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Abstract

SARS-CoV-2 epidemics are expected to change with vaccination. Here, we used an age stratified compartmental model applied to France to anticipate how partial vaccination may modify SARS-CoV-2 epidemiology and determine implications for epidemic control this autumn. In our baseline scenario characterized by R_0=4 and a vaccine coverage of 30%-70%-90% among 12-17, 18-59 and ≥60 y.o., important stress on healthcare is expected in the absence of measures. Unvaccinated individuals contribute 12 times more to transmission than vaccinated ones. Unvaccinated adults ≥60 y.o. represent 3% of the population but 36% of hospitalisations. Given limited coverage, children aged 0-17 y.o. represent about half of infections and of those transmitting disease. Non-pharmaceutical measures have a similar impact whether they apply to all or only to unvaccinated individuals. Of all the interventions considered including repeated testing and non-pharmaceutical measures, vaccination of the unvaccinated is the most effective. Vaccinating children is important to protect them from the deleterious effects of non-pharmaceutical measures. Strategies to control an autumn wave should account for the changing epidemiology of SARS-CoV-2 in partially vaccinated populations.

Introduction

The SARS-CoV-2 pandemic that started in December 2019 has caused more than 3.8 million deaths around the world and led healthcare systems at the brink of collapse in many countries. In addition, the drastic control measures that were implemented to limit its impact have had dramatic socio-economic consequences.

Vaccines have proved effective at reducing the severity of SARS-CoV-2 infection,[1] the risk of infection[2] and transmission[3]. Their roll-out offers a way to exit this difficult period. However, given the high transmissibility and severity of SARS-CoV-2, very high vaccine coverage may be necessary to completely relax control measures[4,5]. Such a target may be difficult to achieve in countries such as France that are affected by vaccine hesitancy[6–8]. In these locations, SARS-CoV-2 may continue to circulate in the autumn 2021 and impact healthcare systems. In this new era where a substantial part of the population will be vaccinated, the epidemiology of SARS-CoV-2 should be different from what it was prior to the distribution of vaccines[9].

It is important to anticipate these changes to determine how control measures might evolve to ensure they maintain the epidemic under control while minimizing costs for society. Here, we developed a mathematical model to characterize the epidemiology of SARS-CoV-2 in a partially vaccinated population and evaluate in this new context the contribution to transmission and healthcare burden of individuals of different ages and vaccination status. This information is used to ascertain control strategies that can optimally mitigate an autumn epidemic rebound. We consider Metropolitan France to illustrate a partially vaccinated population.

Results

Baseline scenario and no control measures

We first present results under the assumption that control measures are completely relaxed in the autumn 2021, for our baseline scenario (basic reproduction number R_0=4 and a vaccine coverage of 30%-70%-90% among teenagers, adults aged 18-59 years old (y.o.) and over 60, respectively). In this case, our model anticipates a wave characterized by a peak of about 2,500 hospital admissions per day which is about the size of the pandemic peak observed in France during the fall 2020.

We anticipate that the roll-out of vaccines will strongly modify the epidemiology of SARS-CoV-2. In a context where most adults are vaccinated but vaccine coverage remains limited among children (0-17 y.o.), we expect 46% of infections will occur in this age group, even though they only represent 22% of the population and are assumed to be less susceptible to SARS-CoV-2 infection than adults (Figure 1A). In each age group, unvaccinated individuals are overrepresented among infected people while vaccinated individuals are under-represented (Figure 1B). For example, the risk of infection for an unvaccinated individual is RR=3.9 times higher than that of a vaccinated individual among those aged 18-59 y.o (RR=2.1 among 0-17 y.o. and RR=4.5 among over 60; Supplementary Table 1). Overall, unvaccinated individuals represent 37% of the population but 75% of infections. Their contribution to the transmission process is even higher with a risk of transmission from an unvaccinated individual that is 12.1 times higher than that from a vaccinated individual (Figure 1C-D).

Vaccination will also impact the age distribution of those hospitalised. While 74% of hospitalisations occurred among those older than 60 y.o. in the pre-vaccination era, this proportion is expected to drop to 52% in our baseline scenario. In parallel, the proportion of 18-59 y.o. among hospitalized individuals increases from 25% in the pre-vaccination era to 40% (Figure 1E). The small group of unvaccinated adults that are older than 60 y.o. has a disproportionate impact on the stress to the healthcare system. They represent 10% of their

age group but 67% of hospitalisations from that age group (RR: 18.0); and 3% of the general population but 35% of all hospitalisations (RR: 19.2) (Figure 1F). Even though we assume that the vaccine is 95% effective against the risk of hospitalisation, in a context where vaccine coverage is high among older individuals, about a quarter of hospitalisations occur among vaccinated people (Figure 1F).

Baseline scenario with control measures

We then investigate the impact of different control strategies targeting different groups for our baseline scenario with a vaccination coverage 30%-70%-90% and R_0=4. Weekly testing of 50% of unvaccinated individuals aged ≥12 y.o. could reduce the peak of hospitalisations by 27% (range: 24-31% for 20-30% of the population infected prior to September 1st 2021) if an autotest is used and 32% (28-37%) if the test is performed by a professional (Figure 2A). In contrast, if the same number of tests were distributed randomly among individuals aged ≥12 y.o. irrespective of vaccination status, the reductions in hospital admissions would only be of 17% and 20%, respectively. The reduction in the peak of hospitalisations would be much larger if 50% of unvaccinated individuals aged ≥12 y.o. agreed to get vaccinated instead of being repeatedly tested (89% vs 27%; Figure 2A), for a cost that would be about five times lower (0.2 vs 1.1 billion euros; Supplementary Figure S1).

Non-pharmaceutical interventions applied to all and reducing the overall transmission rates by 10%, 20%, 30% and 40% would reduce the peak of hospitalisations by 37, 67, 87 and 93%, respectively (Figure 2B). Very similar reductions (34, 62, 83 and 93%, respectively) would be obtained if these measures were only targeted towards unvaccinated individuals.

Sensitivity analyses

Keeping in mind that important uncertainties remain about R_0 and the vaccine coverage in the Autumn, we investigate how our results change if we depart from our baseline assumptions. Figure 3A shows the expected size of the Autumn peak in hospital admissions if all control measures were relaxed, for different R_0s and vaccine coverages. As expected the size of the peak increases with R_0 and declines with the vaccination coverage. For R_0=3, which was the value estimated for the historical lineage, our model anticipates that a vaccine coverage of 0%-50%-90% in teenagers, 18-59 y.o. and over 60 y.o. would be sufficient for the peak of hospital admissions to remain below that of the second pandemic wave. However for such a vaccine coverage, the anticipated peak would be much larger than previous peaks for R_0=4 and 5. For R_0=5 and a vaccine coverage of 30%-70%-90%, we would still expect a peak of about 6,000 hospital admissions per day in the absence of interventions. To obtain a peak lower than the second pandemic wave, a vaccine coverage of 30%-90%-90% would be required for R_0=5.

These results also suggest that the vaccination of teenagers could substantially reduce the stress on the healthcare system. For example, if 70% of 18-59 y.o. and 90% of over 60 are vaccinated, the vaccination of 50% of teenagers could reduce the peak of hospitalisations by 53% and 33% for R_0=4 and 5, respectively, compared to a scenario where they are not vaccinated.

