Epidemic trends of SARS-CoV-2 modulated by economic activity, ethnicity, and vaccination

Yasuhiko Kamikubo[1] and Atsushi Takahashi[2,3,*]

[1]Department of Human Health Sciences, Graduate School of Medicine, Kyoto University, Sakyo-ku, Kyoto, 606-8507, Japan. [2]Graduate School of Health Science Studies and [3]Research Institute of Health and Welfare, Kibi International University, Takahashi, Okayama 716-8508, Japan.

[1]Graduate School of Health Science Studies and [2]Research Institute of Health and Welfare, Kibi International University, Takahashi, Okayama 716-8508, Japan.

*e-mail: atakah7@kiui.ac.jp

Abstract

The second and third waves of SARS-CoV-2 epidemic have peaked out and vaccination has begun worldwide. However, many mysteries remain unsolved, including the impact of newly emerging SARS-CoV-2 variants, the contribution of economic activities to virus transmission, the factors that divided the success and failure of infection control, and the impact of vaccines on epidemic trends. In this study, ecological studies comparing viral genotypes and epidemiological information revealed that the virus was attenuated in the second wave and that three new variants increased case fatality rate (CFR) of COVID-19 in the third wave. In Russia, the infection was widespread in areas with high gross domestic product (GDP) per capita, such as sparsely populated oil field areas and densely populated metropolitan areas. In New Zealand, COVID-19 CFR, prevalence, and mortality were lower in Māori-rich regions, suggesting a protective effect of Polynesian genes. The vaccines transiently increased SARS-CoV-2 prevalence for several weeks, and when vaccination rates reached about 5% and 30%, respectively, CFR and mortality decreased. It is necessary to understand this prevalence trade-off that occurs in the early stage of vaccination and devise vaccination strategies that minimize the morbidity of individuals before the vaccines are effective. Analysing epidemiological data and using it effectively will be essential to reduce human casualties in the process of converging SARS-CoV-2.

Introduction

The second and third waves of the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2)[1] pandemic peaked out, and vaccines are currently desired to control the epidemic.[2] However, there are many uncertainties, such as the possibility that newly emerging variants will invalidate the vaccines,[3] and it is still controversial when the epidemic will end.[4-7]

We previously compared viral variants and multifaceted demographic information with epidemiological data such as prevalence, case fatality rate (CFR), and mortality. The study has revealed that viral genotypes, regional herd immunity, and "poverty and inequality" influence epidemiological trends.[8] It has also shown that the emergence of epidemic-driving mutants peaked out, and predicted that the pandemic will end by the end of March 2021.

However, new variants have since become predominant in many countries, and their epidemiological effects have not been elucidated.[9] Vaccinations have been initiated around the world, but their impact on epidemiological trends remains to be investigated. Moreover, it is unclear how industrial structure and affluence affect infection trends in countries with large regional economic disparities, such as Russia. It also remains enigmatic whether policy is the only factor behind the success of countries resilient to coronavirus disease 2019 (COVID-19), such as New Zealand[10] and Taiwan.

In this study, multifaceted analyses of the epidemiological effects revealed that new viral variants increased CFR. By investigating the relationship of prevalence with gross domestic product (GDP) per capita in BRICS countries, we found that SARS-CoV-2 was epidemic in highly productive areas, even if the area was sparsely populated as in Russia. Analyses of the influence of New Zealand ethnic groups provided evidence that

genetic traits common to Polynesians and Taiwanese indigenous people may prevent COVID-19. Furthermore, we found that vaccines had the paradoxical effect of transiently increasing COVID-19 prevalence while reducing CFR. These findings will help converge the pandemic with fewer casualties.

Results

Second wave of SARS-CoV epidemic

We performed genomic epidemiological analyses comparing SARS-CoV-2 genetic mutations deposited in Global Initiative on Sharing All Influenza Data (GISAID) website[11] and COVID-19 prevalence (number of cases per 1,000,000 people), CFR, and mortality (number of deaths per 1,000,000 people).

The second wave of epidemic in Europe that began in the autumn of 2020 has been mainly due to GISAID Clade GV (ORF10: V30L; N: A220V/ORF14: L67F; Spike: A222V),[12] DN type (N: M234I, A376T; ORF1a: M3087I; ORF1b: A176S, V767L, K1141R, E1184D; Spike: S477N),[8] ORF1a: H1113Y, and Spike: N439K from Clade G (Extended Data Fig. 1a). Since the third wave struck after mid-December, we performed ecological study[13] comparing the genomic and epidemiological data from 15 July to 18 December 2020. Clade GV was correlated with reduced CFR (Fig. 1a) consistent with an ecological study in Spanish Communities,[8] suggesting that it is an attenuated variant. On the other hand, all four types, Clade GV, DN type, ORF1a: H1113Y, and Spike: N439K, had minimal effects on prevalence (Extended Data Fig. 1b), suggesting that variants with equivalent transmissibility had been selected due to viral competition.

