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Antoine Brault,[a] Cécile Tran-Kiem,[a,b] Clément Couteaux,[c] Valérie Olié,[d] Juliette Paireau,[a,d] Yazdan Yazdanpanah,[e] Jade Ghosn,[e] Guillaume Martin-Blondel,[f] Paolo Bosetti,[a,g] and Simon Cauchemez[a,g,*]

[a]Mathematical Modelling of Infectious Diseases Unit, Institut Pasteur, Université Paris Cité, CNRS UMR 2000, Paris, France
[b]Collège doctoral, Sorbonne Université, Paris, France
[c]Agence de Santé de Wallis et Futuna, France
[d]Santé publique France, France
[e]Infections Antimicrobials Modelling Evolution (IAME), INSERM UMR 1137, Université Paris Cité, Paris, France
[f]Service des Maladies Infectieuses et Tropicales, CHU de Toulouse, Institut Toulousain des Maladies Infectieuses et Inflammatoires (Infinity), INSERM UMR 1291 - CNRS UMR 5051 - Université Toulouse III, France

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Summary

Background Ending Zero-COVID is challenging, particularly when vaccine coverage is low. Considering Wallis and Futuna, a French Zero-COVID territory affected by reluctance to vaccination, low immunity and high levels of comorbidities, we investigate how targeted use of nirmatrelvir/ritonavir (brand name Paxlovid) can complement vaccination and non-pharmaceutical interventions (NPIs), and mitigate the epidemic rebound expected when Zero-COVID ends.

Methods We developed a discrete age-stratified compartmental model describing SARS-CoV-2 spread and healthcare impact once Wallis and Futuna reopens. It accounts for comorbidity risk groups (CRG), vaccine coverage (2 doses, 3 doses), the effectiveness of vaccines (recent or old injection), treatments and NPIs. In our baseline scenario, cases aged 65+ in intermediate/high CRG and 40+ in high CRG are eligible for treatment.

Findings The epidemic is expected to start 13–20 days after reopening with a doubling time of 1.6-3.7 days. For medium transmission intensity (R_0 = 5), 134 (115–156) hospital admissions are expected within 3 months, with no pharmaceutical measures. In our baseline scenario, admissions are reduced by 11%–21% if 50% of the target group receive treatment, with maximum impact when combined with NPIs and vaccination. The number of hospitalisations averted (HA) per patient treated (PT) is maximum when 65+ in high CRG are targeted (0.124 HA/PT), quickly followed by 65+ in intermediate/high CRG (0.097 HA/PT), and any 65+ (0.093 HA/PT). Expanding the target group increases both PT and HA, but marginal gains diminish.

Interpretation Modelling suggests that test and treat may contribute to the mitigation of epidemic rebounds at the end of Zero-COVID, particularly in populations with low immunity and high levels of comorbidities.

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Introduction

Confronted with the devastating COVID-19 pandemic, a number of countries such as China, New Zealand and Australia implemented the Zero-COVID approach where strict border control and intense response to local transmission events ensured viral elimination from the country. While Zero-COVID has proved an effective strategy, its endgame is a difficult problem.[3]

For countries and territories that are still implementing Zero-COVID, it is essential to design public

*Corresponding author. Mathematical Modelling of Infectious Diseases Unit, Institut Pasteur, 28 rue du Dr Roux, 75015 Paris, France.
E-mail address: simon.cauchemez@pasteur.fr (S. Cauchemez).
[g]Equal senior contribution.

Research in context

Evidence before this study

We searched PubMed articles using the search query (sars-cov-2 or Covid-19) AND antiviral AND model AND healthcare. The query returned 163 results. Among those, 12 were modelling studies assessing the impact of the use of an antiviral on the healthcare system and only two dealt with nirmatrelvir/ritonavir.[1,2] None of these studies investigated the treatment of different groups according to age and comorbidities to determine optimal target groups.

Added value of this study

Here, we present an age-stratified compartmental model taking into account the prevalence of comorbidities and vaccination coverage in the population to assess the impact of antiviral treatment use, vaccination and NPIs on the healthcare system during a COVID-19 epidemic. The main originality of our study is to assess how a test and treat approach with nirmatrelvir/ritonavir (brand name Paxlovid) targeting different groups according to age and comorbidity can complement vaccination and NPIs to mitigate an epidemic rebound when Zero-COVID ends. Another interesting feature is the study of the relative unique context of Wallis and Futuna, a French territory in the Pacific Ocean that has successfully implemented Zero-COVID but is affected by reluctance to vaccination, low immunity and high levels of comorbidities.

Implications of all the available evidence

The exit of a Zero-COVID strategy is challenging when vaccination coverage is low. This is even more true when comorbidities are frequent in the population and healthcare capacities are limited as in Wallis and Futuna. Modelling suggests that a test and treat approach with nirmatrelvir/ritonavir can complement the effect of vaccination and NPIs, with the treatment of 50% of cases in the baseline target group (65+ in intermediate or high CRG and 40+ in high CRG) leading to 16% reduction of the number of hospitalisations during an epidemic rebound. We document how the numbers of hospitalisations averted and of patients treated vary depending on the age/comorbidity group receiving treatment.

health strategies that limit the risk of a massive wave of hospitalisations when Zero-COVID ends. Vaccination is a key ingredient for successful exit.[2,4] However, increasing vaccine coverage may be difficult if the population is reluctant to get vaccinated, and complementary approaches such as test and treat with antiviral drugs may have to be considered. Nirmatrelvir/ritonavir (brand name Paxlovid), an antiviral drug given orally for five consecutive days, has been shown to reduce the risk of COVID-19-related hospitalisation and death in patients with mild-to-moderate COVID-19 and who are at high risk for progression.[5] Cai et al.[2] evaluated the impact of a theoretical blanket use of the drug (treatment of 50% of all symptomatic infections in individuals aged ≥12 year old (12+)) in the Chinese context. However, in practice, the drug has mostly been recommended to high risk groups (e.g. 65+ individuals with comorbidities in France).[6] Ko et al.[1] considered the targeting of a single age group without accounting for comorbidities. To determine optimal use of the drug, it is important to assess gains associated with the treatment of different risk groups, defined by their age and comorbidities.

