$). Figures 2 and 3 detail the relationship between the country-level mean mortality rate (predicted and observed) and each country-level predictor included in the multivariable regression model.

**DISCUSSION**

**Principal findings**

In this ecological study including data from 31 countries which were most severely affected by COVID-19 in the first wave of current Global pandemic, we assessed 14 country-level socioeconomic, environmental, health and healthcare system, and globalisation parameters as potential predictors of variation in death rates from COVID 19 infection. In the multivariable linear regression model, the only predictor that reached statistical significance was international arrivals, a proxy of global connection.
**Comparison with literature.**

A recently published ecological study analysed the country-level predictors of the case fatality rate of the COVID-19 pandemic using data from 65 countries. This study found that upon adjustment for epidemic age, health expenditure and world region, the case fatality rate was significantly associated with increasing cumulative number of COVID-19 cases and decreasing testing intensity. Nevertheless, no other country-level predictors were included in this study.

Further comparisons can nevertheless be made with data from previous respiratory virus pandemics. Nikolopoulos et al reported a negative association between health expenditure and death rates from the 2009 influenza pandemic in 30 European countries. Several other previous studies have also reported associations between airline travel and spread of the H1N1 influenza virus infection.

Comorbidities may account for differences in mortality rates across countries. A study among laboratory-confirmed cases of COVID-19 in China showed that patients with any comorbidity, including diabetes, malignancy and hypertension, had poorer clinical outcomes than those without. We thus accounted for country-level data on a selection of key comorbidities in our analysis which included prevalent diabetes mellitus, neoplasms, and hypertension. Diabetes mellitus is significantly associated with all-cause and cardiovascular disease mortality globally. BMI ≥ 40kg/m² has been identified as an independent risk factor for severe COVID-19 illness. Finally, a recent systematic review on 5 studies from China showed that smoking is likely associated with negative outcomes and progression of COVID-19.
Interpretation of findings.

In our multivariate model, the only significant predictor for mortality was international arrivals. Travel restrictions and their effectiveness in containing respiratory virus pandemics remains a contentious subject. In 2007 the WHO published a protocol on ‘rapid operations to contain the initial emergence of pandemic influenza’, which included recommendations on travel restrictions. However, subsequent guidance advises such restrictions are not recommended once a virus has spread significantly. A recent systematic review of 23 studies that assessed the effectiveness of internal and international travel restrictions in the containment of influenza demonstrated limited impact from these restrictions. They found that internal travel restrictions delayed pandemic peak by approximately 1.5 weeks, that 90% air travel restriction delayed the spread of pandemics by approximately 3–4 weeks but only reduced attack rates by less than 0.02% and that social and economic impacts need to be evaluated. However, a systematic review of combination strategies for pandemic influenza response showed that combination strategies including travel restrictions increased the effectiveness of individual policies.

The WHO recommendations for pandemic preparedness and resilience recommends that points of entry into the country should be monitored by focusing on surveillance and risk communication to travellers but falls short of closing down international travel. Interestingly, during the COVID-19 pandemic, some countries (such as Thailand) have adopted aggressive international travel screening and isolation policies, which may have led to lower infection rates. Our study suggests that travel restrictions have the potential to influence the impact of the COVID-19 pandemic and should be part of a structured and rapidly instigated pandemic preparedness plan. Any policy on the restriction of international
travel should be developed taking into account the economic and social impacts of such restrictions.

**Strengths and Limitations.**

The main strength of this study lies in its use of comparable and relevant outcome data derived from contemporary death reporting from countries affected by COVID-19. As testing rates for the virus vary across countries, the incidence or prevalence of the disease cannot be compared between countries. While death from the disease is a hard outcome, the denominator information to calculate death rates make between-country comparisons difficult. In addition, the deaths in the community, particularly in the elderly living in care homes, often go untested and thus firm diagnosis remains impossible. Therefore, in this study we have adopted an outcome that is comparable in terms of the increase in the rate of death, rather than death rates per se. Therefore, this may better represent the spread and seriousness of pandemic in individual countries when comparing countries at different stages of the pandemic. The country-level parameters assessed as potential predictors have all been implicated at some point to be associated with severity and consequently mortality. We however found that the only significant predictor to be total number of international arrivals in the country (2018 figures), signifying transmission of the infection through travel. Although the data was from 2018, there is no reason to believe that international travel figures between countries would be different in early 2020. Our model had a reasonably good fit to the data, explaining around 77% of the between country variation in mean death rates.