Plotting prevalence and CFR in the major countries of the world showed that the second wave were quite different from the first wave[8] (Fig. 1b). CFR declined worldwide, especially in Europe, in line with the clinically lower morbidity of hospitalized patients.[14,15] This may be due to the abolition of immune responses to Clade S, which are associated with the exacerbation of COVID-19.[8] On the other hand, there was a marked increase in prevalence in Europe, probably because the above four highly contagious variants were competing against each other. The prevalence decreased in the Middle East

with slight increase in CFR. Overall, there was a global tendency for viral attenuation in the second wave of COVID-19.

Epidemiological outcomes of new variants

The variant of concern (VOC)-202012/01 (N: D3L, S235F; ORF1a: T1001I, A1708D, I2230T, S3675_F3677del; ORF8: Q27*, R52I, Y73C; Spike: H69V70del, Y144del, N501Y, A570D, P681H, T716I, S982A, D1118H) originated from Clade GR in the United Kingdom (UK) and spread worldwide (Extended Data Fig. 2a). An ecological study was performed comparing the frequency of the variant worldwide with prevalence, CFR, and mortality after 18 December 2020. VOC-202012/01 was positively correlated with CFR (Fig. 1c). In contrast, the variant did not tend to increase the prevalence (Extended Data Fig. 2b). The rapid spread of VOC-202012/01 in UK and their recognition as a highly transmissive virus[16] may be due to the simultaneous epidemic in UK being Clade GV, which tends to reduce prevalence (Extended Data Fig. 1b).

The 501Y.V2 variant (ORF1a: K1665N, K3353R; ORF3a: S171L; Spike: L18F, D80A, D215G, L242_L244del, R246I, K417N, E484K, N501Y, A701V) was derived from ORF1a: T265I of Clade GH in South Africa (Extended Data Fig. 3a).[17] 501Y.V2 has dominated the epidemic in South Africa after December 2020, making it difficult to compare with other variants. We therefore performed ecological studies of South African provinces as of 26 December 2020. 501Y.V2 tended to increase CFR, while it did not tend to increase prevalence (Extended Data Fig. 3b), consistent with a report that it does not increase infectivity.[18] More notably, N: S194L/ORF14: Q41* variant from Clade G (tentatively named Q2 type) showed a significant positive correlation with CFR in South African provinces (Fig. 1d). The Q2 type also tended to increase mortality (Extended Data

Fig. 3c), consistent with the positive correlation with mortality in Mexican states.[8] These results suggested that 501Y.V2 is a highly virulent virus and Q2 type is even more dangerous.

Our previous study has demonstrated that racial factors had a strong impact on South African epidemic outcomes. Infection seemed to be widespread among whites, and coloured races and overcrowded urban environment appeared to increase mortality.[8] Multiple regression analyses (MRA) was performed to determine which elements among viral variants or demographic factors had a strong impact on the South African epidemic (Extended Data Table S1). Racial factors contributed primarily to prevalence, while viral variants were major determinants of CFR and mortality. 501.Y2 contributed to increased CFR. Indeed, CFR after October 2020, when this variant appeared, increased in all provinces except Mpumalanga compared to CFR up to September 2020 (Extended Data Table S2). Q2 type contributed to increase in CFR, prevalence, and mortality (Extended Data Table S1), consistent with major contribution of this variant to mortality in Mexican states.[8]

Brazil had the third highest number of infections and the second highest number of deaths in the world as of February 2021. The P.1 variant (ORF1a: S1188L, K1795Q, S3675-, G3676-, F3677-; ORF1b: E1264D; ORF8: E92K, ORF9b: Q77E; Spike: L18F, T20N, P26S, D138Y, K417T, E484K, N501Y, H655Y, T1027I) originated form Spike: V1176F of Clade GR in the Brazilian Amazonas state and spread to neighbouring and the São Paulo states (Extended Data Fig. 4a). An ecological study of the Brazilian states was conducted comparing the frequency of variants (Extended Data Fig. 4b) and epidemiological information after P.1 appeared. The P.1 variant was positively correlated with CFR and tended to increase mortality (Extended Data Fig. 5). N: A119S, M234I,

ORF1a: L3468V, Spike: E484K variant originated from L3930F of Clade GR (tentatively named VK type) and tended to increase CFR and decrease prevalence (Extended Data Fig. 5). MRA showed that P.1 contributed to increased CFR and mortality (Extended Data Table S3). VOC-202012/01 contributed to a decrease in CFR in Brazil, while it was correlated with an increase in CFR globally (Fig. 1b). This suggests that, of the three major variants in the second wave of Brazil, VOC-202012/01 was less virulent than P.1 and VK type. It is also noteworthy that population density contributed to the rise in CFR (Extended Data Table S3) and that prevalence and mortality increased significantly in areas with high GDP per capita (Extended Data Fig. 5).

In summary, VOC-202012/01 and P.1 are highly virulent variants that increase CFR, with P.1 being more virulent than VOC-202012/01. 501Y.V2 can also be a highly virulent variant. However, other variants such as Q2 and VK types should also be recognized, which are at least as toxic as these notable ones.