Consider Wallis and Futuna, a French territory in the Pacific ocean that consists of mainly two islands with a population of 11,558 inhabitants (census of 2018; Fig. 1A). The territory has successfully implemented a Zero-COVID strategy and has gradually reopened since mid-June 2022. However, the limited vaccine coverage (72% and 38% of 18+ inhabitants received 2 and 3 doses, respectively, by mid-May 2022; Fig. 1C) compared to Metropolitan France and high levels of comorbidities (70% of 18+ inhabitants are obese, 31% have hypertension and 15% have diabetes; Fig. 1B) raise the prospect of an important wave and the possible saturation of limited healthcare resources (around 30 hospital beds) following reopening. Here, we present a mathematical model developed to assess this risk. Given the reluctance of the population towards vaccination and the particular comorbidity profile, we investigated how a test and treat approach with nirmatrelvir/ritonavir could complement vaccination and non-pharmaceutical interventions (NPIs) and help mitigate the impact of the wave. We also investigated how health benefits varied with the age/comorbidity group targeted for treatment. This modelling assessment supported planning by national and local authorities of the end of Zero-COVID in Wallis and Futuna.

Methods

Model structure and assumptions

We adapted an age-stratified compartmental model previously used to describe the spread of SARS-CoV-2 in Metropolitan France[7–10] to the context of Wallis and Futuna. Given the small population size, the model is stochastic. We adjusted a contact matrix for Fiji[11] to the demography of Wallis and Futuna (see Supplementary Material). The modelled probability of hospitalisation depends on age, comorbidities and vaccination status. We report mean (95% uncertainty intervals) for numbers and median (95% uncertainty intervals) for

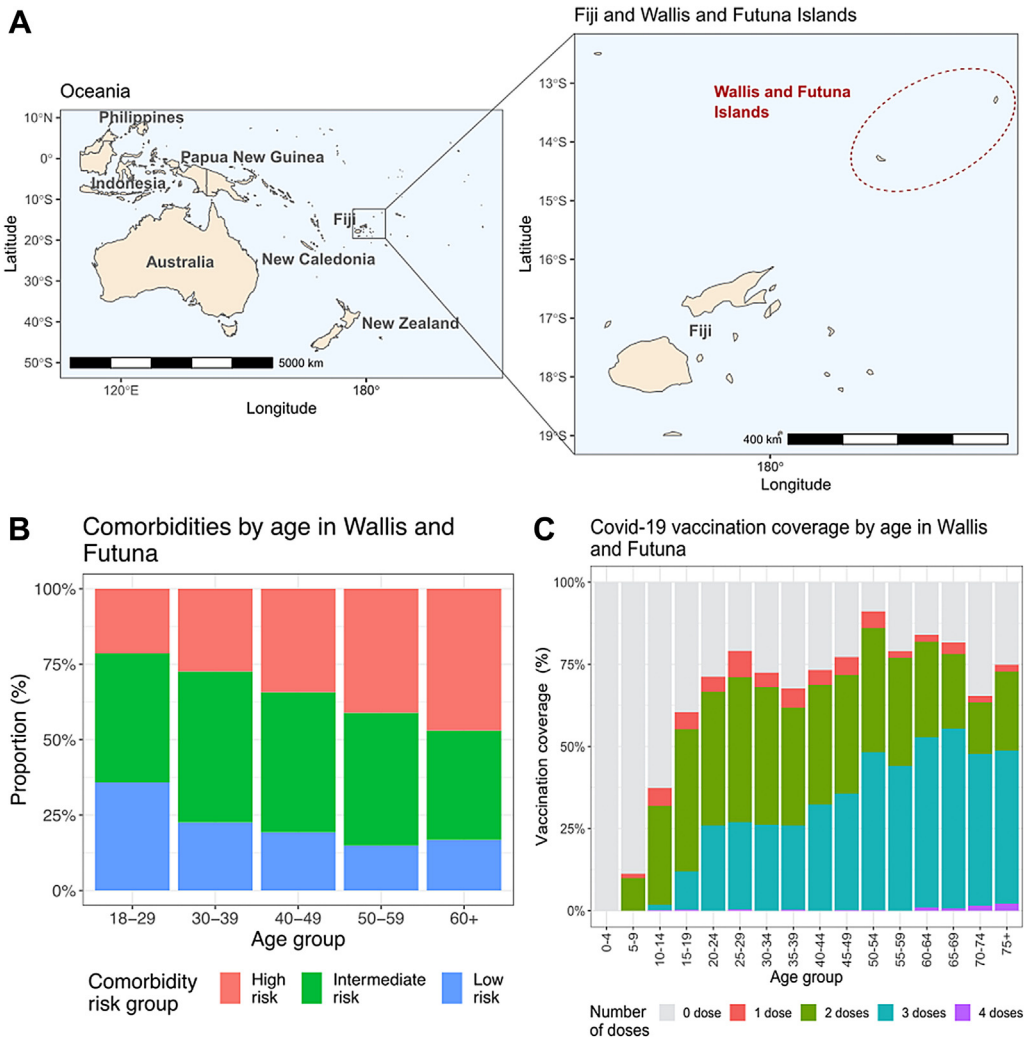

Fig. 1: **Geography and demographic characteristics of Wallis and Futuna. (A)** Map of Wallis and Futuna, a French overseas territory located in the South Pacific (Source: Natural Earth—https://www.naturalearthdata.com/). **(B)** Prevalence of comorbidities by age in Wallis and Futuna. **(C)** Vaccine coverage by age and dose type in Wallis and Futuna in May 2022.

delays. A detailed description of the model is available in Supplementary Material.

