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Covid-19 mortality and local burden of infectious diseases: A worldwide country-by-country analysis

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Abstract

Background: Global differences in the Covid-19 death toll between various countries are still a matter of debate. We evaluated the potential influence of general burden of infectious diseases prior to the onset of the Covid-19 pandemic on the number of Covid-19 deaths during the pandemic.

Methods: We used publicly available data from Worldometer and Our World in Data. In a complete case analysis, 178 countries and territories, where all parameters were available, entered the analysis, representing 99.02% of the global population. Relationships between various parameters of the local burden of infectious diseases as well as childhood mortality, median age, and vaccination as independent variables, on Covid-19 deaths as the dependent variable, were evaluated.

Results: Death from diarrheal disease, respiratory disease, pneumonia, pneumonia in childhood, malaria, and HIV, as well as childhood mortality correlated negatively with number of Covid-19 deaths (Spearman rank correlation test: p < 0.0001 for each parameter), while median age was positively correlated with Covid-19 deaths (p < 0.0001). In a multivariable approach using kernel functions, death from respiratory disease and median age retained statistical significance. When vaccination rate and median age were simultaneously taken into account, vaccination rate showed a significant negative correlation with Covid-19 deaths.

Conclusions: Local burden of infectious diseases as well as childhood mortality prior to the onset of the pandemic have a strikingly negative impact on Covid-19 deaths. This effect might be due to an increase in trained immunity and to the overall younger population. Vaccination appears as an effective preventive measure.

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Introduction

COVID-19 caused by SARS-CoV-2 was declared as pandemic by the World Health Organization (WHO) on 11 March 2020 resulting in 439 million cases and 5.98 million deaths [1]. The burden of cases and deaths varied across continents and countries [2]. Various reasons for differences in cases and risk factors for outcome of COVID-19 were investigated including demographic features, comorbidities, socioeconomic and environmental factors, vaccination rates, acquired immunity by SARS-CoV-2 infections or vaccinations, occurrence of SARS-CoV-2 variants, governmental measures including social distancing, lock downs, masks, contact tracing and availability of treatment options [3–6]. Various demographic factors including socioeconomic status, household composition, environmental factors as well as race/ethnicity were significantly associated with COVID-19 incidence and mortality [4,7]. It remained unclear whether biological or socioeconomic features caused COVID-19 outcome disparities of different ethnicities [4].

Trained innate immunity has recently been suggested to influence COVID-19 resistance and thus outcome of COVID-19 cases [8]. The concept of trained innate immunity with heterologous protection against (secondary) infections is built on functional reprogramming of innate immune cells by previous infections, contact to microorganisms (including Bacillus Calmette-Guérin (BCG)) or their structures including lipopolysaccharides and beta-γ-glucans [9,10]. The assumption of COVID-19 outcome modulation by trained innate immunity was supported by a negative association of BCG vaccination rates and COVID-19 mortality [11].

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If trained immunity as explained above would in fact confer some degree of resistance to a severe course of Covid-19, then countries with a high frequency of various infectious diseases being endemic in their population should have fewer Covid-19 deaths than countries without such previous burden of infections. We hypothesized that continuous exposure to infectious diseases might trigger a higher resistance to COVID-19 and modulates adverse outcomes. We therefore investigated whether the local burden of infectious diseases assessed by comparable surrogate parameters as well as childhood mortality, age and vaccination rates in different countries influence the outcome of COVID-19.

Material and methods

Data collection

The study was based on publicly available data. The primary list of countries and the population per country were retrieved from the Worldometer homepage [12], listing a total of 235 countries and territories. All other data referring to Covid-19 epidemics, vaccination, and burden of infectious diseases were retrieved from Our World in Data [13]. The authors of this database explain that they “track the impact of the pandemic across our publication and … built country profiles for 207 countries to study in depth the statistics on the coronavirus pandemic” [13]. The data are updated daily and rely on information from Johns Hopkins University. In particular, we retrieved data about death from diarrheal disease [14], respiratory disease [15], malaria [16], pneumonia [17], pneumonia in childhood [17], and HIV/AIDS [18]. Additionally, we collected data on childhood mortality [19]. Covid-19-specific data comprised cumulative death due to Covid-19 [13] and data on Covid-19 vaccination [13]. Median age was also retrieved from Our World in Data as “an important single indicator of the age distribution of a population” [20].

From the 235 countries and territories, all entries were removed where at least one of the variables was missing. This procedure left 178 countries and territories available for a complete case analysis, which comprised 99.02% of total world population.