The age distribution of infected and hospitalized individuals depends on vaccine coverage in the different age groups (Figure 3B-C). As vaccine coverage increases in an age group, we observe a reduction of the proportion of infected and hospitalized unvaccinated individuals from that age group. Those distributions are relatively robust to a change in R_0 (Supplementary Figure S2-S3). If children aged 0-9 y.o. are 50% less infectious than adults in addition to being 50% less susceptible, the proportion of children among infections remains stable at 46% while the proportion among those that cause infection drops from 58% to 55% (Supplementary Figure S4). If we assume that vaccines reduce the risk of hospitalisation by 90% (instead of 95%) in our baseline scenario, this increases the

proportion of vaccinated individuals among those hospitalized from 23% to 37% (Supplementary Figure S5-S6).

Figure 4 shows how non-pharmaceutical interventions targeting unvaccinated individuals could complement the effect of vaccination for different values of R_0. For example, for R_0=3, a vaccine coverage of 0%-50%-90% could generate a peak similar to that of the second wave, but the size of the peak could be halved if transmission rates from unvaccinated individuals were reduced by 10%. For R_0=5 and a vaccine coverage of 30%-70%-90%, 20% reductions in transmission rates from unvaccinated individuals would still generate a peak similar to that of the second pandemic wave; 40% reductions would more than halve the size of the peak.

Discussion

Countries with partially vaccinated populations enter a new era in the control of the SARS-CoV-2 epidemic. However, in countries that are affected by vaccine hesitancy, it is expected that a proportion of the population will remain unvaccinated, facilitating viral circulation and potentially affecting the healthcare system. Nonetheless, the partial vaccination of the population should strongly modify the epidemiology of SARS-CoV-2. Here, we used a mathematical model applied to Metropolitan France to anticipate these changes and determine how control measures might evolve in the autumn 2021 to maximize their impact while minimizing costs.

This autumn, the stress on the healthcare system in the absence of any control measures will depend on the vaccine coverage and the transmission potential R_0 of the dominant variant. R_0 was around 3 for the historical lineages[10]. The Alpha variant that is currently dominant in France was found to be about 50% more transmissible than historical lineages[11–13] and the Delta variant that is rising to dominance might be 50% more

transmissible than the Alpha variant [14]. If we simply apply these multiplicative terms, R_0 might be as high as 7 for the Delta variant. However, it is possible that transmissibility differences between variants change with control conditions. We therefore considered R_0=4 in our baseline analysis and explored values between 3 and 5 in our sensitivity analyses. For $R_0 \geq 4$ which appears likely for the Delta variant and under our optimistic baseline vaccine coverage of 30%-70%-90% among teenagers, younger and older adults, we anticipate an important stress on the healthcare system in the absence of any control measure (Figure 3A). It is therefore likely that some form of epidemic control will be required this autumn.

Since vaccines reduce the risk of infection and of transmission if infected, our model anticipates that unvaccinated individuals will contribute much more to disease spread than vaccinated ones. Since vaccine coverage among children aged 0-17 y.o. will be low relative to that in adults, we anticipate a strong increase of children's contribution, with about half of infections occurring in children and being due to this group in our baseline scenario. Adults that are not vaccinated will also disproportionately contribute to the stress on the healthcare system. This is particularly true for those that are older than 60 y.o. In our baseline scenario, this group represents 3% of the population but 35% of hospital admissions.

These observations have important implications for epidemic control. First, they show the importance of obtaining near perfect vaccine coverages in older age groups that contribute disproportionately to the stress on the healthcare system. This likely requires the development of strategies where authorities reach out to individuals to facilitate their access to vaccines. Second, we anticipate that, in a population that is partially vaccinated, most of the gains achieved thanks to social distancing measures are obtained by reducing the contacts of unvaccinated individuals. Requesting vaccinated individuals to socially distance adds very little. This suggests that, in this new era, control measures targeting unvaccinated individuals (for example with the use of a pass available to vaccinated individuals only) may help maximizing epidemic control. Such a targeting strategy may raise a number of ethical and social issues that need to be considered. From an economic perspective, targeting the

unvaccinated would maximize the effectiveness of control while minimizing the cost to society. This is consistent with the theory that in situations where a small group of individuals contributes disproportionately to the spread of disease, it is optimal to target that group[15]. However, targeting unvaccinated individuals would inevitably result in discrimination. While it is true that discrimination between the vaccinated and the unvaccinated is to some extent a voluntary choice, as vaccines are now widely available, these "choices" remain socially stratified and correlated with age and socioeconomic status. Furthermore, the restrictions put in place to target the unvaccinated will not be chosen by the individuals themselves: they will be defined by the authorities. The "choices" could be seen as biased; they could be seen as discrimination, especially by those most affected. Who would then define whether these discriminations - real or perceived - are legitimate, and to what extent? Rather than making such difficult trade-offs, of all the measures we considered, vaccination of the unvaccinated remained by far the most acceptable and cost-effective strategy.

The situation of children is a particular source of concern. Children aged <12 y.o. do not have access to vaccines yet and vaccine coverage may initially remain low among teenagers because of the perception that they do not gain from being vaccinated because they mostly develop mild SARS-CoV-2 infections. However, this assessment does not factor in the need to secure children’s access to education and a normal social life and to protect their mental health. Low vaccine coverage among children puts them at risk of being exposed to class closures, with a deleterious impact on their education and mental health[16]. The vaccination of children would insulate them from that risk. In the case of children, the ethical and social problems are exacerbated. On the vaccination side, discrimination arises from the fact that children cannot be seen as making voluntary choices between vaccination and social restrictions. Vaccination is not offered before the age of 12, and beyond the age of 12, the "choice" to be vaccinated depends primarily on the family environment. As for other measures potentially targeted at schools, a wide range of instruments is available (from mask wearing to physical distancing, air filtration, iterative self-testing, closing rules,

dedicated tracing, isolation of family members...) but their targeted implementation would disproportionately affect young people and their families, raising questions of social justice if society at large is less directly targeted, particularly in certain age groups.

This assessment is performed in a context of important uncertainty about the value of R_0 for the variant that will be dominant and vaccine coverage in the autumn. Our model makes a number of simplifying assumptions. We ignore a potential decay of immunity, whether immunity was acquired through natural infection or vaccination. We also ignore the circulation of variants that might partially escape this immunity. We consider a national model for France and do not account for spatial heterogeneities, that are important[17]. There are two ways to model the impact of a vaccine. Consider for example a vaccine that reduces the risk of infection by 80%. If the vaccine is “leaky”, it is assumed that all those vaccinated benefit from an 80% reduction in the risk of infection each time they are exposed to the virus. In such a model, if R_0 is high, vaccinated individuals may be exposed multiple times to the virus so that a large proportion of them may eventually get infected if R_0 is high enough. For an “all-or-nothing” vaccine, in contrast, it is assumed that 80% of those vaccinated are fully protected and cannot get infected even if they are repeatedly exposed to the virus. The other 20% vaccinated individuals correspond to vaccine failures that remain unprotected against infection. These two types of models give relatively similar results for small values of R_0. However, when R_0 increases, models with leaky vaccines tend to predict larger epidemic sizes than models with all-or-nothing vaccines[18,19]. Like ours, most models for SARS-CoV-2 have so far assumed that SARS-CoV-2 vaccines are leaky[5,20,21]. If the reality lies between these two options, our model predictions for the size of the autumn epidemic might be a bit pessimistic for a given value of R_0. However, this phenomenon should be compensated by the fact that the baseline value for R_0 that we selected was in the lower range of possible estimates for the Delta variant.

We used a mathematical model to anticipate how the epidemiology of SARS-CoV-2 may change in partially vaccinated populations and investigate implications for the control of a possible epidemic rebound this autumn.