Prevalence of comorbidities

The most recent and comprehensive study on the health status of the population of Wallis and Futuna is the 2019 STEP study[12] describing the body mass index (BMI), three measures of blood pressure, treatment for high blood pressure, fasting blood sugar, and treatment for diabetes by age, without information about other comorbidities. An individual is classified with hypertension if the mean of the systolic blood pressure is above 140 mmHg or the mean of the diastolic blood pressure is above 90 mmHg or if he has a treatment for hypertension. An individual is classified with diabete if fasting blood sugar is above 126 mg/dl or if he has a treatment for diabetes. We derived from these data the prevalence of the three mutually exclusive risk-groups:[13]

- a high comorbidity risk group (CRG) with individuals that are: diabetic OR have a body mass index (BMI) $\geq$40,
- an intermediate CRG composed of people who are not in the high comorbidity risk group but have: hypertension OR with 30 $\leq$ BMI < 40,
- a low comorbidity risk group with the rest of the population.

Trajectory of hospitalised patients

For naive individuals in the low-risk group, we obtained the probability of hospitalisation given infection associated with the ancestral strains (viruses circulating in

France during 2020) by adjusting severity estimates for 2020[14] to account for the prevalence of comorbidities in metropolitan France (see Supplementary Material). In our baseline scenario, we assumed that the severity of Omicron in naive individuals is similar to that of the ancestral strains.[15,16] In a sensitivity analysis, the severity of Omicron is reduced by 25%.

We assumed that individuals in the high and intermediate CRG have their risk of hospitalisation increased by 2 and 1.15, respectively, relative to individuals in the low CRG.[13]

In line with estimates from metropolitan France,[17,18] we assumed that the length of hospital stay is 11 days for patients infected by Omicron. In a sensibility analysis, we considered a lower length of stay (6 days).

Risk of introduction

In our baseline scenario, we assumed that on average 3 infections are introduced into the territory per week. This is derived from the number of infections detected in the first flights from Noumea to Wallis and Futuna (3 cases out of 100 passengers) and the expected number of flights per week (1 flight per week in early July 2022). We explored scenarios with 1–6 introductions per week in a sensitivity analysis. The start of the epidemic is defined as the first day with at least 4 cases (detected infections).

Scenarios

For each scenario, we performed 500 simulations over 200 days.

Transmission intensity

To describe the speed at which the virus could spread in the territory, we considered three levels of transmission intensity, parametrized by the basic reproduction number R_0 (i.e. average number of persons infected by an infected individual if there was no immunity in the population): low intensity ($R_0 = 3$), medium intensity ($R_0 = 5$), and high intensity ($R_0 = 7$). Transmission intensity is expected to decline as the intensity of non-pharmaceutical measures (e.g. mask use, hand hygiene, social distancing) increases; and may be impacted by other factors such as mixing patterns in the local population. We compared the doubling time expected in each scenario (computed during the first 7 days following epidemic start) with the one observed when Omicron emerged in metropolitan France in December 2021.[19]

Vaccination

We considered three scenarios for the vaccine coverage:

- Mid-May: the vaccination coverage as of mid-May 2022 (as reported by Wallis and Futuna health agency).
- Reinforced with boosters: 50% of individuals vaccinated with 2 doses receive a booster, and 50% of boosted individuals that are 60+ or are 20+ in intermediate/high CRG receive a 4th dose.
- Reinforced with boosters and primary vaccinations: like the previous scenario with 70% of non-vaccinated individuals receiving 2 vaccine doses.

For the Omicron variant, vaccine effectiveness against infection has been estimated in the UK as: 49% (2 doses) and 55% (3 doses) if vaccination is recent (<6 months for 2 doses, < 2.5 months for 3 doses); and 9% (2 doses) and 46% (3 doses) otherwise.[20] However, these values will underestimate vaccine effectiveness in a naive population since a large proportion of unvaccinated individuals in the UK have acquired partial protection through natural infection. We therefore inflated these values by +20%, leading to estimates similar to those obtained in Hong Kong where viral circulation has been more limited.[21] Vaccine effectiveness against hospitalisation is assumed to be 78% (2 doses) and 92% (3–4 doses) if vaccination is recent; and 67% (2 doses) and 84% (3–4 doses) otherwise.[22]

We expect that most vaccinations done before mid-May 2022 occurred between January 2021 and January 2022, i.e. more than 6 months before the start of the epidemic rebound. As a result, we assumed that vaccine effectiveness for those individuals corresponded to that estimated in individuals with a longer delay since last vaccination. In contrast, vaccine effectiveness for individuals vaccinated in the ongoing vaccination campaign corresponded to estimates from individuals with a recent vaccination.

Vaccine effectiveness against transmission (i.e. risk of transmission from a vaccinated individual experiencing a breakthrough infection), is assumed to be 25% for all doses.

In a sensitivity analysis, we reduced vaccine effectiveness against infection by 20% for all doses (i.e. using values estimated in the UK) and assumed 0% effectiveness against transmission.

Limited viral circulation occurred in March–May 2021, with ≤4% of the population tested positive. We assumed past reported infections were equivalent to an additional vaccine dose and ignored unreported infections.

