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Why Has COVID-19 Spread More Extensively in Europe than Asia?

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Abstract

It is unclear why European countries have been more severely affected by COVID-19 than East Asian countries. In this ecological study we compared the COVID-19 epidemics (cumulative incidence and mortality rates), host genetic susceptibility and national responses (testing intensity) in all European versus all Western Pacific/East Asian countries reporting cases in the first month of the epidemic. The host-genetic-susceptibility assessment was limited to the frequency of the D-allele of the angiotensin converting enzyme-1 (ACE-1) which has been found to be positively associated with COVID-19 incidence within European countries. Despite earlier epidemics, countries from the Western Pacific reported lower cumulative numbers of COVID-19 cases/100 000 inhabitants than European countries (P=0.0002). The Western Pacific countries also reported fewer cumulative COVID-19 deaths/100 000 (P=0.0024). Whilst there was little difference in the cumulative number of tests conducted/100 000, the percent of COVID-19 tests reported positive was higher in Europe than the Western Pacific (P=0.0076). The frequency of the ACE-1 D-allele was lower in the Western Pacific than European countries (P=0.0007). Our results suggest that a combination of different testing strategies and host genetic susceptibility contribute to difference in severity of the COVID-19 epidemics in the Western Pacific/East Asia and Europe.

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Background

Despite the SARS-CoV-2 virus first emerging and spreading in Asian countries, European countries appear to have experienced more severe COVID-19 epidemics [1-3]. The reasons underpinning this are unknown but of crucial importance in retarding the further spread of this virus [4]. To this end, we compared the COVID-19 epidemics (cumulative incidence and mortality rates), host genetic susceptibility, and national responses (testing intensity) in all European versus all Western Pacific/East Asian countries reporting cases in the first month of the epidemic. The host genetic susceptibility assessment was limited to the frequency of the D-allele of the angiotensin converting enzyme-1 (ACE-1) which has been found to be positively associated with COVID-19 incidence within European countries [5].

Methods

Variables

Start of COVID-19 epidemic. The date the first case of COVID-19 was diagnosed in each country. This data was obtained from the ECDC data repository on 8 April 2020: https://www.ecdc.europa.eu/en/geographical-distribution-2019-ncov-cases

Cases/capita. The cumulative number of cases of COVID-19 infection per 100 000 inhabitants on 8 April 2020 per country. This data was obtained from the World of Meters data repository on 8 April 2020: https://www.worldometers.info/coronavirus/

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Mortality/capita. The COVID-19 attributable mortality per 100 000 inhabitants. This data was obtained from the World of Meters data repository on 8 April 2020: https://www.worldometers.info/coronavirus/

Tests/capita. Cumulative number of nucleic acid amplification SARS CoV-2 tests conducted per country per 100 000 inhabitants up till 8 April 2020. This data was obtained from the World of Meters data repository on 8 April 2020: https://www.worldometers.info/coronavirus/

Test positivity. The proportion of all COVID-19 tests conducted with a reported positive result. This data was obtained from the World of Meters data repository on 8 April 2020: https://www.worldometers.info/coronavirus/

ACE-1 D-allele frequency. Country level ACE-1 D frequencies were taken from a recent publication that provided national estimates for these based on a literature review [6].

WHO regions. Countries were categorized according to the 6 WHO world regions: Americas, Africa, Europe, Eastern Mediterranean, South East Asia and Western Pacific/East Asia: https://www.who.int/choice/demography/by_country/en/

Data analysis

The Wilcoxon rank-sum test was used to compare the values of the variables in Europe and the Western Pacific. The primary analysis was limited to countries who reported COVID-19 cases within the first 28 days of the outbreak. The justifications for

this strategy include the desire to compare similarly aged epidemics. Sensitivity analyses were conducted limiting the analysis to countries whose epidemics were older than 16 March 2020. The most recent data available as of 8 April 2020 was used for all variables. A p-value of < 0.01 was considered statistically significant. The analyses were performed in STATA version 16 (Stata Corp, College Station, Tx).

Results

The first country to report a case was China on 10 January 2020. A total of 28 countries reported cases within 28 days, including 12 from the Western Pacific and 9 from Europe (STable 1). Eight of the Western Pacific countries were amongst the first 10 countries reporting cases whereas 7 European countries were amongst the last 10 countries to report their first case (Fig. 1; STable 1). Despite earlier epidemics, countries from the Western Pacific (WP) reported lower cumulative numbers of COVID-19 cases/100 000 inhabitants than European (EU) countries (WP: median 6.3 [IQR 2.5-16.5] vs. EU: median 130.5 [IQR 81.4-201.9]; P=0.0002; Fig.1). The Western Pacific countries also reported fewer cumulative COVID-19 deaths/100 000 (WP: median 0.2 [IQR 0.07-0.2] vs. EU: median 9.1 [IQR 2.5-19.3]; P=0.0024; Fig.1).