Methods

Deterministic model

We developed a deterministic age-stratified compartmental model describing the spread of SARS-CoV-2 in metropolitan France. The model, which accounts for French age-specific contact patterns[22], has been described in detail elsewhere.[10] It accounts for a gradient of severity with age[23] and an increased severity of 64% of the Alpha VOC compared to previously circulating strains[24] (assuming similar severity for variants that might circulate this autumn). It has been extended to account for the roll-out of vaccines[4] as well as the deployment of self-administered rapid antigenic tests.[25] A full description of the model and equations is reported in the Supplement.

Scenarios

Vaccine coverages and characteristics

We assume that vaccines are 95% effective at reducing the risk of hospitalisation[1], 80% at reducing the risk of infection[2] (impact on susceptibility) and 50% at reducing the infectivity of vaccinated individuals[3]. In a sensitivity analysis, we show results if vaccines are 90% effective against hospitalisation. We build several scenarios regarding vaccine coverage achieved in the different age groups by September 1st, 2021: 90% among those older than 60 years old (y.o.); 50%, 70% or 90% among those aged 18-59 y.o. and 0%, 30%, 50%, 70% among the 12-17 y.o. (called teenagers in the following). To give some context, 78% of those older than 60 y.o., 41% of the 18-59 y.o. and 0% of the 12-17 y.o. have received a first dose of vaccines against SARS-CoV-2 by date June 7th, 2021. In our baseline scenario that we

label 30%-70%-90%, we assume vaccination coverage will reach 30%, 70% and 90% among 12-17 y.o., 18-59 y.o. and over 60 on September 1st, 2021. In this analysis, we consider that the vaccine coverage corresponds to the proportion of the population having acquired vaccine protection after two doses if required.

Epidemic dynamics with and without control measures

We assume that, by September 1st, 2021, 25% (range: 20-30%) of the French population will have been infected by SARS-CoV-2, benefiting from natural protection against reinfection. We then explore scenarios where different types of control measures are implemented.

First, we explore scenarios where control measures are completely relaxed in the Autumn. These scenarios are characterized by the basic reproduction number R_0, i.e. the average number of persons infected by a case in a population with no immunity and no control measures. In March 2020, R_0 was estimated around 3 in France prior to the implementation of a nation-wide lockdown.[10] The emergence of more transmissible variants of concerns (VOC) (such as the Alpha and Delta VOCs)[12–14,26] is expected to increase R_0. We therefore explore scenarios in which R_0 ranges between 3.0 and 5.0 when measures are completely relaxed. We assume that from September 1st, 2022, the structure of contacts in the population comes back to the one measured during the pre-pandemic period.[22]

We then consider scenarios where different types of control measures are implemented, targeting different groups:

- Iterative testing: we assume that a proportion of the population is targeted for iterative testing with antigenic tests. These individuals test at regular intervals (every 7 days in the baseline scenario; twice a week and every 2 weeks in sensitivity analyses). We assume that individuals testing positive isolate in a way that reduces onward transmission by 75%. We consider a scenario where 50% of unvaccinated individuals aged ≥12 y.o. get tested iteratively and a scenario where the same number of

individuals randomly drawn among individuals aged ≥12 y.o. (vaccinated or unvaccinated) are tested iteratively. We consider scenarios where the antigenic test is performed by the individual (self-swabbing and reading of the result; sensitivity: 75%) or by a professional (sensitivity 90%). In a sensitivity analysis, we also explore a scenario where 25% of unvaccinated individuals ≥12 y.o. get tested iteratively.

- Non-pharmaceutical interventions: Non-pharmaceutical interventions such as social distancing, protective measures and mask wearing may be used to reduce transmission rates. We consider scenarios where such measures target the whole population, leading to reductions of transmission rates of 10%, 20%, 30% or 40% from any infected individual, whether they have been vaccinated or not. We also consider scenarios where such measures only target unvaccinated individuals, leading to reductions of transmission rates of 10%, 20%, 30% or 40% from unvaccinated individuals, while transmission rates from vaccinated individuals remain unchanged.
- Increased vaccine coverage among unvaccinated individuals: We compare the performance of these interventions to that obtained if 50% of the unvaccinated individuals aged ≥12 y.o. were to get vaccinated.

Children are defined as individuals aged 0-17 y.o. We assume that children aged 0-9 y.o. are 50% less susceptible to infection than adults while those aged 10-17 y.o. are 25% less susceptible to infection than adults [10,27]. In a sensitivity analysis, we also assume that children aged 0-9 y.o. are 50% less infectious than adults.

We assume an antigenic test costs 5 euros if performed by the individual, 11 euros if performed by a professional and a 2-doses vaccine costs 32 euros. Models are run until March 20th 2022.

Funding: We acknowledge financial support from the Investissement d'Avenir program, the Laboratoire d'Excellence Integrative Biology of Emerging Infectious Diseases program (grant ANR-10-LABX-62-IBEID), HAS, Santé Publique France, the INCEPTION project (PIA/ANR-16-CONV-0005), the European Union's Horizon 2020 research and innovation program under grant 101003589 (RECOVER) and 874735 (VEO), AXA and Groupama.

Author contributions: PB, CTK and SC conceived the study. PB, CTK and AA performed the analyses. PB, CTK and SC wrote the first draft. All authors contributed to revisions of the manuscript.

Competing interests: None declared.

Data and materials availability: Data and code will be published online upon publication.

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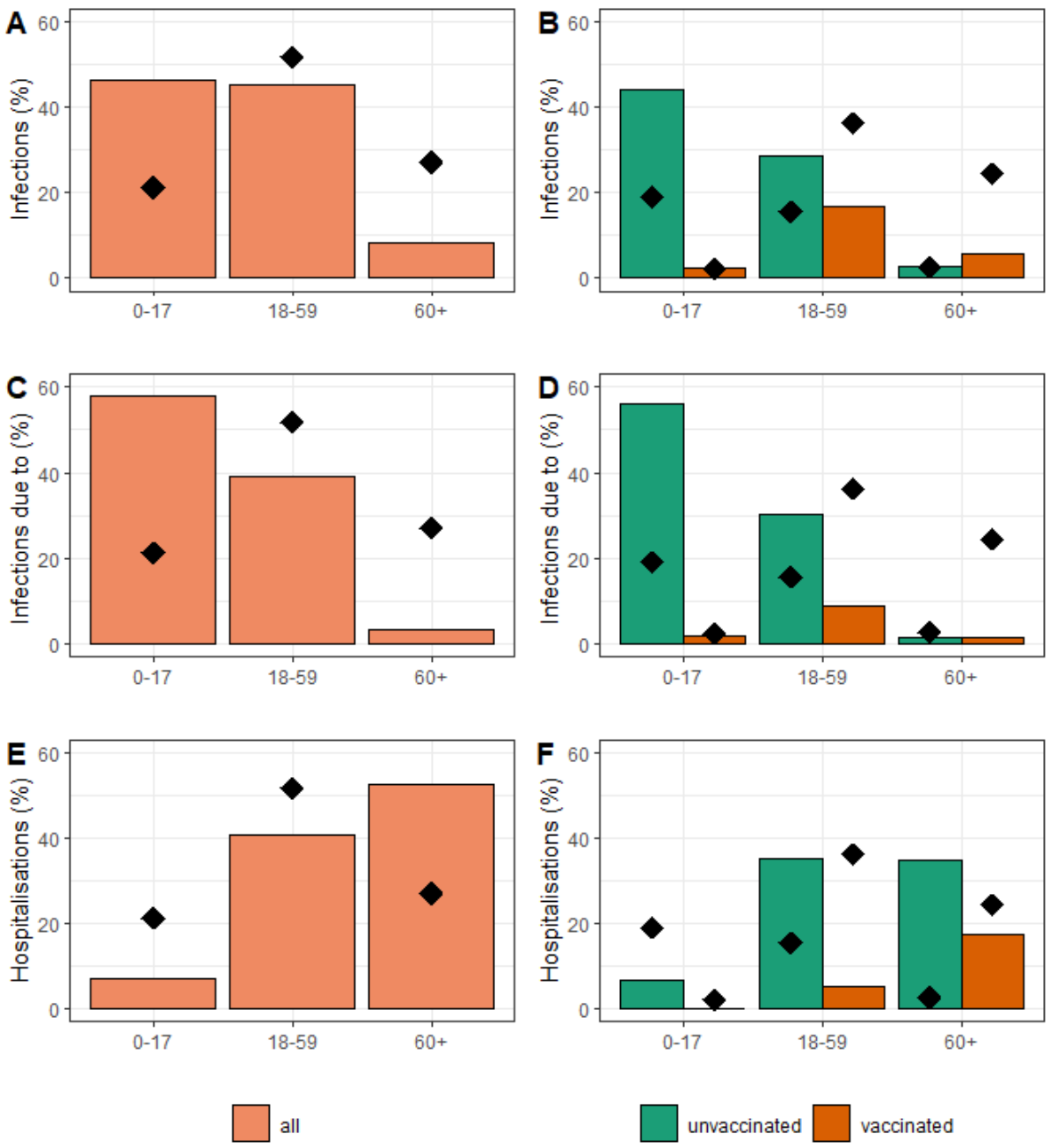