Surveillance for cases

Only a proportion of infections are detected by surveillance. We assumed that asymptomatic infections (25% of infections)[23–25] are not detected and do not require hospitalisation and that, among the remaining 75% of symptomatic infections, 70% are detected by surveillance and labelled as "cases". Under these assumptions, 53% of all infections are detected, in line with estimates obtained in France in 2020–2021.[26,27]

Use of antiviral treatments

In our baseline scenario, the target population for treatment with nirmatrelvir/ritonavir consists of (i) 65+ cases in the intermediate or high CRG and (ii) 40+ cases in the high CRG. This choice reflects likely use in the territory, with an adaptation of the national recommendations (targeting 65+ cases with comorbidities)[6] to the specific comorbidity profile of the population. In a sensitivity analysis, we considered alternative target groups according to (20+, 40+ and 65+) and CRG (high, intermediate and low).

We assumed that treatment is received by 50% or 80% of cases in the target population.

In our baseline scenario, we assumed that treatment is 70% effective in reducing hospitalisation, in line with a real-world effectiveness study.[28] In a sensitivity analysis, we explored 90% treatment effectiveness (consistent with the first clinical trial[5]) and 50% treatment effectiveness.[29]

Role of the funding source

The funders of the study had no role in the study design, data collection, data analysis, data interpretation, or writing of the report.

Results

Epidemic start

In our baseline scenario with 3 SARS-CoV-2 introductions per week, we expect that the epidemic will quickly take off (Fig. 2A), with a median delay from reopening to epidemic start of 20 (12–35), 15 (8–25) and 13 (8–23) days for low (R_0 = 3), medium (R_0 = 5) and high (R_0 = 7) transmission intensity, respectively (Fig. 2B). This median delay can be as high as 30 (14–72) days (1 introduction per week and R_0 = 3) and as low as 10 (6–16) days (6 introductions per week and R_0 = 7).

In the scenario with medium transmission intensity (R_0 = 5) and with the mid-May vaccination coverage, the median doubling time when the epidemic starts is 2.1 (1.7–2.8) days (Fig. 2C). This value is comparable to the one observed when Omicron emerged in metropolitan France in December 2021.[19] The doubling time is 3.7 (2.2–8.3) days and 1.6 (1.4–1.9) days for low (R_0 = 3) and high (R_0 = 7) transmission intensity, respectively.

The doubling time increases marginally with increasing vaccination coverage, from 2.1 (1.7–2.8) days with the mid-May vaccination coverage to 2.1 (1.8–2.9) days with boosting and 2.3 (1.8–3.2) days with boosting and primary vaccination (Fig. 2C).

Scenarios with NPIs only

In the absence of pharmaceutical measures, for low (R_0 = 3), medium (R_0 = 5) and high transmission intensity (R_0 = 7), an average of respectively 84 (68–100), 134 (115–156) and 158 (136–181) hospital admissions are expected within three months (Fig. 3A), while respectively 26 (19–34), 50 (38–63) and 64 (51–80) beds are required at the peak (Fig. 3B). The territory has about 30 hospital beds and there is therefore a risk of saturation in the absence of pharmaceutical measures, even in an optimistic scenario for NPIs.

Scenarios with pharmaceutical measures

In the scenario of medium transmission intensity (R_0 = 5), the reinforcement of vaccination with booster doses only reduces the cumulative number of hospitalisations and the number of beds at the peak by 15% and 16%, respectively; while the reinforcement with boosters and primary vaccinations reduces these quantities by 52% and 54%, respectively (Fig. 3A and B).

The implementation of a test and treat approach with nirmatrelvir/ritonavir can also reduce healthcare impact. In the scenario with medium transmission intensity (R_0 = 5) and no reinforcement of vaccination, treating 50% and 80% of our baseline target group (65+ within intermediate or high CRG and 40+ within high CRG) reduces the cumulative number of hospitalisations by 16% and 26%, respectively, and the peak number of beds by 14% and 24%, respectively. The treatment of 50% and 80% of our baseline target group necessitates treatments for 442 (403–481) and 703 (657–746) patients, respectively (Fig. 3C).

The greatest impact on healthcare demand is achieved when combining NPIs (which can help lower R_0), vaccination reinforcement and treatment use. For example, the cumulative number of hospitalisations can be as high as 158 (136–181) (R_0 = 7, mid-May vaccination coverage and no treatment) and as low as 23 (14–33) (R_0 = 3, reinforcement with booster and primary vaccination and 80% of cases treated in the target population).

Sensitivity analysis

In the scenario with lower vaccine effectiveness and medium transmission intensity (R_0 = 5), the cumulative number of hospital admissions and peak number of beds are 160 (139–184) and 64 (51–79), respectively, in the absence of pharmaceutical measures (instead of 134 and 50 in the baseline scenario) (Fig. 4A and B). These quantities are reduced by 12% and 14%, respectively, if booster doses are distributed (instead of 15% and 16%) and by 38% and 41%, respectively, if booster and primary doses are distributed (instead of 52% and 54%).

If the severity of Omicron is 25% lower than that of ancestral strains, with medium transmission intensity (R_0 = 5) and no pharmaceutical measure, the cumulative number of hospital admissions and peak number of beds move to 100 (83–119) and 38 (27–49), respectively (Fig. 4A and B).