Whilst there was little difference in the cumulative number of tests conducted/100 000 (Fig. 1), the percent of COVID-19 tests reported positive was higher in Europe than the Western Pacific (EU: median 17.9% [IQR 11.9-27.8] vs. WP: median 2.1% [IQR 1.0-7.1]; P=0.0076; Fig.1). The frequency of the ACE-1 D-allele was lower in the Western Pacific than European countries (WP: median 66.2% [IQR 55.5-67.2%] vs. EU median 78.6% [IQR 76.7.0-82.0%]; P=0.0007; Fig. 1).

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The results were similar in the sensitivity analysis limited to countries with epidemics starting prior to 16 March (STable 2).

Discussion

Both in terms of cases and attributable mortality, the COVID-19 epidemics have been larger in Europe than the Western Pacific [1, 2, 7]. A number of explanations are possible. Firstly, differences in testing-intensity, contact tracing and isolation likely play a role [3, 8]. To some extent, our results are compatible with this explanation. Although there was little difference in the number of tests conducted per capita between the two regions, the proportion testing positive was considerably lower in the Western Pacific. This fits with findings of narrative reviews that Western Pacific countries responses typically involved rapid, timeous, large scale screening, contact tracing and isolation early on in their epidemics that resulted in subsequent declines in incidence [3, 8, 9]. Responses in European countries on the other hand tended to be slower, and less intense in terms of screening, contact tracing and isolation [1, 2, 4, 7-10]. This was particularly evident in countries such as Sweden and the United Kingdom [11]. The United Kingdom briefly proposed pursuing a strategy of allowing the controlled spread of SARS-CoV-2 so as to develop 'herd-immunity' [11]. The finding of lower test positivity in Western Pacific is compatible with the theory that intensive testing early on in the epidemics here played an important role in controlling the epidemics here [3, 4].

Secondly, differences in host susceptibility may play a role. One such possibility is the ACE-1 I/D polymorphism which has been shown to account for around 50% of the variation in ACE-1 expression between individuals. The D-allele has been found to be

a risk factor for some of the comorbidities linked to COVID-19 disease severity, such as hypertension, diabetes and cancer [12]. The D-allele has also been shown to be a risk factor for developing acute respiratory distress syndrome (ARDS) from all causes [12, 13]. Since COVID-19 typically progresses to severe disease via an ARDS-type process, this may explain why populations with a high D-allele frequency, such as Europe, have a higher COVID-19 related mortality than Asian populations that have a lower frequency of D-allele.

Thirdly, differences in lock-down, quarantining, social-distancing or face mask usage may play a role. There were however considerable differences in how these strategies were applied in the Western Pacific countries and these strategies have also been applied in European countries [3, 4, 8]. One possible exception is the widespread use of face masks in public which was common in a number of the Western Pacific countries under consideration prior to COVID-19 and which has been noted to be even more widespread in response to COVID-19 [3, 14, 15]. With the recent exceptions of Czechia, Slovakia and Austria, all European national authorities have either not persuaded or actively dissuaded their populations from using face masks in public unless they are symptomatic [14, 15].

Our analysis did not control for the age of the national epidemics, age structure of populations, prevalence of comorbidities and other host or viral genetic differences, all of which may have played a role in differential spread [3]. Furthermore, one should guard against sweeping conclusions so early in a pandemic. It is possible, for example, that subsequent waves of COVID-19 may be more severe in the Western Pacific than Europe. Despite these caveats, the available data reveals an order of magnitude

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difference in incidence and mortality between the countries considered from Europe and Western Pacific. This finding suggests that countries would be best advised to, as far as possible, implement all the components used to successfully control COVID-19 spread in the Western Pacific countries, including the use of face masks in public.

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Authors' contributions

CK conceptualized the study, was responsible for the acquisition, analysis and interpretation of data and wrote the analysis up as a manuscript.

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Conflict of interest

The author declares that he/she has no competing interests.

Ethical approval

The analysis involved a secondary analysis of public access ecological level data. As a result, no ethics approval was necessary.

Informed consent

Not applicable

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Figure 1. Comparison of COVID-19 epidemics and testing intensity by WHO world region in in 28 countries with COVID-19 epidemics starting before 8 February 2020. a) Cumulative number of cases of COVID-19/100 000 (Cases/100 000), b) COVID-19 mortality rate/100 000 inhabitants (Deaths/100 000), c) number tested for COVID-19/100 000 (Tests/100 000), d) percent of the test positive (Test Positive) and e) frequency of D-allele of angiotensin converting enzyme-1(%).

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