Figure 1: Contribution of groups defined by their age and vaccination status to infections, disease spread and hospital burden, in our baseline scenario with R_0=4 and a vaccine coverage of 30%-70%-90% among 12-17 y.o., 18-59 y.o. and over 60 y.o. Age distribution of new infections **A.** in the entire population and **B.** among vaccinated and unvaccinated individuals. Proportion of infections **C.** attributable to different age groups and **D.** attributable to different age groups among vaccinated and unvaccinated individuals. Age distribution of hospitalisations **E.** in the entire population and **F.** among vaccinated and unvaccinated individuals. In all panels, the diamonds indicate the age distribution of the different groups in the population.

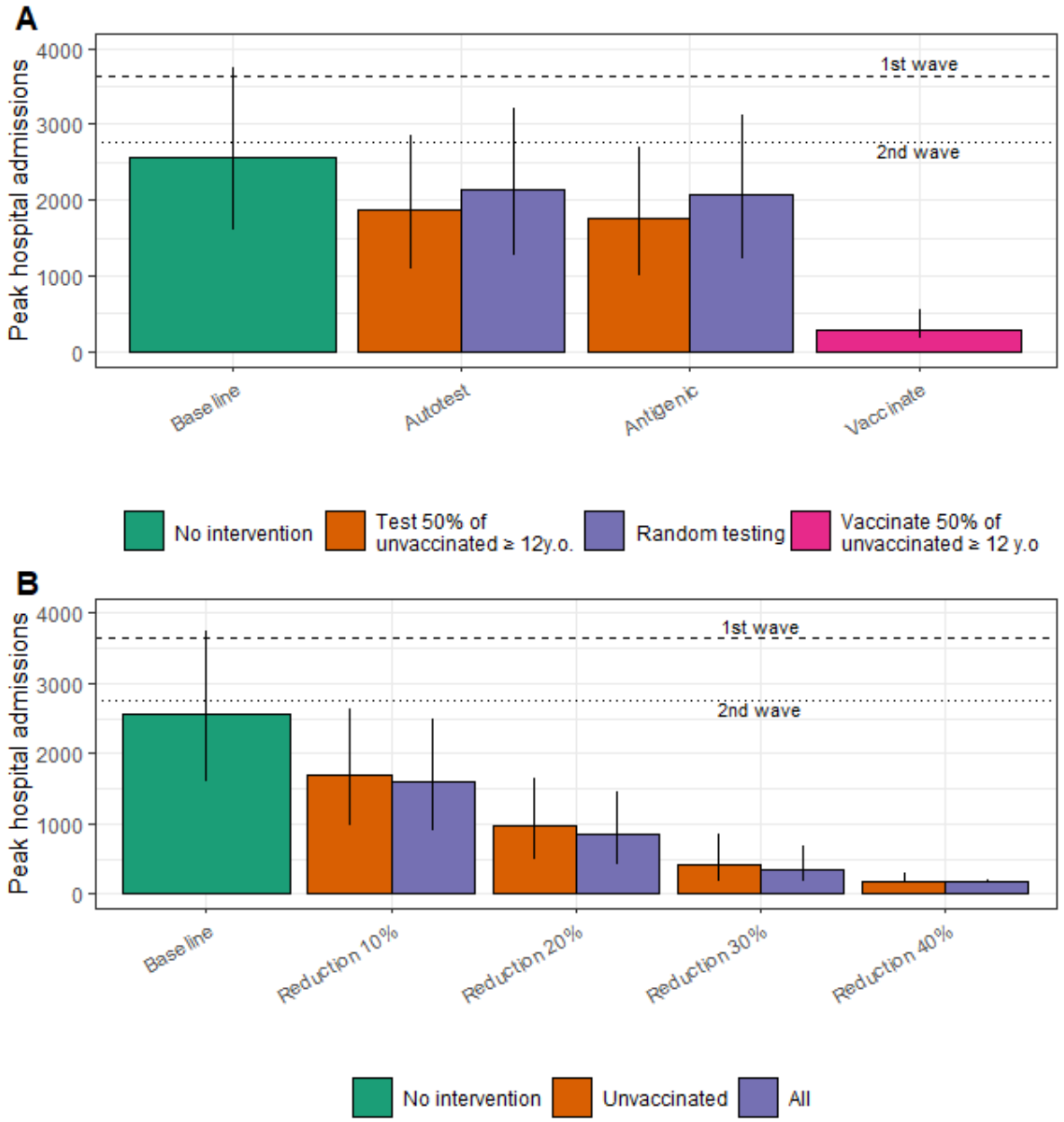

Figure 2: Comparison of the impact of control strategies targeting the entire population vs unvaccinated individuals only, in our baseline scenario with R_0=4 and a vaccine coverage of 30%-70%-90% among 12-17 y.o., 18-59 y.o. and over 60 y.o. A. Peak in daily hospital admissions under different testing strategies. *Baseline* - no intervention; *Autotest unvaccinated* - 50% of the unvaccinated individuals aged ≥12 y.o. are tested weekly (sensitivity of 75%); *Autotest random* - the same number of individuals as in the *Autotest unvaccinated* are tested but among individuals aged ≥12 y.o., irrespective of vaccine status; *Antigenic unvaccinated* - same as in *Autotest unvaccinated* but with tests performed by a professional (sensitivity of 90%); *Antigenic random* - same as in *Autotest random* but with tests performed by a professional (sensitivity of 90%); *Vaccinate* - 50% of the unvaccinated individuals aged ≥12 y.o. are vaccinated. **B.** Peak in daily hospital admissions under non-pharmaceutical interventions of varying intensities. *Baseline* - no intervention; *Reduction of x% unvaccinated* - The transmission rate of unvaccinated individuals is reduced by x%; *Reduction of x% all* - The transmission rate at the population

level is reduced by x%. We assume 25% of the population has acquired protection through natural infection (range 20%-30% corresponding to the vertical bars).