Parameter definitions

The parameters rely on the Our World in Data data set. Reported annual death rates of several conditions served as surrogate markers of burden of infection. In particular, death from diarrheal disease, respiratory disease, pneumonia, pneumonia in childhood (under 5 years of age), malaria, and HIV/AIDS is given as the annual number of deaths per 100,000 people in 2019. Childhood mortality was defined as the percentage of children dying before 5 years of age. Size of population is given in millions (year 2022), and median age in years (year 2020). Death from Covid-19 was given as cumulative number of deaths per million people during the pandemic (up to February 10, 2022). Vaccination was calculated as the share of people having received a full initial course of a Covid-19 vaccine until February 10, 2022, irrespective of the time when the doses had been administered.

Statistical analysis

Statistical analysis was performed using STATA statistical program version 17 (STATA Corp., College Station, TX, USA). Descriptive statistics comprised mean, standard deviation, median and range. Relationships between parameters were assessed using Spearman’s rank correlation test for univariable analysis. Univariable analysis was additionally done by non-parametric regression analysis using kernel functions. The latter was also used for multivariable analysis. A two-tailed p of < 0.05 was considered to indicate statistical significance.

Results

Geographical distribution

Complete data were available from 178 countries, with a total population of 7718.942 million. This comprises 90.02% of the global population of 7795.233 million people. The countries investigated were distributed throughout all continents, with the highest number of countries in Africa (52) and the lowest number in Australia and Oceania (7; Table 1).

Range of infectious disease burden

The highest number of death from infectious diseases was found for death from pneumonia in childhood, followed by death from pneumonia in the total population and death from chronic respiratory disease (which need not necessarily be due to infection). Death from diarrheal disease, HIV/AIDS and from malaria was less common. Remarkably, there was a very broad variation between countries for all parameters, with HIV/AIDS being the most extreme example with a range from 0.04 to 581.4 deaths per 100,000 population per year. An additional remarkable finding is the wide disparity of median age, ranging from 15.1 to 48.2 years (Table 2). Table 3 shows the five countries with the lowest and highest values, respectively, for each parameter.

Correlation of parameters of infectious disease burden

There was a very strong positive correlation between all parameters of infectious disease burden, with values of Spearman’s rho ranging from 0.4119 between death from respiratory disease and HIV/AIDS, up to 0.9248 between death from pneumonia in childhood and childhood mortality (Table 4), indicating that pneumonia is one of the most important causes of childhood mortality. All these correlations were statistically highly significant (p = 0.0000) indicating

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**Table 1**

Geographic localization of 178 countries and territories with availability of complete data.

| No. (%) of countries/territories |
|----------------------------------|
| Africa                           |
| Asia                             |
| Europe                           |
| North America                    |
| South America                    |
| Australia and Oceania            |
| Total                            |

**Table 2**

Basic statistics of the individual countries and territories included in the analysis (n = 178).

| Parameter                                      |(mean ± standard deviation) | (median (range)) |
|------------------------------------------------|-----------------------------|------------------|
| Covid-19 mortality                             | 1064.1 ± 1189.1             | 629.6 (3.1–6221.2) |
| Death from diarrheal disease                   | 23.5 ± 36.4                 | 3.34 (0.1–226.2)  |
| Death from respiratory disease                 | 40.7 ± 31.7                 | 32.2 (9.32–231.2) |
| Death from pneumonia                           | 49.2 ± 40.8                 | 31.7 (5.2–161.5)  |
| Death from pneumonia in childhood              | 71.2 ± 96.2                 | 28.5 (0.39–412.6) |
| Death from malaria                              | 12.4 ± 27.8                 | 0 (0–146.9)       |
| Death from HIV/AIDS                            | 27.5 ± 68.5                 | 3.6 (0.04–581.4)  |
| Childhood mortality                            | 2.81 ± 2.90                 | 1.6 (0.20–11.72)  |
| Median age                                      | 30.2 ± 9.1                  | 29.4 (15.1–48.2)  |
| Vaccination                                    | 44.6 ± 27.2                 | 46.5 (0.06–93.8)  |
| Population                                     | 43.4 ± 154.0                | 10.0 (0.1–1439.3) |
that all parameters might depend on common social circumstances and sanitary conditions of the various countries. Each parameter of infectious disease burden correlated negatively with median age, with the highest correlation for childhood mortality (\( \rho = -0.9144 \)), and the lowest for HIV/AIDS (\( \rho = -0.6427 \)). Again, all correlations were highly significant (\( p = 0.0000; \) Table 4). Obviously each of these parameters of infectious disease burden contributes to a decreased median age of the particular population.