If 50% of cases in the target population are treated, the cumulative number of hospital admissions is

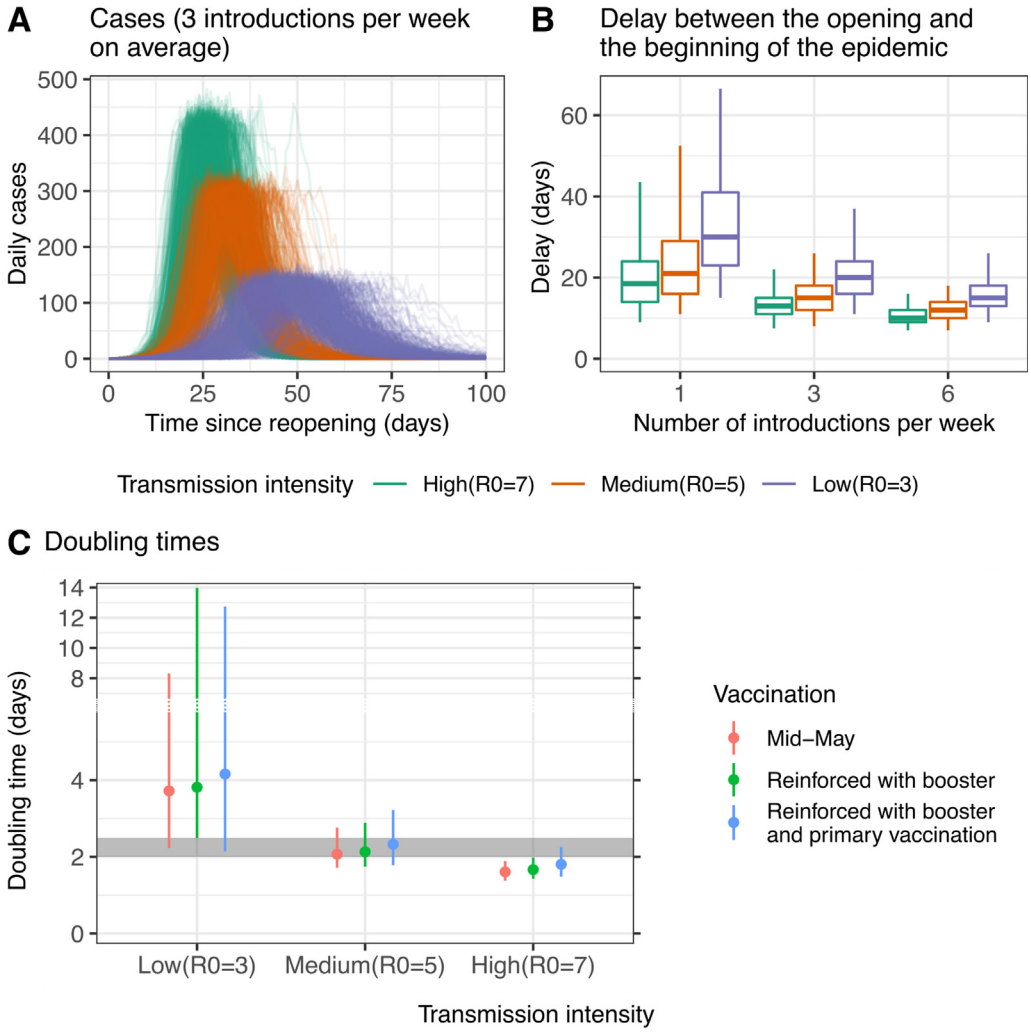

Fig. 2: **Timing of the epidemic rebound and initial growth. (A)** Time series of daily cases since the reopening of Wallis and Futuna assuming 3 introductions on average per week, across 500 simulations. **(B)** Boxplot (5%, 25%, 50%, 75% and 95% quantiles) of the delay between reopening and the start of the epidemic, defined as the first day when more than 4 new cases are detected. **(C)** Doubling time at the start of the epidemic, depending on transmission intensity and scenarios regarding reinforcement of vaccine coverage. The grey shaded area corresponds to the values measured in France when Omicron emerged in December 2021. Doubling times were computed during the first 7 days following the start of the epidemic.

reduced by 11%, 16%, and 21%, for treatment effectiveness of 50%, 70% (baseline) and 90%, respectively, while the peak number of beds is reduced by 10%, 14% and 19%, respectively (Fig. 4C and D).

When the average duration of hospital stay is 6 days (instead of 11 days in the baseline scenario), in the absence of pharmaceutical measures, the peak number of beds is 19 (13–25), 35 (26–46) and 45 (35–57), respectively, for low (R_0 = 3), medium (R_0 = 5) and high (R_0 = 7) transmission intensity (Figure S2).

Targeting different groups with antiviral treatment

The number of hospitalisations averted (HA) per patient treated (PT) is maximum when 65+ in high CRG are targeted (0.124 HA/PT), quickly followed by 65+ in intermediate/high CRG (0.097 HA/PT), and any 65+ (0.093 HA/PT) (Fig. 5A). The number of HA/PT drops to 0.048 HA/PT and 0.033 HA/PT when the targeted group also includes 40+ in high CRG and 40+ in intermediate/high CRG. Strategies that include 20+ in intermediate/high CRG have a number of HA/PT in the range 0.024–0.042 while the targeting of all 20+ leads to about 0.021 HA/PT.

As we expand the use of treatments to groups with lower risk, we observe both an increase in the number of PT and of HA (Fig. 5B), but as seen in Fig. 5A, marginal gains progressively diminish. Treating 84 patients in 65+ in high CRG averts 10 hospitalisations