Russia

Russia had the fourth highest number of infections and the eighth highest number of deaths in the world as of February 2021. Clade GR was the mainstream in Russia, and downstream Spike: M153T and N: A211V variants were associated with the spread of infection (Extended Data Fig. 6a). Ecological studies of the subjects of the Russian Federation showed that Clade GH and N: A211V were negatively correlated with prevalence and mortality, respectively (Extended Data Fig. 6b).

Interestingly, population density showed a bimodal correlation with prevalence, with prevalence decreasing in low-density areas and increasing in highly dense areas (Fig. 2a). Since population density shows a similar bimodal correlation with GDP per capita

(Fig. 2b), we compared GDP per capita and prevalence. Prevalence tended to increase in areas with high per capita GDP (Fig. 2c). Indeed, MRA showed that both per capita GDP and population density were important determinants of prevalence (Extended Data Table S4). In the Russian epidemic, viral virulence determined CFR, and per capita GDP, population density, and viral subtypes contributed to prevalence. This may reflect the epidemic trend peculiar to Russia, where infections were widespread in sparsely populated remote areas where natural resources for export (mainly oil and natural gas) are produced, and in densely populated metropolitan areas.

We investigated whether such economic activity-related outbreaks also occurred in other BRICS countries. GDP per capita was positively correlated with prevalence in Brazil, India, and China, and also tended to increase prevalence in South Africa (Extended Data Fig. 7a). In other BRICS countries, per capita GDP increased as population density increased (Extended Data Fig. 7b), none of which showing a decline like Russia. In all BRICS countries, COVID-19 was prevalent in areas with high economic activity and, in Russia, even if the area was sparsely populated. The Russian epidemic was characterized by influx from other countries.[19] In areas where crude oil exports are active, the virus may spread due to inflows from other countries even in remote areas with a small population.

Ethnic factors in New Zealand

New Zealand has been highly rated for the effectiveness of SARS-CoV-2 epidemic prevention measures.[10] Despite the influx of many variants that are prevalent in the world, New Zealand has maintained low prevalence and mortality. Ecological studies of District Health Board (DHB) areas in New Zealand were conducted as of 18 December 2020, since P.1 invaded in January 2021 and VOC-202012/01 was detected after 19 December

2020 (Extended Data Fig. 8a), possibly changing epidemic outcomes. Q type (N: S194L/ORF14: Q41* from Clade GH)[8] was correlated with higher CFR and mortality (Fig. 3a), consistent with increased CFR in India and increased mortality in Asia.[8] Spike: P681R from Clade GR tended to increase CFR and mortality (Extended Data Fig. 8b). ORF1a: T1246I from Clade GR tended to increase prevalence.

Racial factors also had a strong influence on the New Zealand epidemic. The proportion of Asians was positively correlated with prevalence (Fig. 3b), suggesting influxes from the Asian region. Interestingly, Māori had a negative correlation with CFR, prevalence, and mortality (Fig. 3c). This result contradicts the reported susceptibility of Māori to COVID-19.[20] Low population density of Maori settlements may have reduced mortality. Indeed, MRA showed that population density contributed to lower CFR and mortality (Extended Data Table S5). However, Māori contributed to lower prevalence and mortality independent of population density. It was notable that the contribution of Māori to prevalence was stronger than SARS-CoV-2 variants (Extended Data Table S5). The Māori are indigenous Polynesians. In the Polynesian Islands, with the exception of French Polynesia, COVID-19 had low CFR, prevalence, and mortality (Extended Data Table S6). Being isolated for centuries, Māori developed their own culture, independent of other Polynesian cultures. It is therefore likely that genetic factors confer SARS-CoV-2 resistance on Polynesians, and the reported high Māori exacerbations are due to social factors such as poverty, disparity,[20] and underlying illness.

Vaccination

Vaccination rates of countries worldwide were compared with CFR, prevalence, and mortality after 18 December 2020, 10 days after the start of vaccination for the general

public. Countries before the start of vaccination were excluded due to possible confusion factors such as mild epidemics that do not require vaccination. Vaccines tended to lower CFR (Fig. 4a, upper panel), suggesting their ability to prevent exacerbations of COVID-19. However, the effect was not apparent until the vaccinations per population exceeded 5% (Fig. 4a, lower panel). In contrast, vaccination rates were positively correlated with prevalence (Fig. 4b). As a result, mortality tended to increase until vaccination rates exceeded 30% (Fig. 4c, lower panel) and decreased only after high vaccination rates were achieved (Fig. 4c, upper panel). We also examined the correlation between epidemiological data and the proportion of people who received at least one vaccination (Extended Data Fig. 9a) or two vaccinations (Extended Data Fig. 9b), with similar results.