### Covid-19 deaths and parameters of local infectious burden

Total number of Covid-19 deaths per million people differed widely between countries, ranging from 3.1 (Burundi) to 6222.2 (Peru), with a median of 629.6 (Table 2 and Table 3). In Spearman’s rank correlation analysis, number of Covid-19 deaths correlated negatively with each parameter of infectious disease burden, with the highest absolute value for death from diarrheal disease (\( \rho = -0.6717 \)), and the lowest for the incidence of HIV/AIDS (\( \rho = -0.3981 \)). All these negative correlations were highly significant (\( p = 0.0000; \) Table 5). The results of the rank correlation analysis were qualitatively confirmed by non-parametric regression analysis using kernel functions, though the levels of significance were slightly lower (Table 5). In addition, there was a strong positive correlation between number of Covid-19 deaths and median age of the country population (\( \rho = 0.6952 \)), again with a high level of significance (\( p = 0.0000; \) Table 5). The relationships are visualized in Fig. 1.

When all parameters were taken into account in a multivariable non-parametric regression model using kernel functions, death from respiratory disease (negative correlation with COVID-19 deaths) and median age (positive correlation with COVID-19 deaths) were significant (Table 5).

#### Effect of Covid-19 vaccination

For the analysis of the effect of Covid-19 vaccination, we limited the number of Covid-19-related deaths to the time period from

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**Table 3**

List of countries with lowest and highest values of various parameters: Covid-19 mortality, death from diarrheal disease, death from respiratory disease, death from pneumonia, death from pneumonia in childhood, death from malaria, death from HIV/AIDS, childhood mortality, median age, vaccination, population.

| Ranking | Covid-19 mortality | Death from diarrheal disease | Death from respiratory disease |
|---------|--------------------|-----------------------------|-------------------------------|
| 1.      | Burundi            | Montenegro                  | Montenegro                    |
| 2.      | Vanuatu            | Belarus                     | Latvia                        |
| 3.      | China              | Estonia                     | Estonia                       |
| 4.      | Bhutan             | Slovenia                    | Singapore                     |
| 5.      | Kiribati           | Latvia                      | Japan                         |
| ...     | ...                | ...                         | ...                           |
| 174.    | Montenegro         | South Sudan                 | India                         |
| 175.    | Hungary            | Niger                       | Kiribati                      |
| 176.    | Bosnia and Herzegovina | Somalia              | Solomon Islands               |
| 177.    | Bulgaria           | Chad                        | Papua New Guinea              |
| 178.    | Peru               | Central African Republic    | Nepal                         |

**Death from pneumonia**

| Ranking | Finland | Norway | Germany |
|---------|---------|--------|---------|
| 1.      | 5.20    | 0.54   | 0.87    |
| 2.      | 5.56    | 0.84   | ...     |
| 3.      | ...     | ...    | ...     |
| 174.    | ...     | ...    | ...     |
| 175.    | ...     | ...    | ...     |
| 176.    | ...     | ...    | ...     |
| 177.    | ...     | ...    | ...     |
| 178.    | ...     | ...    | ...     |

**Death from HIV/AIDS**

| Ranking | Bosnia and Herzegovina | Iceland | Slovenia | Cyprus | Montenegro | Finland | Central African Republic | Chad | Burkina Faso | Sierra Leone |
|---------|-------------------------|---------|----------|--------|------------|---------|--------------------------|------|--------------|--------------|
| 1.      | 0.04                    | 0.20    | 0.21     | 0.23   | 0.23       | 0.24    | 0.10                     | 0.92 | 0.28         | 0.87         |
| 2.      | 0.06                    | 0.21    | 0.23     | 0.24   | 0.24       | 0.24    | 0.10                     | 0.92 | 0.28         | 0.87         |
| 3.      | ...                     | ...     | ...      | ...    | ...        | ...     | ...                      | ...  | ...          | ...          |
| 174.    | ...                     | ...     | ...      | ...    | ...        | ...     | ...                      | ...  | ...          | ...          |
| 175.    | ...                     | ...     | ...      | ...    | ...        | ...     | ...                      | ...  | ...          | ...          |
| 176.    | ...                     | ...     | ...      | ...    | ...        | ...     | ...                      | ...  | ...          | ...          |
| 177.    | ...                     | ...     | ...      | ...    | ...        | ...     | ...                      | ...  | ...          | ...          |
| 178.    | ...                     | ...     | ...      | ...    | ...        | ...     | ...                      | ...  | ...          | ...          |