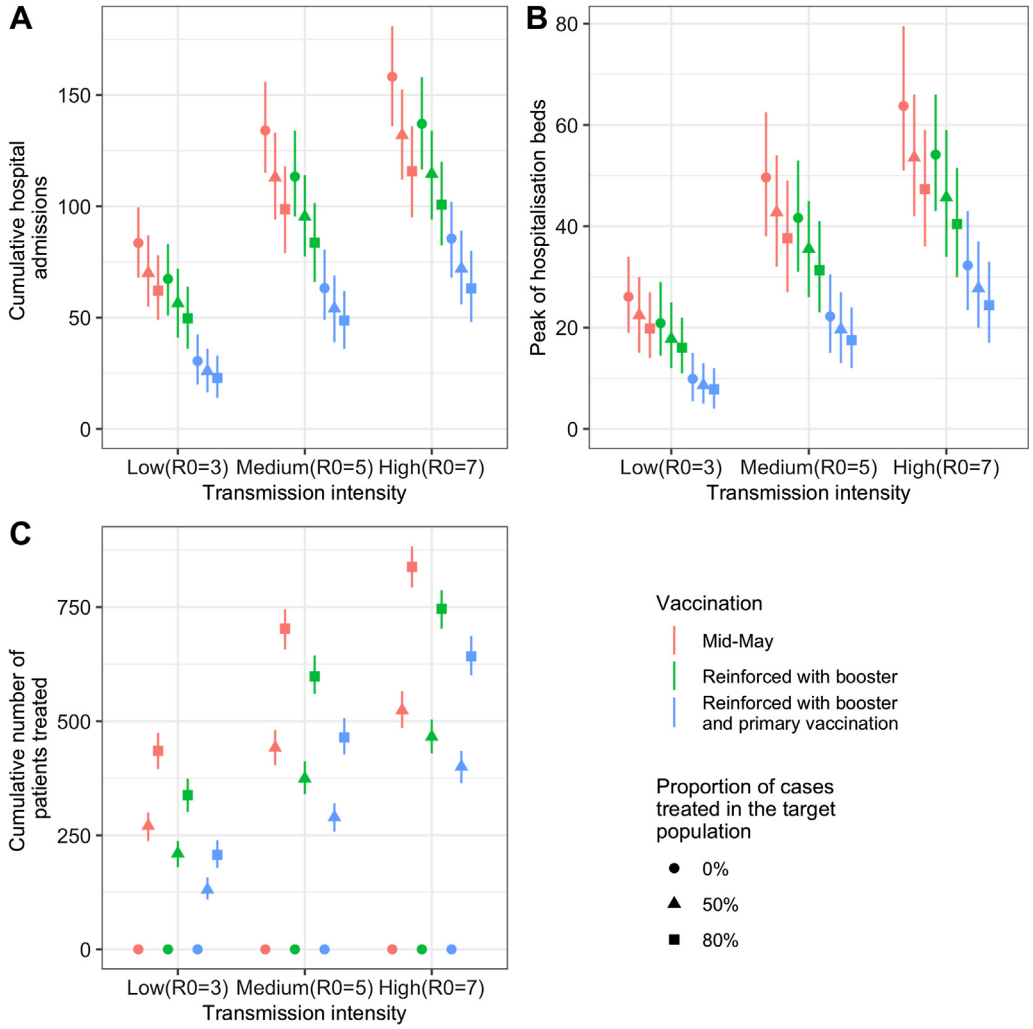

***Fig. 3:* Impact of pharmaceutical on healthcare demand, for different transmission intensities. (A)** Cumulative hospital admissions, **(B)** Peak of hospital beds (both general wards and ICUs) and **(C)** cumulative number of patients treated. Different assumptions are explored regarding vaccine coverage and the proportion of cases treated in the target population (40+ in the high risk comorbidity group and 65+ in the intermediate and high risk comorbidity groups).

(Fig. 5B). If we also target 65+ in intermediate CRG, we need to treat 65 more patients and obtain 5 more hospitalisations averted. Adding 40+ in high CRG in the target group leads to 293 more PT and 6 more HA. Further expanding treatment to 40+ in intermediate CRG adds 333 PT and 4 HA. Finally, targeting all 20+ would almost double the number of PT (+719) for 6 additional hospitalisations averted.

Discussion

For countries and territories that are still implementing Zero-COVID, it is essential to design effective exit strategies. While vaccination has a key role to play, increasing vaccine coverage may be difficult in places where adherence to vaccination is low. Here, we used a mathematical model to assess how, in populations with low immunity and high levels of comorbidities such as in Wallis and Futuna, implementing a test and treat approach targeting risk groups with nirmatrelvir/ritonavir could complement the effect of COVID vaccination and help mitigate the epidemic rebound expected at the end of Zero-COVID.

We expect that treating 50% (80%) of cases in the baseline target group (65+ in intermediate or high CRG and 40+ in high CRG) with nirmatrelvir/ritonavir could reduce the cumulative number of hospitalisations by 11%–21% (19%–34%). The number of hospitalisations averted per patient treated is maximum when targeting individuals that are most at risk (65+ in high CRG).