The main limitation of the study stems from the ecological study design. Despite the fact that we did not find any association between comorbidities such as diabetes, cancer
and hypertension and the mean death rates at country level, it is possible for an individual with any or all of these comorbid conditions to be more susceptible to the infection and consequently at increased risk of dying. Only including countries that had reported at least 25 deaths reduced our sample and consequently the power. This may also result in the regression model overfitting the data. Other explanatory variables associated with COVID-19 related mortality may have been missed and some of the covariate data used in our model predates the COVID outbreak and may not be relevant at this time point. Furthermore, as new countries are affected by the epidemic, the virulence of the virus and resistance of the human body may have changed over time which was not accounted for in our model. Lastly, it is possible that the quality of data, especially underreporting of deaths, may have been associated with some of the predictors in our model and thus biased our results.

CONCLUSION

Out of all the country-level parameters assessed, international travel was the only significant predictor of the severity of the first global wave of the COVID-19 pandemic. Given that many of world middle and lower-income countries are showing signs of continued rise in infection rates, international travel restrictions applied early in the pandemic course may be an effective measure to avoid rapidly increasing infection and death rates globally.
CONTRIBUTORSHIP

PKM and SB conceived the idea. TAP, DTG, ZP, WAS, JAP collected data and performed literature search. TAP, PKM, DJM and SB developed analysis plan. TAP analysed the data under supervision of DJM. TAP and SB drafted the paper. All authors contributed to the interpretation of results and in making an important intellectual contribution to the manuscript. All authors read and approved the final manuscript.

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CONFLICTS OF INTEREST

None.

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Tables

**Table 1.** Observed mean mortality rate and number of international arrivals in 2018 (millions) for each country included in the analyses. Countries were categorised in 3 groups: high mean mortality rate group (>20 additional daily deaths), medium mean mortality rate group (2-20 additional daily deaths) and low mean mortality rate group (<2 additional daily deaths).

| Country Name                  | Mean Mortality Rate (daily increase in deaths) [up to 01/05/20] | International Arrivals (millions) [2018] |
|------------------------------|-----------------------------------------------------------------|------------------------------------------|
| **High Mean Mortality Rate**  |                                                                 |                                          |
| United States of America     | 52.26                                                           | 79.75                                    |
| Spain                        | 34.90                                                           | 82.77                                    |
| United Kingdom               | 27.64                                                           | 36.32                                    |
| France                       | 25.61                                                           | 89.32                                    |
| Italy                        | 21.67                                                           | 61.57                                    |
| **Medium Mean Mortality Rate** |                                                               |                                          |
| Brazil                       | 10.71                                                           | 6.62                                     |
| Belgium                      | 9.65                                                            | 9.12                                     |
| Germany                      | 7.21                                                            | 38.88                                    |
| Netherlands                  | 6.47                                                            | 18.78                                    |
| Mexico                       | 4.30                                                            | 41.31                                    |
| Canada                       | 3.69                                                            | 21.13                                    |
| Turkey                       | 3.69                                                            | 45.77                                    |
| Russian Federation           | 3.19                                                            | 24.55                                    |
| Peru                         | 3.15                                                            | 4.42                                     |
| Sweden                       | 3.00                                                            | 7.44                                     |
| **Low Mean Mortality Rate**   |                                                                 |                                          |
| India                        | 1.86                                                            | 17.42                                    |
| Switzerland                  | 1.82                                                            | 10.36                                    |
| Ireland                      | 1.64                                                            | 10.93                                    |
| Algeria                      | 1.37                                                            | 2.66                                     |
| Portugal                     | 1.25                                                            | 16.19                                    |
| Romania                      | 1.00                                                            | 11.72                                    |
| Ecuador                      | 0.98                                                            | 2.54                                     |
| Poland                       | 0.93                                                            | 19.62                                    |
| Indonesia                    | 0.91                                                            | 15.81                                    |
| Austria                      | 0.78                                                            | 30.82                                    |
| Philippines                  | 0.62                                                            | 7.17                                     |
| Dominican Republic           | 0.61                                                            | 6.57                                     |
| Finland                      | 0.52                                                            | 3.22                                     |
| Egypt                        | 0.48                                                            | 11.20                                    |
| Hungary                      | 0.45                                                            | 17.55                                    |
| Japan | 0.01 | 31.19 |
Table 2. Results of the linear regression assessing the country-level predictors of the daily increase in deaths. The predictors achieving a 30% statistical significance level at univariable levels ($P < 0.3$) were included in the multivariable model.