**Population**

| Ranking | Antigua and Barbuda | Seychelles | Saint Vincent and the Grenadines | Grenada | Kiribati | Pakistan | Indonesia | United States | India | China |
|---------|---------------------|------------|----------------------------------|---------|----------|----------|-----------|---------------|-------|-------|
| 1.      | Burundi             | 0.10       | 0.10                             | 0.11    | 0.12     | 0.12     | 0.10      | 0.10         | 0.10  | 0.10  |
| 2.      | Democratic Republic of Congo | 0.23 | 0.23                             | 0.23    | 0.23     | 0.23     | 0.23      | 0.23         | 0.23  | 0.23  |
| 3.      | Chad                | 0.20       | 0.20                             | 0.20    | 0.20     | 0.20     | 0.20      | 0.20         | 0.20  | 0.20  |
| 4.      | Haiti               | 0.21       | 0.21                             | 0.21    | 0.21     | 0.21     | 0.21      | 0.21         | 0.21  | 0.21  |
| 5.      | Yemen               | 0.22       | 0.22                             | 0.22    | 0.22     | 0.22     | 0.22      | 0.22         | 0.22  | 0.22  |
| ...     | ...                 | ...        | ...                              | ...     | ...      | ...      | ...       | ...          | ...   | ...   |
| 174.    | ...                 | ...        | ...                              | ...     | ...      | ...      | ...       | ...          | ...   | ...   |
| 175.    | ...                 | ...        | ...                              | ...     | ...      | ...      | ...       | ...          | ...   | ...   |
| 176.    | ...                 | ...        | ...                              | ...     | ...      | ...      | ...       | ...          | ...   | ...   |
| 177.    | ...                 | ...        | ...                              | ...     | ...      | ...      | ...       | ...          | ...   | ...   |
| 178.    | ...                 | ...        | ...                              | ...     | ...      | ...      | ...       | ...          | ...   | ...   |

* There are 103 countries with 0 cases of death from malaria. The first five countries are listed in alphabetical order.
January 1st, 2021, to February 10th, 2022. The starting point of this period was chosen because a broad rollout of vaccination campaigns had only started after this date, and any vaccination effects can only be evident beyond it.

A positive correlation of Covid-19 deaths of this period with the degree of vaccination was found in univariable analysis (Spearman's rho = 0.4231, p = 0.0000). Non-parametric regression yielded an ambiguous relationship (z = 0.92, p = 0.3588). However, as soon as vaccination and median age were simultaneously accounted for, non-linear regression showed a highly significant negative correlation between Covid-19 deaths and vaccination (z = -3.76, p = 0.0000), with median age remaining positively correlated (z = 0.787, p = 0.0000). The same holds true when all parameters were simultaneously included in the multivariable non-parametric regression model (z = -4.72, p = 0.0000 for vaccination, and z = 4.05, p = 0.0000 for median age).

**Discussion**

Covid-19 deaths markedly varied between countries with the lowest rate in Burundi, Vanuatu and China and highest rates in Bosnia Herzegovina, Bulgaria and Peru. In our analysis, we found that death from diarrheal diseases, respiratory diseases, pneumonia in childhood, malaria, HIV/AIDS as well as childhood mortality were negatively correlated with death from Covid-19 in univariable correlation analyses. In multivariate analysis, death from respiratory diseases was negatively correlated and age was positively correlated with Covid-19 deaths.

Overall, the higher the death toll due to various infectious diseases and also due to chronic respiratory disease was in a particular country before the onset of the Covid-19 pandemic, the lower was the number of Covid-19 deaths during the pandemic. These relationships between Covid-19 mortality on one hand and various indicators of previous disease burden were all highly significant.

The negative correlation between death from respiratory disease and Covid-19 deaths may need special consideration. In our data source respiratory diseases were WHO defined diseases of the airways and of other structures of the lung including chronic obstructive pulmonary disease (COPD), asthma, occupational lung diseases and pulmonary hypertension [21]. Beside frequent lower respiratory infections during childhood tobacco smoke, air pollution, occupational exposure to chemicals and dusts are listed as risk factors for chronic respiratory diseases. Though patients with chronic pulmonary disease are considered to have a higher risk for severe Covid-19 [22], in our data death from all pulmonary disease was inversely related to Covid-19 deaths on a country-by-country level.