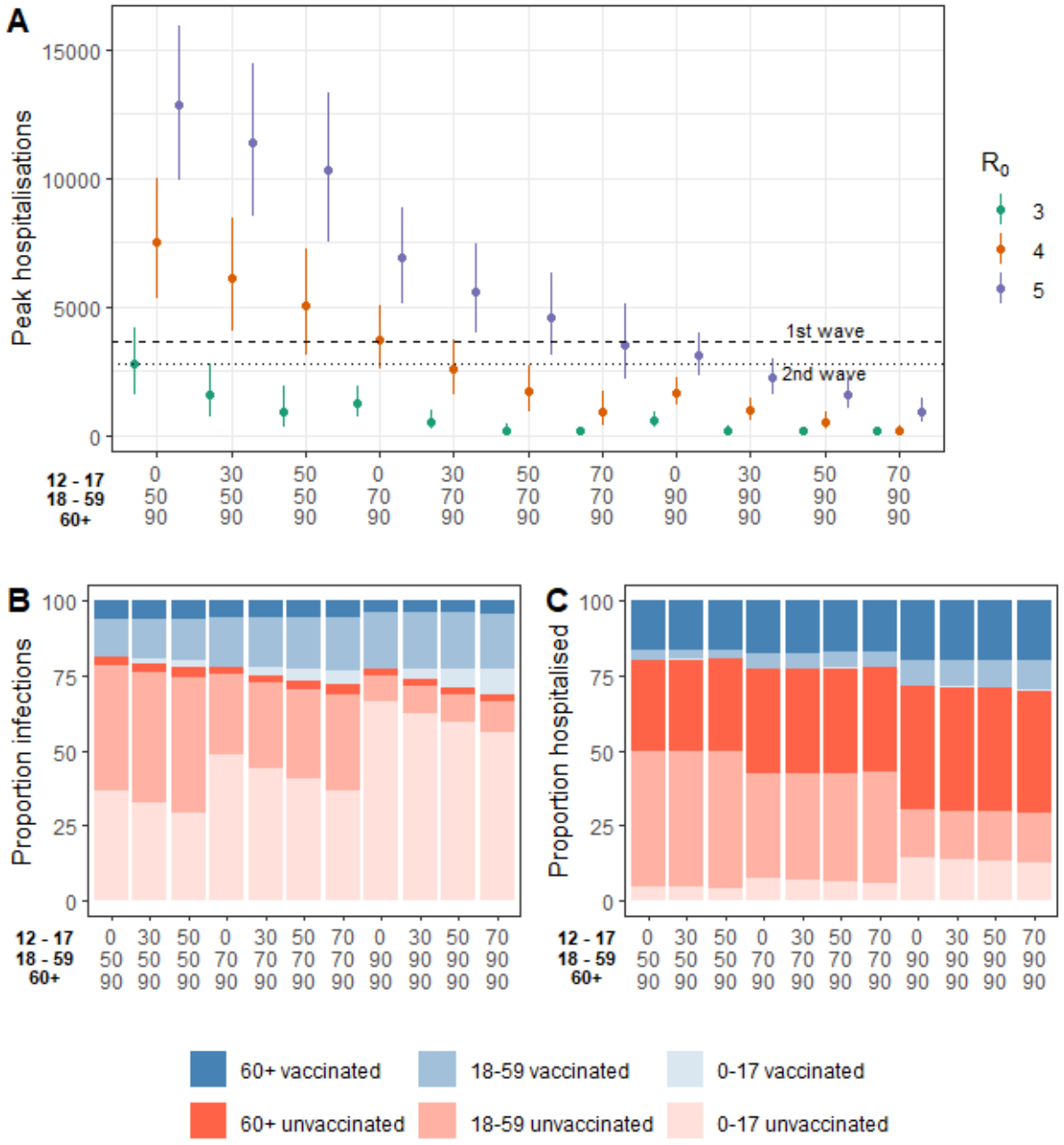

Figure 3: Projections in the absence of control measures, as a function of the basic reproduction number R_0 and vaccine coverage in the 12-17 y.o., 18-59 y.o. and over 60 y.o.. A. Peak in daily hospital admissions in the absence of control measures. **B.** Distribution of infections between groups defined by their age and vaccination status. **C.** Distribution of hospitalizations between groups defined by their age and vaccination status. In (B-C), the distribution is reported for infections and hospitalizations occurring between September 1st, 2021 and March 20th, 2022 (end of the study period), for R_0=4.0. Projections for other values of R_0 are presented in Supplementary Figure S3. We assume 25% of the population has acquired protection through natural infection (range 20%-30% corresponding to the vertical bars in A).