To clarify whether vaccination was the cause or the consequence of the increased prevalence, we divided each into a first period before 28 January 2021 and a second period thereafter. Then, we re-analysed the relationship between the vaccination rate and the prevalence for each period. Vaccines may be preferentially distributed to countries with high prevalence, leading to higher vaccination rates. Indeed, the vaccination rate of period 2 was positively correlated with the prevalence of period 1 (Spearman correlation coefficient $\rho = 0.354$, $P = 0.0164$; Extended Data Table S7), suggesting that countries with widespread infection were preferentially vaccinated. However, period 2 vaccination rates were more positively correlated with period 2 prevalence ($\rho = 0.413$, $P = 0.00465$) than period 1 prevalence, suggesting that vaccination is more of a cause of infection spread rather than a consequence. Indeed, although many of Israel's population has been vaccinated, the increase in infections has not stopped until recently.[21] Period 1 vaccination rates showed a positive correlation with period 1 prevalence ($\rho = 0.404$, $P = 0.00467$; Extended Data Table S7) and the significant correlation disappeared with period 2

prevalence ($\rho = 0.214$, $P = 0.144$), suggesting that the increased prevalence was a transient phenomenon that occurs within a few weeks after vaccination.

Discussion

VOC-202012/01, 501Y.V2, and P.1 seemed to be highly virulent virus strains that increase CFR. We have previously shown that mutations that increase CFR often involve B and T lymphocytes epitopes.[8] Indeed, the variants have mutations located in antibody epitopes,[22] HLA-DR T cell epitopes,[23] and predicted antibody and HLA-DR T cell epitopes[24] (Extended Data Table S8). Spike: N501Y mutation, which is present in all three new variants, increases the binding affinity for the angiotensin converting enzyme 2 (ACE2) receptor.[25,26] Spike: N501Y has also been shown to reduce neutralization by immune plasma.[27] Spike: E484K, present in 501Y.V2, P.1, and VK type, also escapes neutralizing antibodies.[27,28] Due to Spike: N501Y, VOC-202012/01 is difficult to neutralize by monoclonal antibodies.[29] Due to Spike: E484K and N501Y mutations, 501Y.V2 is resistant to antibody neutralization.[18,30] P.1 may be more virulent than VOC-202012/01 due to the addition of Spike: E484K, which further reduces the effectiveness of neutralizing antibodies.

In the Amazonas state of Brazil, 76% of the population had antibodies to SARS-CoV-2, exceeding herd immunity threshold, but the epidemic failed to converge.[31] This may be due to immune evasion by the prevalent P.1 variant. It is noteworthy that the immune evasion can also increase transmissibility.[8] Spike: N439K tended to increase prevalence in the second wave of Europe. The mutation has been shown to increase affinity for ACE2[26] and confer resistance to neutralizing antibodies.[32] In New Zealand, Spike: P681R from Clade GR tended to increase CFR and mortality. This mutation and P681H of VOC-202012/01 are immediately adjacent to the furin cleavage site, which enhances viral replication and pathogenesis.[33] These mutations may increase viral toxicity by regulating proteolysis at this site.

There was a global trend for SARS-CoV-2 attenuation in the second wave of COVID-19. It is also noteworthy that the three highly toxic variants attracting attention in the third wave were at most as toxic as the Q, Q2, and VK types that were prevalent from the first wave. In other words, despite the worldwide spread of variants, the tendency for SARS-CoV-2 attenuation remains unchanged in the third wave.

Ecological analysis in New Zealand showed that Māori was negatively correlated with CFR, prevalence, and mortality, suggesting that Polynesians are resistant to COVID-19. The roots of the Lapita culture, the origin of Polynesian culture, can be traced back to the expansion of Austronesians from Taiwan.[34] Moreover, Taiwan, along with New Zealand, is known as the most successful country in the world for containing SARS-CoV-2. Identification of genetic loci involved in SARS-CoV-2 resistance of Polynesians, including Māori, and Taiwanese indigenous peoples may contribute to the development of therapeutic and preventive measures for COVID-19. New Zealand and Taiwan have succeeded in adopting a zero COVID strategy with large-scale PCR testing, thorough quarantine, and border measures. However, it is advisable to carefully discuss whether other countries with different genetic backgrounds can succeed with the same policy.

The SARS-CoV-2 vaccines temporarily increased COVID-19 prevalence in the weeks following vaccination. There are several possible causes for this transient viral spread in the early stage of inoculation. First, social isolation can be loosened both institutionally and psychologically once vaccination is initiated. Vaccinated people may be released, feel relaxed, and have increased mobility. Second, logistics and human mobility for huge vaccinations may lead to the spread of infection. Third, non-specific inflammatory responses from vaccination may promote viral replication.[35] Fourth,

vaccine-resistant viruses may already exist and the resistant strains may be highly transmissible. Vaccine resistance is more likely to be selected by the vaccinated body than other competing virus strains, leading to the spread of resistant strains after the start of vaccination. Finally, and most likely, low levels of low-affinity antibodies are produced early in the vaccine's immune response, which can lead to antibody-dependent enhancement (ADE).[36] Numerous spike mutations in VOC-202012/01, 501Y.V2, and P.1 may further reduce the affinity of vaccine-induced antibodies for spike antigens and promote ADE.