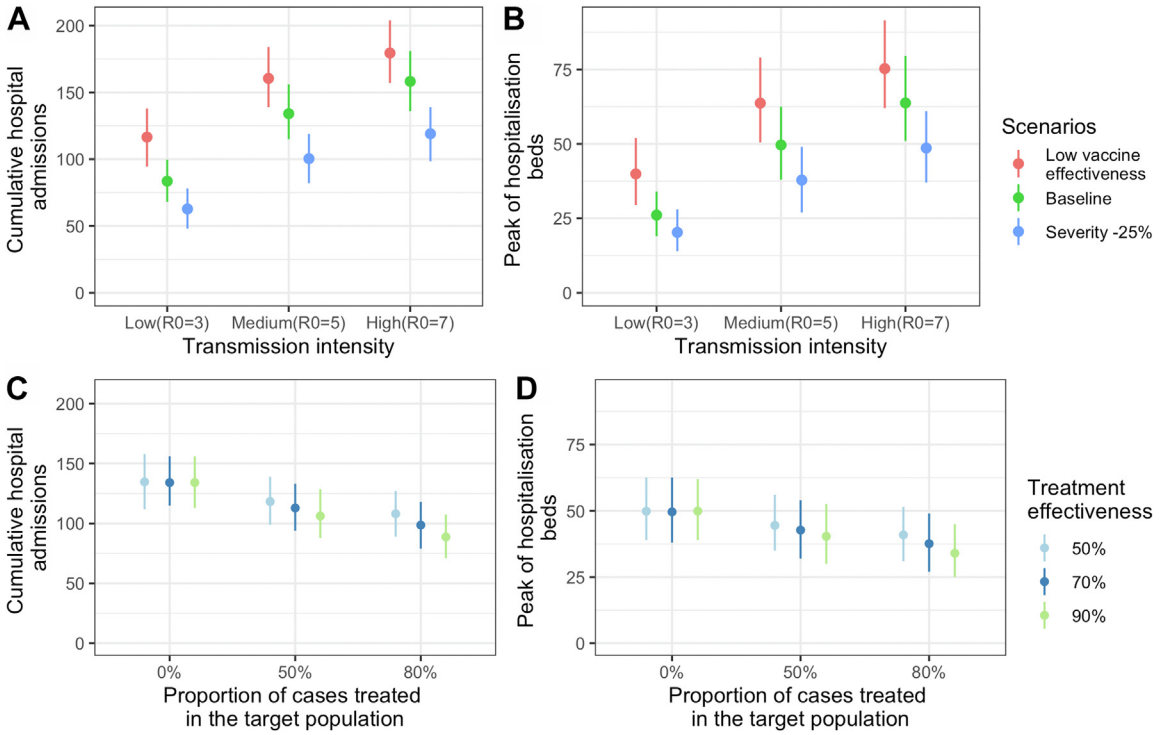

Fig. 4: **Sensitivity analyses. (A)** Cumulative hospital admissions and **(B)** peak of hospital beds (general wards and ICUs) for different transmission intensities (i) in a scenario with lower vaccine effectiveness, (ii) in our baseline scenario and (iii) in a scenario where the Omicron variant is associated with a 25% reduction in the risk of hospitalisation compared with the viruses circulating in 2020. **(C)** Cumulative hospital admissions and **(D)** peak of hospital beds (general wards and ICUs) as a function of the proportion of cases treated in the target population (65+ in intermediate/high CRG and 40+ in high CRG) for different assumptions regarding treatment effectiveness.

However, expanding the target group substantially increases the number of hospitalisations averted, although with diminished marginal gains. In practice, managing the treatment of a large proportion of the population in a quickly growing epidemic can be challenging and each country must therefore identify the appropriate trade-off between the number of hospitalisations averted and the number of cases that need to receive treatment. Indeed, the effectiveness of a test and treat strategy is contingent on the ability of local surveillance to quickly identify and treat symptomatic cases in the target population. To be effective, treatment should be initiated in the five days that follow symptom onset.[30] Since it usually takes a few days for cases to be identified after symptom onset, it is essential that the delay between case detection and treatment is as short as possible.[31] This requires the development of a comprehensive system that integrates both testing and treatment, ensuring rapid detection of symptomatic cases, fast turnaround of test results and delivery of treatment. An important challenge is that contraindications for nirmatrelvir/ritonavir, mainly related to drug–drug interactions, are common so that, in France, a medical consultation is required before treatment can be delivered. This may lead to congestion in the system particularly when incidence is high. In order to expand access to timely treatment, US Food and Drug Administration has recently authorised licensed pharmacists to prescribe nirmatrelvir/ritonavir to eligible patients who have tested positive for SARS-CoV-2, with limitations and emphasising the need for clinical monitoring for side effects and follow-up care. Clear guidelines are necessary to ensure that the most common contraindications can be managed in an effective and fast way. Ensuring patients' compliance with the prescribed treatment will also be a key ingredient for success. As countries progressively resolve these challenges, they might consider expanding test and treat to a wider group of individuals with risk factors to further increase health benefits and reduce healthcare burden. In the context of developing countries, organisational challenges appear to be a bigger barrier to the general use of antiviral drugs than the cost of the drugs.

We did not consider the use of monoclonal antibodies or other antiviral drugs as early treatment in our study. Except Bebtelovimab which has shown preserved in vitro activity against Omicron subvariants, but is not accessible outside the US, other currently available monoclonal antibodies have decreased in vitro activity

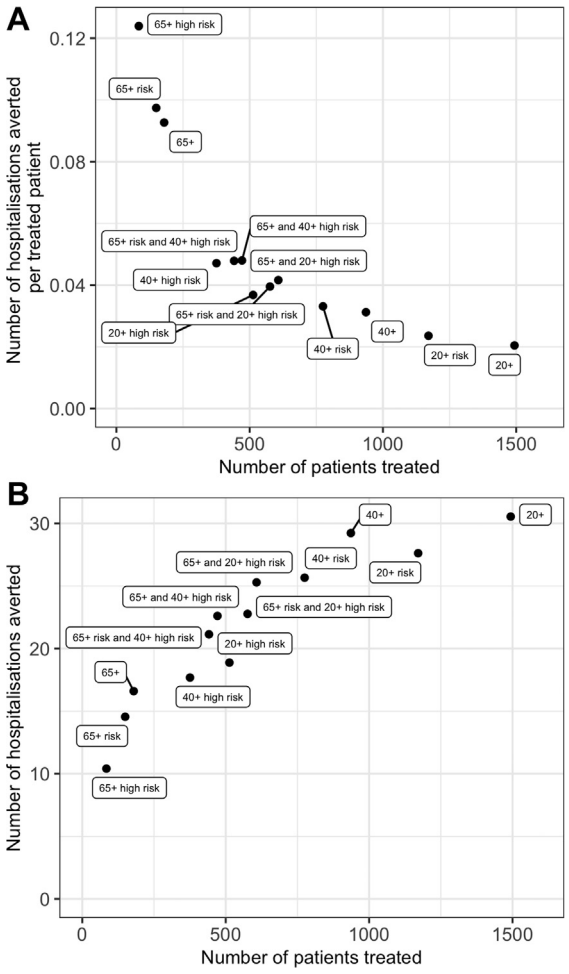

Fig. 5: **Number of hospitalisations averted and of patients treated depending on the group targeted for treatment. (A)** Number of hospitalisations averted per patient treated as a function of the number of patients treated, for different target groups. **(B)** Number of hospitalisations averted as a function of the number of patients treated, for different target groups. Results are presented assuming 50% of cases in the target population receive treatment, in the scenario with medium transmission intensity (R_0 = 5) and no reinforcement of vaccination. Here "high risk" corresponds to high CRG and "risk" to intermediate/high CRG (see Methods).