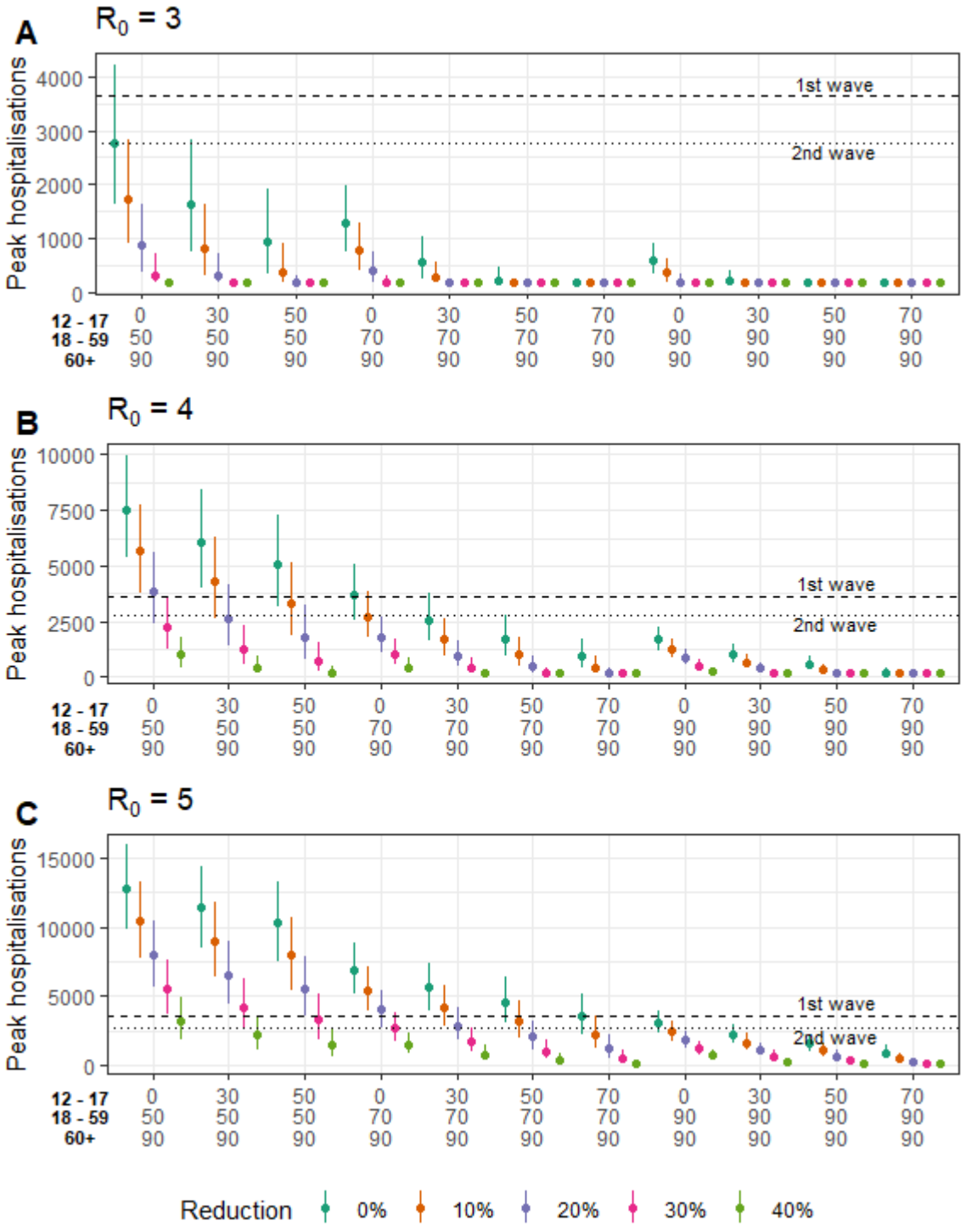

Figure 4: Peak of hospitalisations when non-pharmaceutical interventions target unvaccinated individuals, as a function of the basic reproduction number R_0 and vaccine coverage in the 12-17 y.o., 18-59 y.o. and over 60 y.o. Non-pharmaceutical interventions reduce the transmission rate of unvaccinated individuals by 0%, 10%, 20%, 30%, 40%. R0 takes the values **A.** 3.0, **B.** 4.0, and **C.** 5.0. We assume 25% of the population has acquired protection through natural infection (range 20%-30% corresponding to the vertical bars).

Supplement for: Epidemiology and control of SARS-CoV-2 epidemics in partially vaccinated populations: a modeling study applied to France

Supplementary materials

Model parametrization

We developed a deterministic SEEIR model stratified by age similar to the one used in Salje et al.[1] The model has been extended to account for the roll-out of vaccines[3] as well as the deployment of self-administered rapid antigenic tests[4]. The metropolitan French population is divided into the following 13 age groups: [0-10), [10-18), [18-30), [30-40), [40-45), [45-50), [50-55), [55-60), [60-65), [65-70), [70-75), [75-80) and ≥ 80. We assume that individuals aged 0-9 y.o. and 10-17 y.o are respectively 50% and 25% less susceptible compared to adults[5,6]. The model is implemented with the R software using the *odin* package[7].

Transmission model accounting for iterative testing

Upon infection, susceptible individuals (S) move to the compartment E1. After an average duration of 4.0 days, infected individuals move to the E2 compartment where they become infectious. They stay in this compartment for an average duration of 1.0 day before moving to the I compartment (IM for mild infections or IH for infections requiring an admission in hospital) in which a fraction of them will develop symptoms. The average length of stay in I is equal to 3.0 days. The proportion of individuals that will require an admission in hospital is age dependent and is 64%[8] higher with respect to the age-specific probabilities of hospitalization estimated in France by Lapidus et al[9], to account for the increased severity associated with the emergence of the Alpha variant of concern. Finally, individuals in the IM compartment will recover (R compartment), while individuals in the IH will move to the $\bar{I}H$ compartment before being admitted in hospital (compartment H). Individuals who have been vaccinated follow the same path as those who have not been vaccinated, but they are less susceptible to infection, have a reduced risk of being hospitalized, and are less likely to transmit the disease.(Tran Kiem et al. 2021).

Our framework accounts for the deployment of iterative testing strategies. Upon receiving a positive test, we assume that infectious individuals (in compartments E2, IM, and IH) detected isolate, resulting in a reduction of their transmission rate by 75%. This corresponds to the compartments E2iso, IMiso, and IHiso. We assume that individuals tested while in E1 remain undetected and therefore do not isolate. The average length of stay in isolated compartments is identical to the one in non-isolated ones.

Model Equations

The model can be described by the following set of ordinary differential equations:

$$dS_i/dt = -S_i\ \beta\left(\Sigma_j C_{ij}\left((1-\rho_{int})(E2_j + I_j^{mild} + I_j^{hosp} + (1-\rho_{iso})(E2iso_j + Iiso_j^{mild} + Iiso_j^{hosp})\right) +\right.$$

$$\left. + (1-\rho^v_{int})(1-VE_{inf})(E2^v_j + I^v_j{}^{mild} + I^v_j{}^{hosp} + (1-\rho_{iso})(E2iso^v_j + Iiso^v_j{}^{mild} + Iiso^v_j{}^{hosp})\right)$$

$$dS^v_i/dt = -(1-VE_{susc})\,S^v_i\ \beta\left(\Sigma_j C_{ij}\left((1-\rho_{int})(E2_j + I_j^{mild} + I_j^{hosp} + (1-\rho_{iso})(E2iso_j + Iiso_j^{mild} +\right.\right.$$

$$\left.\left. + (1-\rho^v_{int})(1-VE_{inf})(E2^v_j + I^v_j{}^{mild} + I^v_j{}^{hosp} + (1-\rho_{iso})(E2iso^v_j + Iiso^v_j{}^{mild} + Iiso^v_j{}^{hosp})\right)\right.$$

$$dE1_i/dt = -S_i\ \beta\left(\Sigma_j C_{ij}\left((1-\rho_{int})(E2_j + I_j^{mild} + I_j^{hosp} + (1-\rho_{iso})(E2iso_j + Iiso_j^{mild} + Iiso_j^{hosp})\right) +\right.$$

$$\left. + (1-\rho^v_{int})(1-VE_{inf})(E2^v_j + I^v_j{}^{mild} + I^v_j{}^{hosp} + (1-\rho_{iso})(E2iso^v_j + Iiso^v_j{}^{mild} + Iiso^v_j{}^{hosp})\right)$$

$$- g_1 \cdot E1_i$$

$$dE1^v_i/dt = (1-VE_{susc})\,S^v_i\ \beta\left(\Sigma_j C_{ij}\left((1-\rho_{int})(E2_j + I_j^{mild} + I_j^{hosp} + (1-\rho_{test})(E2iso_j + Iiso_j^{mild} + Ii\right.\right.$$

$$\left.\left. + (1-\rho^v_{int})(1-VE_{inf})(E2^v_j + I^v_j{}^{mild} + I^v_j{}^{hosp} + (1-\rho_{test})(E2iso^v_j + Iiso^v_j{}^{mild} + Iiso^v_j{}^{hosp}\right.\right.$$

$$- g_1 \cdot E1^v_i$$

$$dE2_i/dt = g_1 \cdot E1_i - g_2 \cdot E2_i - \nu_{test,i} \cdot E2_i$$

$$dE2^v_i/dt = g_1 \cdot E1^v_i - g_2 \cdot E2^v_i - v^v_{test,i} \cdot E2^v_{ki}$$

$$dE2iso_i/dt = \nu_{test,i} \cdot E2_i - g_2 \cdot E2iso_i$$

$$dE2iso^v_i/dt = v^v_{test,i} \cdot E2^v_{ki} - g_2 \cdot E2iso^v_i$$

$$dI_i^{mild}/dt = (1-p^{hosp}_i) \cdot g_2 \cdot E2_i - g_3 \cdot I_i^{mild} - v_{test,i} \cdot I_i^{mild}$$

$$dI^v_i{}^{mild}/dt = (1-p^{hosp}_i \cdot (1-VE_{sev}))\, g_2 \cdot E2^v_i - g_3 \cdot I^v_i{}^{mild} - v^v_{test,i} \cdot I^v_i{}^{mild}$$