Sera from severe COVID-19 patients trigger FcγRIIb (CD32b) signalling in monocytes that block interferon α responses.[37] Interestingly, ADE of SARS-CoV is also primarily dependent on FcγRIIb,[38] suggesting that antibodies of severe COVID-19 patients also cause FcγRIIb-dependent ADE with signal transduction. Since SARS-CoV-2 proliferates in alveolar macrophages,[39] the viral load increases as more virus enters the alveolar macrophages through ADE. High viral load has been linked to high infectivity,[40] which may increase prevalence. In this case, the transient increase in prevalence may be unavoidable due to the nature of the vaccine. In other words, it should be understood as a trade-off that must occur in the early stages of vaccination. Until herd immunity is established by vaccination, it is necessary to thoroughly implement infection prevention measures such as social isolation and contact tracing to prevent an increase in mortality.

The results provide lessons on how to proceed with vaccination. While the prevalence increases after vaccination, a strategy of mass vaccination of people at risk may be desirable to prevent the death of non-vaccinated individuals. Detailed studies of the epidemiological consequences of vaccination will clarify the true nature of vaccination and lead to more efficient use of the vaccines.

Methods

Sources of data

Data were obtained from websites including the Worldometer,[41] Wikipedia,[42-55] Our World in Data,[56] Bloomberg L.P.,[57] Department of Health, Republic of South Africa,[58] the Ministry of Health and Family Welfare, Government of India,[59] and Ministry of Health, New Zealand Government.[60,61] The GISAID database[11] was used for the phylogenetic analyses of SARS-CoV-2 gene mutations. The country and race names used on these websites were adopted.

Modelling analysis

Mathematical modelling was performed according to the practice of theoretical epidemiology.[13] Statistical analyses were performed with the use of the Statcel4 add-in package (OMS Publishing, Tokorozawa, Japan) for Microsoft Excel.

Data availability

All data are available on request.

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Author contributions YK and AT conceived the study and performed the analyses. AT collected data, performed statistical analyses, and wrote the first draft of the manuscript. YK and AT discussed the results and contributed to revisions of the manuscript.

Competing interests The authors declare no competing interests.

Correspondence and requests for materials should be addressed to AT

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Figure legends

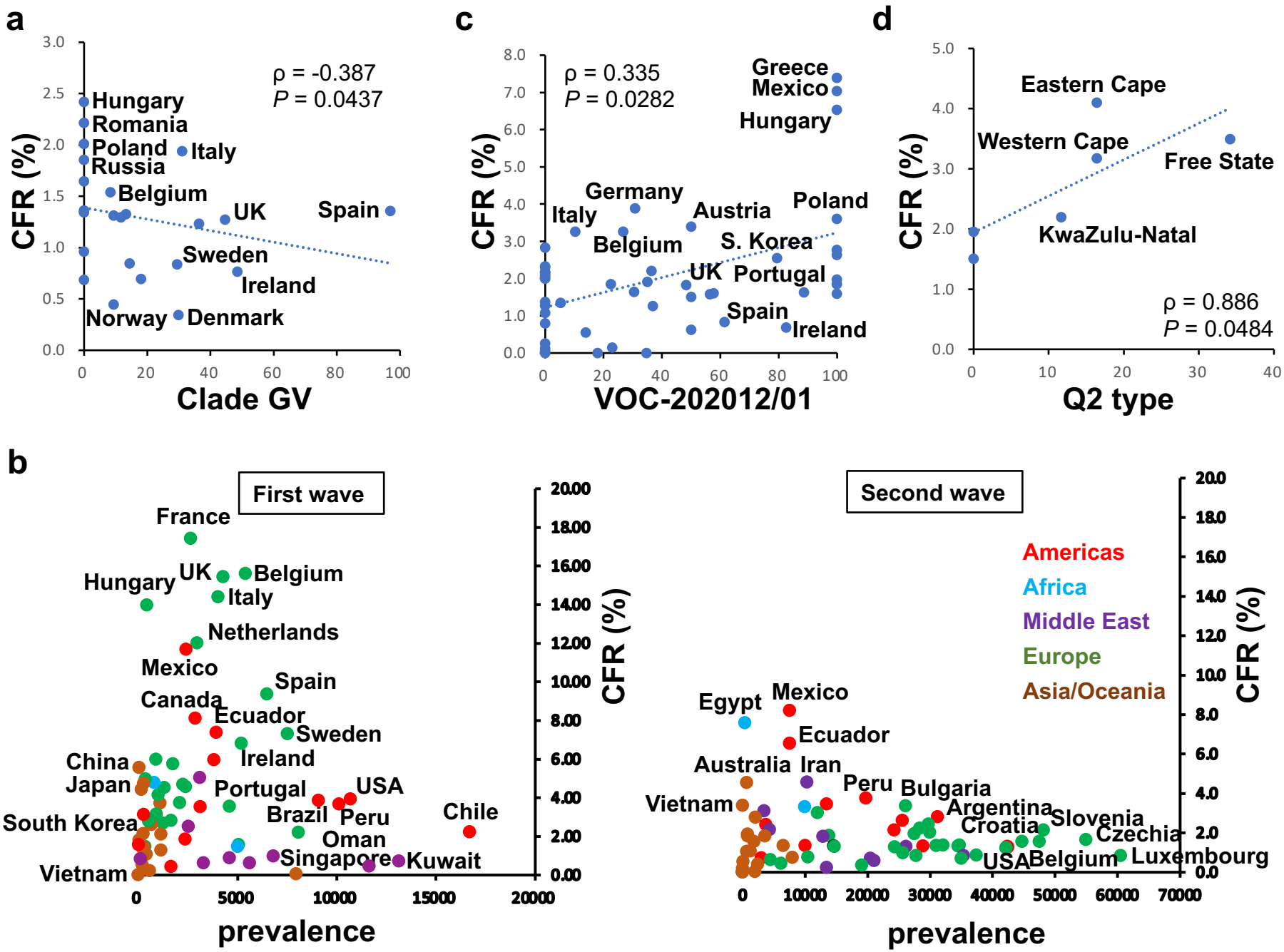
Fig. 1 | Epidemic outcomes of COVID-19 second wave and SARS-CoV-2 variants. a, Correlation between the percentage of Clade GV and CFR in the second wave of COVID-19 in Europe. **b,** A scatter plot showing the relationship between prevalence (cases per 1,000,000) and CFR (%) in the first and second wave of COVID-19 in 67 major countries of the world. The countries in Americas, Africa, the Middle East, Europe, and Asia/Oceania are shown in magenta, light blue, purple, green, and brown, respectively. **c,** Correlation between VOC-202012/01 and CFR in 67 major countries of the world. **d,** Q2 type (N: S194L from Clade G) was positively correlated with CFR in South African provinces as of 26 December 2020. ρ: Spearman correlation coefficient.

