COMMENTARY
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Deciphering SARS-CoV-2 mortality: H1N1 as an aid

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To the Editor:

The severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) pandemic has globally disrupted contemporary life[1]. It has caused 73,996,237 confirmed cases and 1,663,474 deaths since December 19, 2020, with a global mortality rate of 2.25%[2]. While efforts to understand, cure, and prevent the disease are ongoing, the mortality rate and disease burden imposed by SARS-CoV-2, as well as the appropriateness of pandemic containment measures, are also being discussed[3-5]. To this end, geographic distributions of disease burden and disease-specific mortality are often key to understand disease vulnerabilities, formulate policies, and aid in opinion-making[6].

In this issue of Revista da Associação Médica Brasileira, Kant and colleagues report on their multi-center retrospective experience with 143 patients with H1N1 and 309 patients with SARS-CoV-2 from seven centers in Turkey[7]. Among their pertinent findings related to the clinical profiling of the two diseases, one result is striking: in their hands, H1N1 was more lethal than SARS-CoV-2! In more detail, Kant et al[7]. report that although H1N1 patients required fewer hospitalization days compared with SARS-CoV-2 patients (mean±SD: 4.4±5.7 *versus* 10.9±7.6 days; p<0.001; Mann-Whitney U test), they actually required more intensive care support (H1N1 *versus* SARS-CoV-2: 41 *versus* 18%; p<0.001; χ^2 test), more mechanical ventilatory support (H1N1 *versus* SARS-CoV-2: 28 *versus* 9%; p=0.004; χ^2 test), and succumbed more frequently (H1N1 *versus* SARS-CoV-2 mortality: 8.4 *versus* 3.2%; p=0.004; χ^2 test). Data from Turkey have been properly reported, are plausible, and in accordance with data from the United States reported earlier this year[8].

To put the work of Kant et al.[7] into perspective, the author analyzed current SARS-CoV-2 data and compared them with global H1N1 data obtained after the end of the H1N1 pandemic, in the 27 most heavily affected countries (Table 1)[2,9]. According to the multi-center results provided by Kant et al.[7], nationwide, Turkish H1N1 death rates exceeded by far SARS-CoV-2 death rates, and this is also applicable to 12 other countries including the United States, Spain, and Brazil. However, the opposite was true for 15 other countries that experienced far higher death rates from SARS-CoV-2, such as Mexico, Egypt, China, and Italy. Overall, when the 27 countries that were most affected from both outbreaks were examined, death rates from SARS-CoV-2 and H1N1 were not statistically significantly different (Figure 1A). These data show that the study by Kant et al.[7] is accurate in reflecting the Turkish experience from the two viral outbreaks, and that both pandemics cause comparable mortality, as anticipated for severe viral pneumonias.

But how can the astonishing fact that SARS-CoV-2 is less lethal than H1N1 in at least 12 countries be associated with a response that has been disproportionately greater, with stricter measures, and economic stagnation worldwide and in these countries (including in Brazil and Turkey) due to SARS-CoV-2 as compared to twhe H1N1 outbreak 11 years ago? Table 1 and Figure 1B illustrate the answer, which is the disproportional size of both outbreaks in terms of number of cases and deaths. To this end, H1N1 caused 6.14 million (16 thousand on average) cases and 227 thousand (593 on average) deaths in the 27 countries examined, while SARS-CoV-2 has already caused 56.7 million (1.3 million on average) cases and 2.1 million (47 thousand on average) deaths in the same countries, while the pandemic is still at large. Thus, one can argue that the SARS-CoV-2 outbreak has already taken a ten-fold higher toll than the H1N1 outbreak 11 years ago, underpinning its societal and financial impacts[10].

But what are the determinants of these strikingly different death rates? At a global scale, we have shown earlier this year that SARS-CoV-2 incidence and mortality are linked with economic growth, while H1N1 rates were rather associated with overpopulation