There are several hypotheses, which might explain the strong negative associations between infectious disease burden and Covid-19 deaths. At first, there is a close association of each of the disease burden parameters and median age. Frequent and early occurrence of death in a certain population reduces median age, as it is evident from the unambiguous negative correlations of disease burden parameters on one hand and median age on the other. Since age is one of the most important risk factors for Covid-19 mortality [23], the resulting younger population may render a country more resistant against a fatal course of Covid-19. Secondly, people who have survived the perilous exposures to numerous infectious pathogens until adult age may be more resistant against Covid-19 infection. As a third hypothesis, repetitive exposure to infectious agents may trigger non-specific trained immunity [8] and thereby mitigate the course of a subsequent Covid-19 infection. These considerations are in part in accordance with the four hypothesis about the differences in Covid-19 mortality between Central Europe and East Asia as reported by Yamamoto and Bauer [24].
Seasonal effects with different time courses on the northern and southern hemisphere as a confounding factor can be ruled out, since the observation period from the beginning of the pandemic until February 2022 covers roughly two whole years.

At present, our data do not provide evidence in favor or against any of these three hypotheses. Since there is such a strong correlation between all of the parameters investigated, none of them can be identified as the most important or solely responsible factor. It should be particularly emphasized that all parameters of disease burden correlate strongly with high overall childhood mortality, and again with low median age of the population. For these correlations, at least, a causal relationship can be assumed.

In univariable analysis, in fact a high vaccination rate seems to correlate with a high number of Covid-19 deaths across the globe. When, however, median age was additionally taken into account, Covid-19 deaths were positively correlated with increasing median age of the population, but inversely with the vaccination rate per country. Obviously this reflects a global trend with a broader roll-out of vaccination in developed countries with an ageing population, which are per se more susceptible to severe and fatal Covid-19 disease, and low vaccination rates in countries with a high burden of other infectious diseases and a young population, being more resistant against Covid-19 fatalities. So in concordance with previous data we found that vaccination protected from COVID-19 death as

Table 5
Correlation analysis of total number of covid-19 deaths per million and parameters of infectious disease burden and median age. Univariable analysis was performed using spearman rank correlation test and non-parametric regression by kernel functions. The latter was also used for multivariable analysis taking into account all parameters simultaneously (n = 178).

| Covid-19 deaths                      | Spearman rank correlation test | Kernel function univariable | Kernel function multivariable |
|--------------------------------------|--------------------------------|-----------------------------|-----------------------------|
| Death from diarrheal disease        | -0.6717                        | -6.62                       | -0.45                       |
| Death from respiratory disease      | -0.5915                        | -6.89                       | -2.33                       |
| Death from pneumonia                | -0.6817                        | -4.60                       | 0.20                        |
| Death from pneumonia in childhood   | -0.4840                        | -8.81                       | 0.30                        |
| Death from malaria                  | -0.6347                        | -8.73                       | -0.50                       |
| Death from HIV/AIDS                 | -0.3981                        | -6.34                       | -0.25                       |
| Childhood mortality                 | -0.6495                        | -3.13                       | 0.27                        |
| Median age                           | 0.6952                         | 9.72                        | 2.63                        |

Fig. 1. Relationship of total number of Covid-19 deaths and parameters of infectious disease burden and median age, using non-parametric regression analysis with kernel functions. There were significant negative correlations with each parameter of infectious disease burden (A – G), and a positive correlation with median age (H). The quantitative statistical results are given in Table 5.
local vaccination rates were inversely correlated with COVID-19 deaths in a multivariable approach.

We based our analysis on mortality data from a single source – namely Our World in Data –, since these data are widely used. Additionally, keeping strictly to a single data base avoids any arbitrary changes of data, as it would occur, for example, if we would select some data values of particular countries from another source. We are aware that data may be influenced by reporting bias, but judging which data are and which are not would introduce a risk of arbitrary data management. For the same reason, we also did not limit our analysis on a particular subset of countries which supposedly high data reliability, because such a selection could again skew the results.

As to our knowledge, this is the first study evaluating the potential impact of local burden of infectious disease on subsequent COVID-19 mortality in a country-by-country analysis at a global scale. There are, however, several limitations, which have to be taken into account. The publicly available data used in this study largely rely on the reporting by the authorities of the particular countries. Furthermore, Covid-19 mortality has not been analyzed in a stratified approach considering different age groups. Factors like gross domestic product, sanitary conditions and health care facilities, as well as non-pharmacologic and pharmacologic measures have not been considered. The former will have an impact on infectious disease burden before the onset of the Covid-19 pandemic, and the letter may have some influence on the course of the pandemic. Remarkably, a positive correlation of high health care standards and the number of Covid-19 deaths has been observed in the past [4], indicating that both features may have a common cause such as a high gross domestic product and an ageing population. However, the statistically overwhelming inverse correlation of infectious disease burden on one hand and of Covid-19 mortality on the other points to a strong interdependence of these factors. It warrants further studies addressing specifically the underlying mechanisms of this relationship.

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Competing interests

None declared.

Ethical approval

Not required.

Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.jiph.2022.10.018.

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