Fig. 2 | COVID-19 prevalence in Russia showing a unique correlation with population density. a, Correlation between population density and prevalence of COVID-19 in subjects of the Russian Federation as of 16 January 2021. Note that the prevalence was high in densely populated urban areas and in extremely sparsely populated areas. **b,** Bimodal distribution of GDP per capita in Russia, which is high in very low-population areas and high-population urban areas. **c,** Correlation between GDP per capita and prevalence of COVID-19 in federal subjects of Russia as of 16 January 2021. ρ: Spearman correlation coefficient.

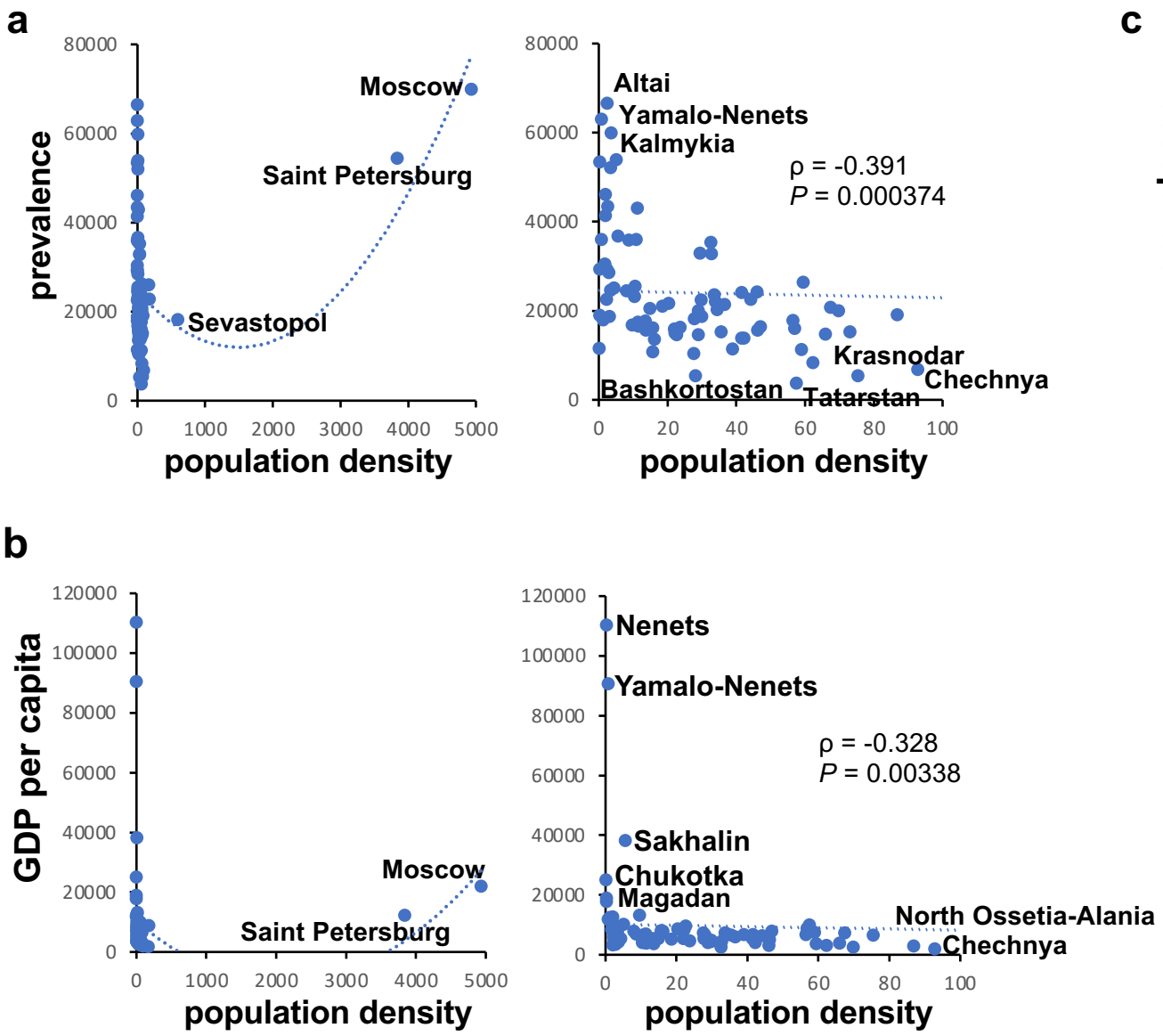
Fig. 3 | Epidemic outcome in New Zealand associated with SARS-CoV-2 variants and ethnicity. a, Q type (N: S194L/ORF14: Q41* from Clade GH) showed positive correlation with CFR and mortality in DHB areas in New Zealand as of 18 December 2020. **b,** Percentages of Asian were positively correlated with prevalence. **c,** Negative