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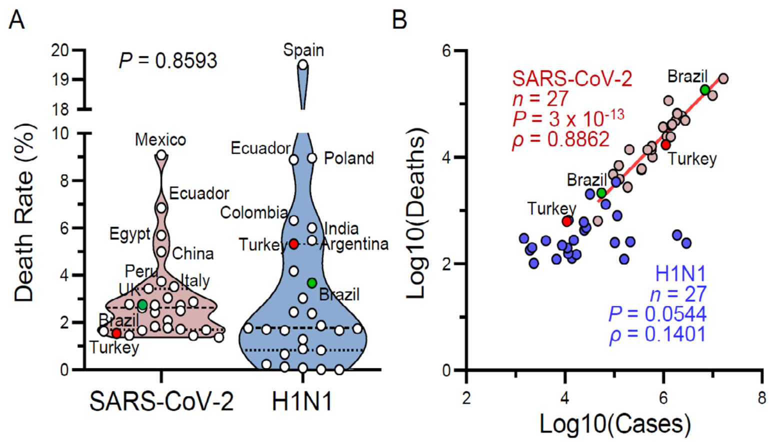
and urbanization, like a true airborne disease[10]. In an elegant recent prospective two-center case-control study, Sesé et al. showed the correlation between poor socioeconomic status and SARS-CoV-2 severity in terms of disease presentation and outcome[11]. It is also well known that co-morbidities largely define SARS-CoV-2 death rates, implying increased vulnerability of high-income countries with elderly populations to SARS-CoV-2[12]. To this end, biomarkers of SARS-CoV-2 susceptibility in elderly patients and populations with cardiovascular, cerebral, and pulmonary co-morbidities have been proposed, including low circulating CD3+CD8+T-cells and cardiac troponin[13]. One cannot overemphasize the importance of such clinical, cellular, and molecular biomarkers of risk, as well as of clinical studies such as that by Kant et al.[7], which will hopefully be considered by policy-makers and their health care advisors during future infectious outbreaks to prevent lockdown measures and economic recession, and to enforce viral containment measures that are more focused and effective.

Table 1: Raw data used for plots shown in Figure 1, expressed as person numbers (n) or percentages (%).

County	WHO Region	SARS-CoV-2 Cases (n)	SARS-CoV-2 Deaths (n)	H1N1 Cases (n)	H1N1 Deaths (n)	SARS-CoV-2 Death Rate (%)	H1N1 Death Rate (%)
Czechia	Europe	602404	10036	2445	102	1.67	4.17
Romania	Europe	571749	13862	7006	122	2.42	1.74
Portugal	Europe	358296	5815	166922	122	1.62	0.07
Saudi Arabia	Eastern Mediterranean	360335	6080	14500	128	1.69	0.88
Greece	Europe	127557	3870	17977	149	3.03	0.83
Chile	Americas	576731	15959	12258	156	2.77	1.27
Poland	Europe	1171854	24345	2024	181	2.08	8.94
Japan	Western Pacific	187103	2739	11636	198	1.46	1.70
Ecuador	Americas	203461	13915	2251	200	6.84	8.89
Peru	Americas	987675	36817	9165	223	3.73	2.43
Italy	Europe	1888144	66537	3064933	244	3.52	0.01
Republic of Korea	Western Pacific	46453	634	107939	250	1.36	0.23
Germany	Europe	1406161	24125	222360	258	1.72	0.12
Colombia	Americas	1444646	39356	4310	272	2.72	6.31
Egypt	Eastern Mediterranean	123153	6990	15812	278	5.68	1.76
Spain	Europe	1773290	48596	1538	300	2.74	19.51
France	Europe	2367648	58989	1980000	344	2.49	0.02
Canada	Americas	475214	13659	25828	429	2.87	1.66
United Kingdom	Europe	1913281	65520	28456	474	3.42	1.67
Russian Federation	Europe	2762668	49151	25339	604	1.78	2.38
Argentina	Americas	1510203	41204	11458	626	2.73	5.46
Turkey	Europe	1113827	17121	12316	656	1.54	5.33
China	Western Pacific	95375	4764	120940	800	5.00	0.66
Mexico	Americas	1267202	115099	70715	1316	9.08	1.86
India	South-East Asia	9956557	144451	33783	2024	1.45	5.99
Brazil	Americas	6970034	182799	58178	2135	2.62	3.67
United States of America	Americas	16446844	301536	113690	3433	1.83	3.02



Stathopoulos GT. Deciphering SARS-CoV-2 mortality: H1N1 as an aid. **Figure 1**

Raw data were from references WHO[2] and Tang et al.[8] and are summarized in Table 1. (A) Case fatality rate (%). Each circle denotes one country (Brazil in green and Turkey in red). Data are shown as rotated kernel density plots (violins) with medians (dashed lines) and quartiles (dotted lines), names of top-affected counties, Turkey and Brazil, and probability (p) by Wilcoxon's matched-pairs signed rank test. (B) Dot plot of number of deaths ***versus*** number of cases. Each circle denotes one country (Brazil in green and Turkey in red). Raw data for SARS-CoV-2 (blue circles and regression line) and H1N1 (red circles) are shown together with Spearman's correlation probabilities (p) and coefficients (ρ). Note the strong correlation between SARS-CoV-2 deaths and cases, which is not evident for H1N1.

Figure 1. Cases and deaths from SARS-CoV-2 and H1N1 in 27 countries.

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