| Predictor                                      | Univariable | Multivariable |
|------------------------------------------------|-------------|---------------|
|                                                | Coefficient (95% CI) | P value | Coefficient (95% CI) | P value |
| Population (10 million increase) [2018]         | 0.0306 (-0.1519, 0.2132) | 0.745 | - | - |
| Median age                                      | 0.4126 (-0.1826, 1.0077) | 0.185 | -0.3384 (-1.1747, 0.4979) | 0.410 |
| Pollution levels                                | -0.1735 (-0.4358, 0.0888) | 0.205 | -0.0754 (-0.3191, 0.1684) | 0.527 |
| Mean Temperature (January-April) [2010-2016]    | -0.1194 (-0.4792, 0.2404) | 0.521 | - | - |
| International Arrivals (1 million increase) [2018] | **0.4060 (0.2956, 0.5163)** | <0.001 | **0.3798 (0.2414, 0.5182)** | <0.001 |
| Population Density                              | -0.0045 (-0.0365, 0.0276) | 0.787 | - | - |
| Diabetes prevalence (% of population ages 20 to 79) [2019] | -0.0870 (-1.5605, 1.3865) | 0.909 | - | - |
| Prevalence - Neoplasms - Sex: Both - Age: Age-standardized (Percent) (%) [2017] | **5.6603 (2.4890, 8.8315)** | **0.002** | 3.1323 (-1.5069, 7.7714) | 0.175 |
| Median BMI                                      | 1.6387 (-0.9172, 4.1946) | 0.219 | 0.4291 (-1.4926, 2.3508) | 0.647 |
| Prevalent Hypertension (%), [2015]              | **-1.1013 (-1.9963, -0.2064)** | **0.022** | -0.2588 (-1.2957, 0.7780) | 0.609 |
| Smoking prevalence, 2016 total (ages 15+)       | 0.1512 (-0.3796, 0.6819) | 0.581 | - | - |
| Hospital beds (per 10,000 population)           | -0.0280 (-0.1820, 0.1260) | 0.724 | - | - |
| WHO health index, [2000]                        | 28.6444 (-1.1255, 58.4144) | 0.069 | -9.7157 (-43.9728, 24.5414) | 0.562 |
| Population living in urban areas (%)            | 0.2660 (-0.0180, 0.5501) | 0.077 | 0.0214 (-0.2850, 0.3278) | 0.886 |
| GDP per capita, PPP ($1000 increase), [2018]    | 0.1968 (-0.0192, 0.4127) | 0.085 | -0.0140 (-0.3099, 0.2818) | 0.922 |

$R^2$ for multivariable linear regression = 0.7565

BMI – body mass index; WHO – world health organisation; GDP – gross domestic product; PPP – purchasing power parity;
Figure 1. Graphical representation of the smoothed* number of daily deaths of each country (before reaching mortality peak, if applicable) as a function of the number of days passed since the first day when an excess of 3 deaths were reported. Countries with higher mortality rates are depicted in blue, while those with lower mortality rates are depicted in red.

*smoothed using a local regression (lowess) function with a bandwidth of 0.4
Figure 2. Predicted (based on the results of the multivariable linear regression) and observed country-level mortality rate (mean daily increase in deaths until the peak in mortality) as a function of the recorded country-level number of international arrivals in 2018 (millions).
**Figure 3.** Predicted (based on the results of the multivariable linear regression) and observed country-level mortality rate (mean daily increase in deaths until the peak in mortality) as a function of each country-level predictor included in the multivariable model, except for international arrivals in 2018 (see *Figure 2*).