against BA.4 and BA.5 and are not used anymore although the use of Evusheld remains a subject of debate.[32] Furthermore, their intravenous administration, as for Remdesivir, which has also proven efficacy as early treatment,[33] limits their use in outpatients. Finally, Molnupiravir has not been recommended in French guidelines due to questions regarding its efficacy and safety.[34]

As expected, we find that the best approach to mitigate the impact of Zero-COVID in Wallis and Futuna combines different strategies: increasing the proportion of individuals with booster doses among vaccinated individuals and the proportion with primary vaccination, treating at-risk individuals and implementing non-pharmaceutical measures. Given efforts already made, it will be challenging to convince a substantial proportion of those that have always refused vaccination to get vaccinated. Increasing boosters among vaccinated individuals seems a more achievable objective. In the period mid-May to mid-July, about 22 individuals received a booster dose per day leading to an increase of 17% of the proportion with boosters among vaccinated individuals older than 18.

In almost all countries, case counts have grown extremely quickly when Omicron rose to emergence. In metropolitan France for example, case count doubled about every 2 days in December 2021. However, it is hard to extrapolate from such an experience to Wallis and Futuna. Both the vaccine coverage and the fraction of the population already infected is substantially lower in Wallis and Futuna than in metropolitan France, which might support the hypothesis of even faster expected growth in the context of Wallis and Futuna. However, these are small Islands with contact rates that are likely lower than in metropolitan France potentially leading to slower case growth. This uncertainty about initial growth is reflected in our three scenarios with low (R_0 = 3), intermediate (R_0 = 5) and high (R_0 = 7) transmission intensity.

After the partial reopening of Wallis and Futuna on June 23, 2022, a first local transmission was detected on June 27, 2022. The epidemic start (defined as the first day with more than 4 cases) occurred on July 9, 2022, i.e. 17 days after reopening. This is consistent with our baseline scenario predicting a median delay between reopening and epidemic start in the range 13–20 days. We estimate that the number of cases doubled every 3.3 days (95% confidence interval [2.8–4]) on average between July 18 and 26, 2022 (Figure S3 in Supplementary Material), which is consistent with the scenario with low transmission intensity (R_0 = 3; doubling time of 3.7 days) (Fig. 2C). Overall, observed dynamics for the number of cases, the cumulative number of hospitalisations and the number of patients treated are roughly consistent with model projections for the scenario with low transmission intensity (R_0 = 3) (Figure S4). However, the model overestimated the number of hospital beds required, because the observed duration of hospital stay in Wallis and Futuna was substantially shorter (average of approximately 4 days) than what was anticipated based on data from metropolitan France[17,18] (average of 11 days).

This work has a number of limitations. First, given the assumption of homogeneous mixing, our model predicted that epidemics in the islands of Wallis and of Futuna would be synchronised. However, the two islands are separated by about 200 km and the epidemic started in Wallis with a delayed start in Futuna. In such a scenario, we might expect the same cumulative number of hospitalisations but with a lower peak across

the two islands (i.e. 2 smaller peaks instead of 1 large peak). This might facilitate the management of the epidemic although the epidemic may last longer. We accounted for infections that had been detected by surveillance but ignored unreported ones which seems fine given the prior success of Zero-COVID in the territory. Data documenting comorbidities in the territory date back from 2019. However, it is unlikely the comorbidity distribution by age group changed substantially since then. Our model used available data on age, obesity, diabetes and hypertension to appreciate population levels of risk of severe COVID in the population of Wallis and Futuna. We note that other comorbidities that have been associated with severe COVID (immunosuppression, pulmonary and heart diseases, cancer) were not documented in the data even though we believe our dataset already provides a good picture of the major drivers of severe COVID in the islands. Given limited epidemiological data available from Wallis and Futuna, key model parameters were mostly derived from studies performed in other locations. However, some of these parameters may differ in Wallis and Futuna and it will be important to estimate them from local data. This is for example the case of duration of hospital stay (see above).

Numerous studies have quantified the impact of NPIs and increased vaccine coverage on COVID-19 epidemic dynamics.[35–38] In this study, we used a mathematical model to investigate the additional benefits of a test and treat strategy with nirmatrelvir/ritonavir on the control of the COVID-19 epidemic in Wallis and Futuna, a territory with a highly vulnerable population. Such a strategy could also be useful in other locations where Zero-COVID has been implemented, confronted with similar challenges as Wallis and Futuna.

Contributors

AB, CTK, PB, and SC designed and planned the study. AB, CTK, JP, PB, and SC contributed to the statistical analysis. CC, VO, and JP contributed to data collection. GMB, JG, and YY brought their medical expertise on Covid-19, treatments and vaccines. AB, CTK, PB, and SC wrote the original draft. All authors critically edited the manuscript. AB, CTK, PB, and SC directly accessed and verified the data. All authors had access to all the data reported in the study and had final responsibility to submit for publication.

Data sharing statement

The code and data to reproduce the results of the article are available at https://gitlab.pasteur.fr/mmmi-pasteur/wallisandfutuna.

Declaration of interests

JG reports receiving support as an advisor for Gilead Sciences, Merck, Janssen, Roche, AstraZeneca, Theratechnologies, and ViiV; and research grants from Gilead Sciences and ViiV, outside the submitted work. Other authors declare no competing interests.

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Appendix A. Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.lanwpc.2022.100634.

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