correlation of Māori with CRF, prevalence, and mortality in DHB areas. ρ: Spearman correlation coefficient.

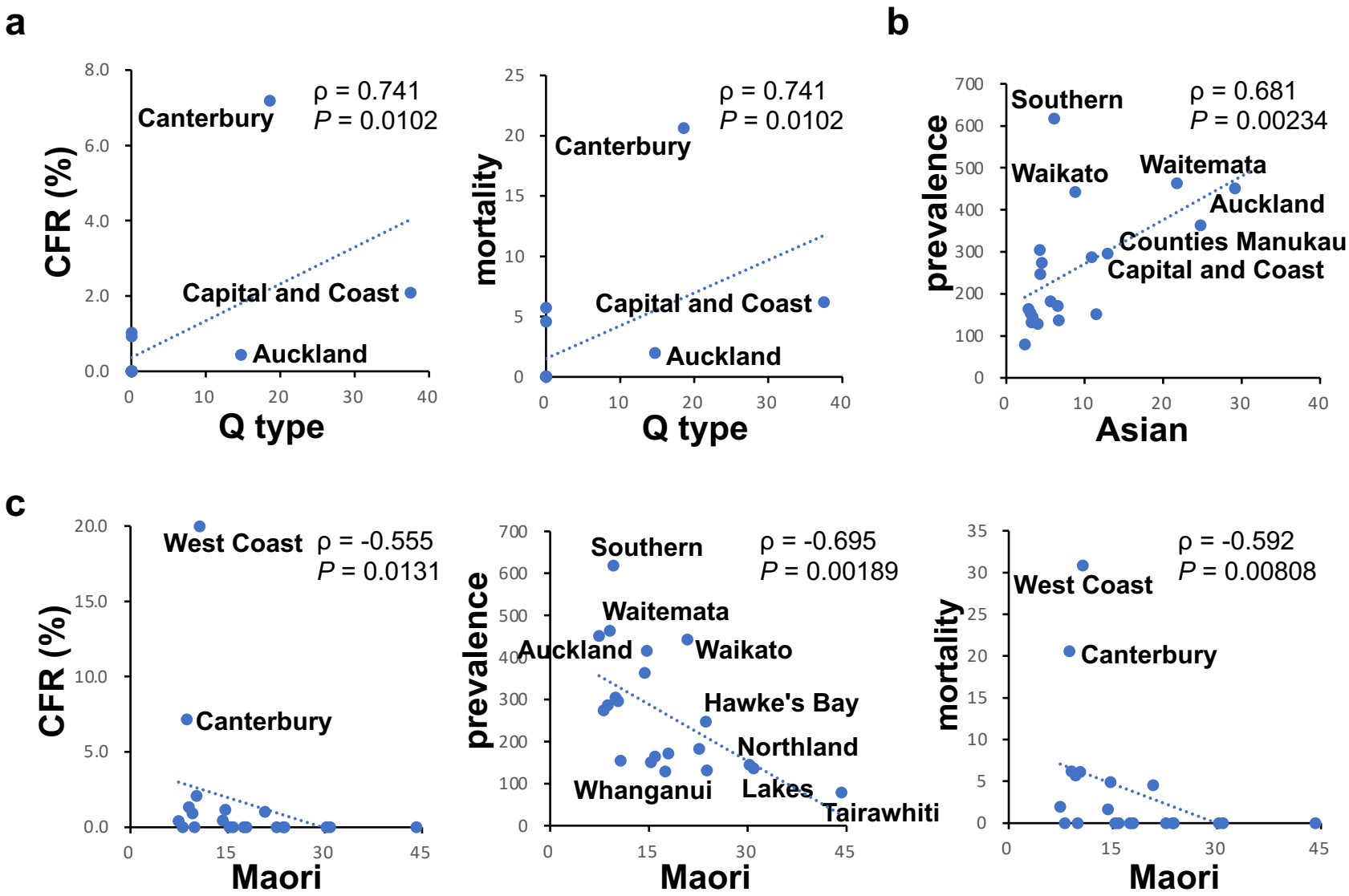
Fig. 4 | Decrease in CFR and increase in prevalence with increasing SARS-CoV-2 vaccination rate. Correlation between the number of vaccinations per population and CFR (**a**), prevalence (**b**), and mortality (**c**) as of 20 February 2021. In the lower panels, the horizontal axis has been changed to show trends in countries with low immunization rates. Countries where vaccination has not started were excluded. ρ: Spearman correlation coefficient.