$$dIiso_i^{mild}/dt = (1-p^{hosp}_i) \cdot g_2 \cdot E2iso_i + v_{test,i} \cdot I_i^{mild} - g_3 \cdot Iiso_i^{mild}$$

$$dIiso^{v}_{i}{}^{mild}/dt = (1 - p^{hosp}_{i} \cdot (1 - VE_{sev}))\, g_2 \cdot E2iso^{v}_{i} + v^{v}_{test,i} \cdot I^{v}_{i}{}^{mild} - g_3 \cdot Iiso^{v}_{i}{}^{mild}$$

$$dR_i/dt = g_3 \cdot I_i^{mild} + g_3 \cdot Iiso_i^{mild}$$

$$dR^{v}_{ki}/dt = g_3 \cdot I^{v}_{ki}{}^{mild} + g_3 \cdot Iiso^{v}_{i}{}^{mild}$$

$$dI_i^{hosp}/dt = p^{hosp}_{i} \cdot g_2 \cdot E2_i - g_3 \cdot I_i^{hosp} - v_{test,i} \cdot I_i^{hosp}$$

$$dI^{v}_{i}{}^{hosp}/dt = p^{hosp}_{i} \cdot (1 - VE_{sev}) \cdot g_2 \cdot E2^{v}_{i} - g_3 \cdot I^{v}_{i}{}^{hosp} - v^{v}_{test,i} \cdot I^{v}_{i}{}^{hosp}$$

$$dIiso_i^{hosp}/dt = p^{hosp}_{i} \cdot g_2 \cdot E2iso_i + v_{test,i} \cdot I_i^{hosp} - g_3 \cdot Iiso_i^{hosp}$$

$$dIiso^{v}_{i}{}^{hosp}/dt = p^{hosp}_{i} \cdot (1 - VE_{sev}) \cdot g_2 \cdot E2iso^{v}_{i} + v^{v}_{test,i} \cdot I^{v}_{i}{}^{hosp} - g_3 \cdot Iiso^{v}_{i}{}^{hosp}$$

$$d\bar{I}H_i/dt = g_3 \cdot I_i^{hosp} + g_3 \cdot Iiso_i^{hosp} - g_4 \cdot \bar{I}H_i$$

$$d\bar{I}H^{v}_{i}/dt = g_3 \cdot I^{v}_{i}{}^{hosp} + g_3 \cdot Iiso^{v}_{i}{}^{hosp} - g_4 \cdot \bar{I}H^{v}_{i}$$

$$dH_i/dt = g_4 \cdot \bar{I}H_i$$

$$dH^{v}_{i}/dt = g_4 \cdot \bar{I}H^{v}_{i}$$

where we let:

- C_{ij}, $(i, j) \in \{1, \ldots, 13\}^2$ denote the coefficient of the contact matrix,
- the superscripts v indicate the different vaccinated compartments,
- the subscripts i indicate the age groups,
- N_j denote the population size for the age class j,
- β denote the transmission rate,
- g_1 denote the rate at which an exposed individual becomes infectious and we set its value $1/g_1 = 4$ days. We set $1/g_2 = 1$ day, and $1/g_3 = 3$days resulting in an average infectious period of 4 days,
- $g_4$denote the rate of hospital admissions and we set $1/g_4 = 4$days,[1]

- ρ_{int} denote the reduction in the transmission rate for unvaccinated individuals (impact of non-pharmaceutical interventions),
- ρ^{v}_{int} denote the reduction in the transmission rate for vaccinated individuals (impact of non-pharmaceutical interventions),
- ρ_{iso} denote the reduction in the transmission rate for isolated individuals,
- $\nu_{test,i}$ denote the rate of testing for unvaccinated individuals.
- $\nu^{v}_{test,i}$ denote the rate of testing for vaccinated individuals,
- VE_{sev}, VE_{inf}, and VE_{susc} denote the effectiveness of the vaccines on reducing the probability of hospitalization, the infectiousness and the probability of becoming infected of vaccinated individuals compared to unvaccinated individuals.

Iterative testing

Let assume p_i^{test} the proportion of the population of the age class i participating in iterative testing. In the scenario where only unvaccinated individuals aged ≥12 y.o. take part in iterative testing, we set

$$\nu_{test,i} = p_i^{test} \cdot Sensitivity \cdot (1/test_{delay}) \text{ and}$$

$$\nu^{v}_{test,i} = 0$$

where $Sensitivity$ denotes the test sensitivity (equal to 75% if the test is self administered and or 90% if it is performed by a professional), and $test_{delay}$ represents the number of days between two consecutive tests (7 days in the baseline scenario).
In the scenario where individuals participating in the testing campaign are drawn randomly in the population aged ≥12 y.o. (vaccinated and unvaccinated) we set

$$\nu_{test,i} = \nu^{v}_{test,i} = p_i^{test} \cdot p_{unvaccinated,i} \cdot Sensitivity \cdot (1/test_{delay}),$$

where $p_{unvaccinated,i}$ represent the proportion of unvaccinated individuals of the age class i.

Initialization of the model on September 1st, 2021

On September 1st, 2021, we assume that 25% of the metropolitan French population (range: 20%-30%) developed immunity through natural infection. To account for heterogeneity in the risk of infection between the different age groups of the population, we use the distribution of infections predicted by a dynamical model calibrated on data until May 2021[1]. The natural infections are thus distributed across different age groups to reproduce both the distribution of infections obtained from the model and the proportion of the population having acquired immunity. We also build several scenarios regarding the vaccine coverages reached in different groups of the population:

- 90% among those older than 60 years old (y.o.)
- 50%, 70% or 90% among those aged 18-59 y.o.
- 0%, 30%, 50%, 70% among the 12-17 y.o.

In our baseline scenario we assume a vaccination coverage of 30%, 70% and 90% among 12-17 y.o., 18-59 y.o. and over 60 y.o. respectively on September 1st, 2021.

Additional results

Supplementary Table 1: Relative risk of infection, transmission and hospitalization for unvaccinated individuals relative to vaccinated individuals, in different age groups. This is for our baseline scenario characterized by R_0=4 and a vaccine coverage of 30%-70%-90% among 12-17 y.o., 18-59 y.o. and over 60 y.o..

Age group	Infection	Transmission	Hospitalisation
0-17	2.1	3.7	11.8
18-59	3.9	7.9	15.6
60+	4.5	9.0	18.0
All	5.1	12.1	5.7