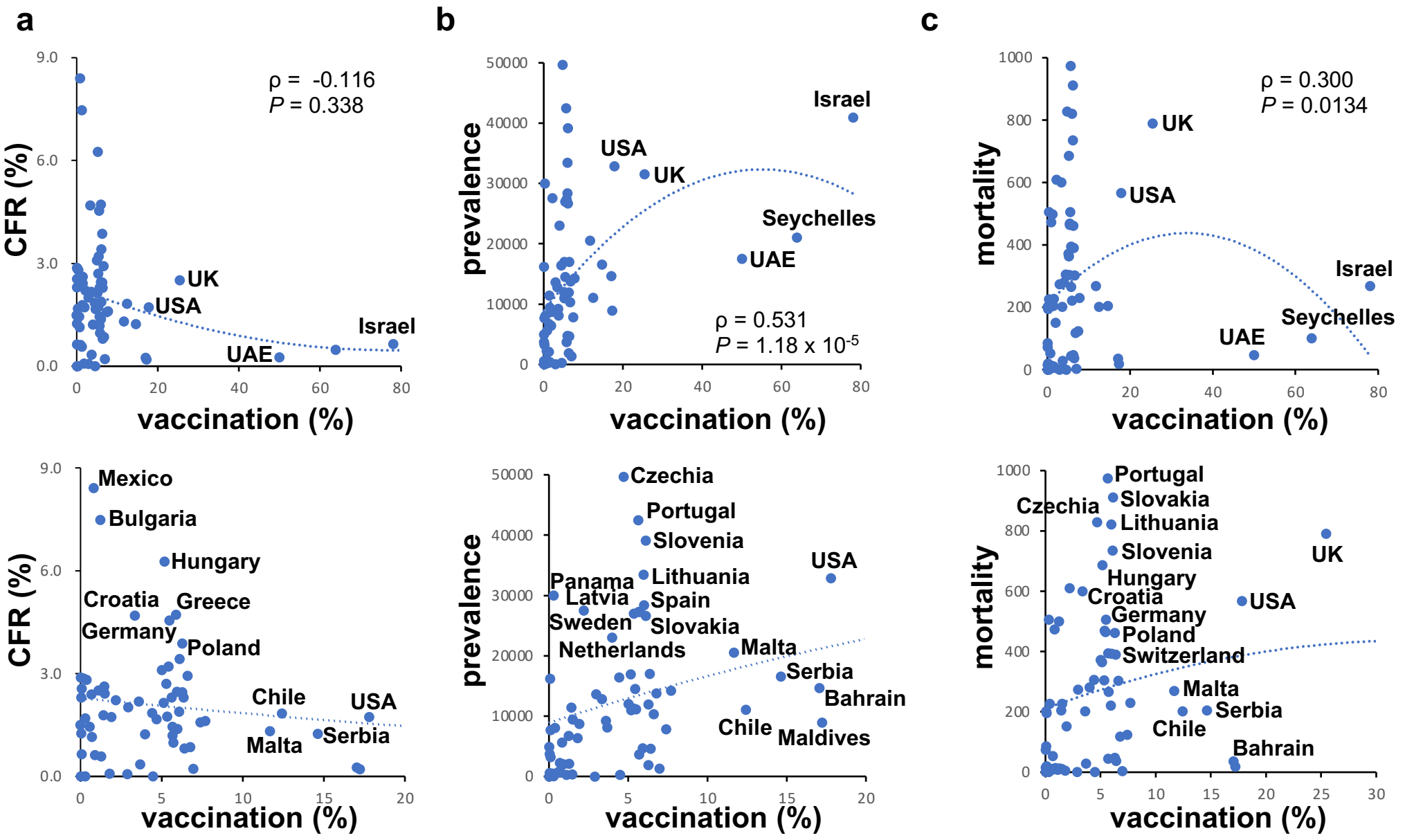
Kamikubo and Takahashi, Figure 1



Kamikubo and Takahashi, Figure 2



Kamikubo and Takahashi, Figure 3



Kamikubo and Takahashi, Figure 4