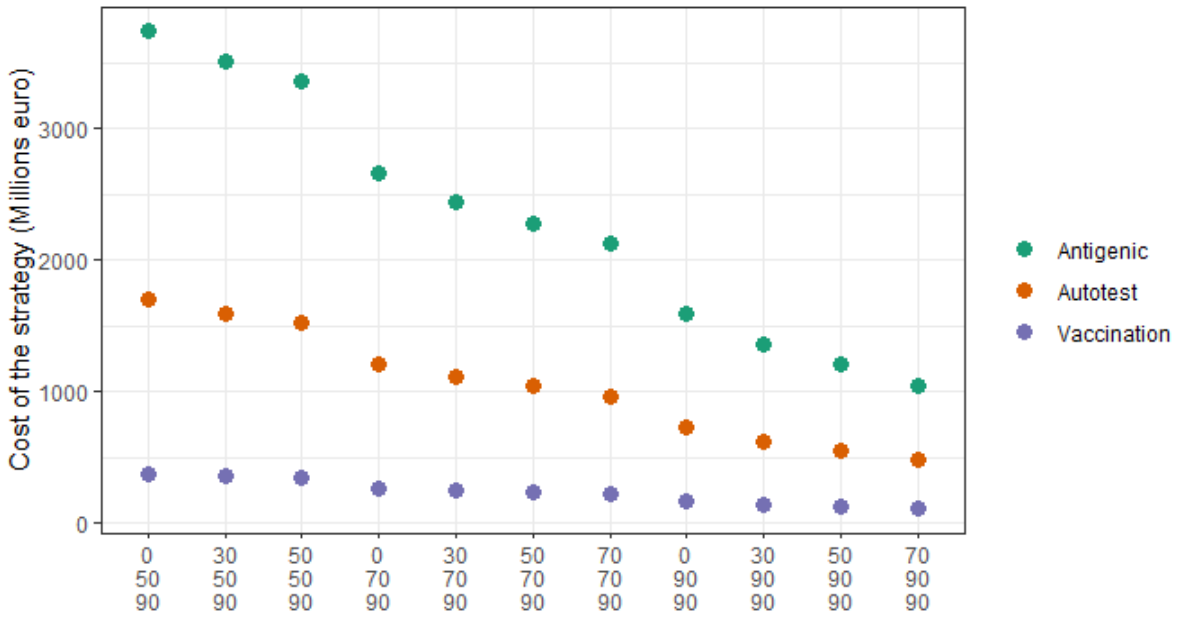

Figure S1: Comparison of the costs of different strategies. Costs of strategies targeting 50% of the unvaccinated individuals older than 12 y.o. as a function of the vaccine coverage reached in different groups. The 3 strategies are: weekly testing with an antigenic test performed by a professional (“antigenic”), weekly testing with an antigenic test performed by the individual (“autotest”), vaccination.

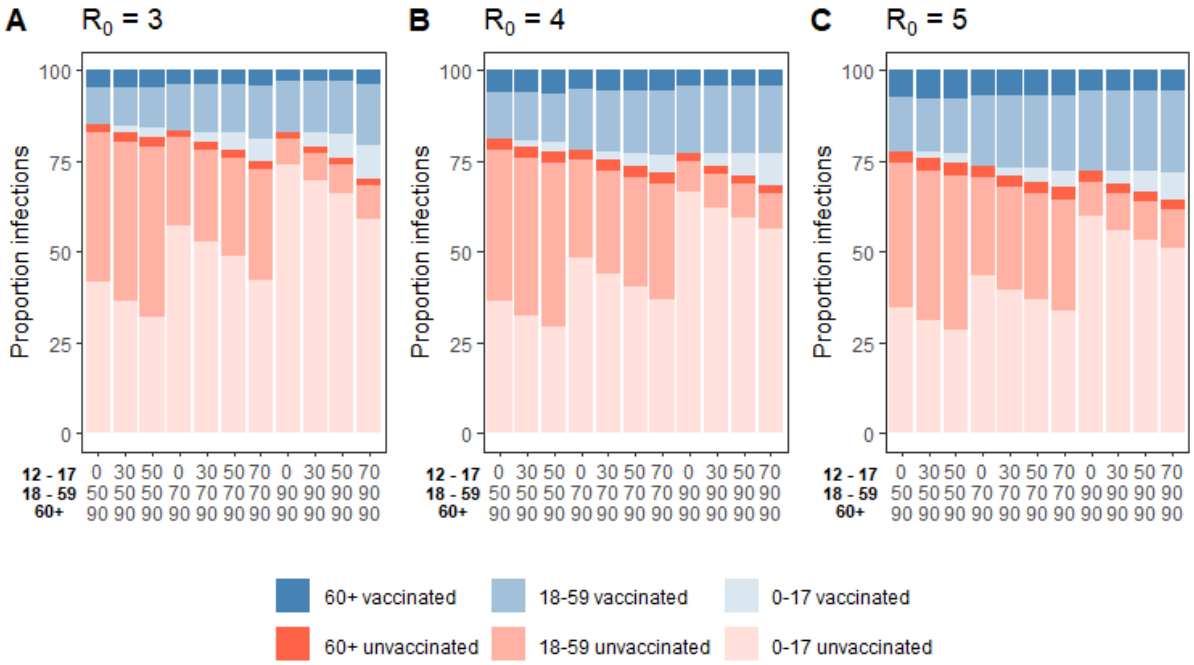

Figure S2: Distribution of infections between groups defined by their age and vaccination status. A. for R_0 = 3. **B.** for R_0 = 4. **C.** for R_0 = 5. The distribution is reported for infections occurring between September 1st, 2021 and March 20th, 2022 (end of the study period) and as a function of the vaccine coverage reached in the 12-17 y.o., 18-59 y.o. and over 60 y.o.

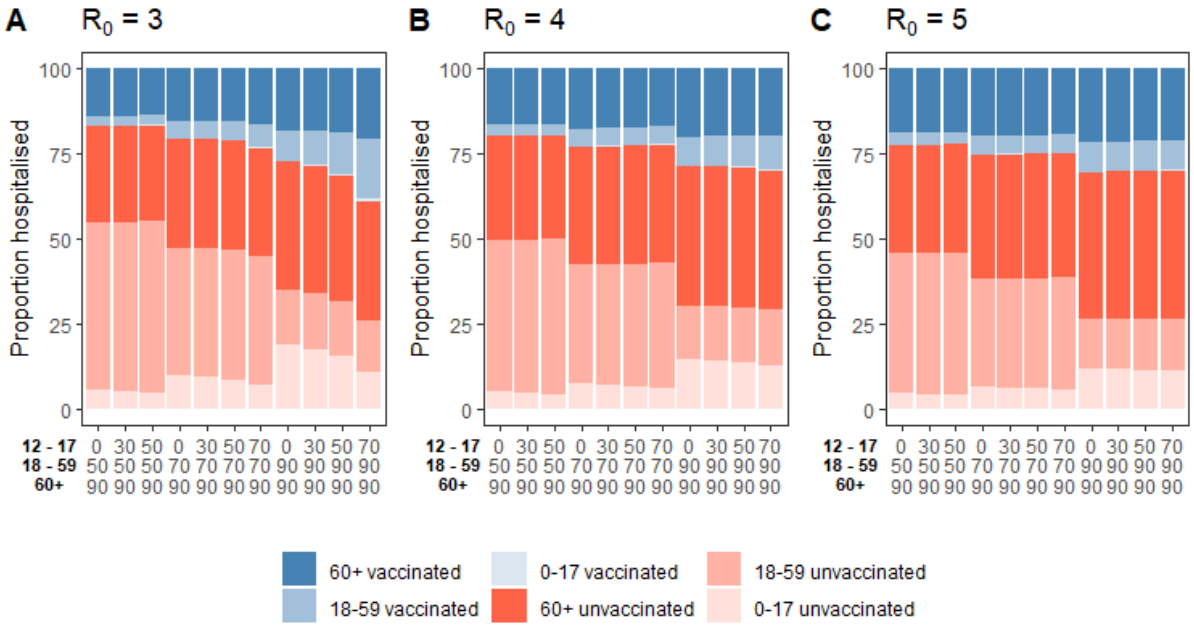

Figure S3: Distribution of hospitalisations between groups defined by their age and vaccination status. A. for R_0 = 3. **B.** for R_0 = 4. **C.** for R_0 = 5. The distribution is reported for hospitalizations occurring between September 1st, 2021 and March 20th, 2022 (end of the study period) and as a function of the vaccine coverage reached in the 12-17 y.o., 18-59 y.o. and over 60 y.o.

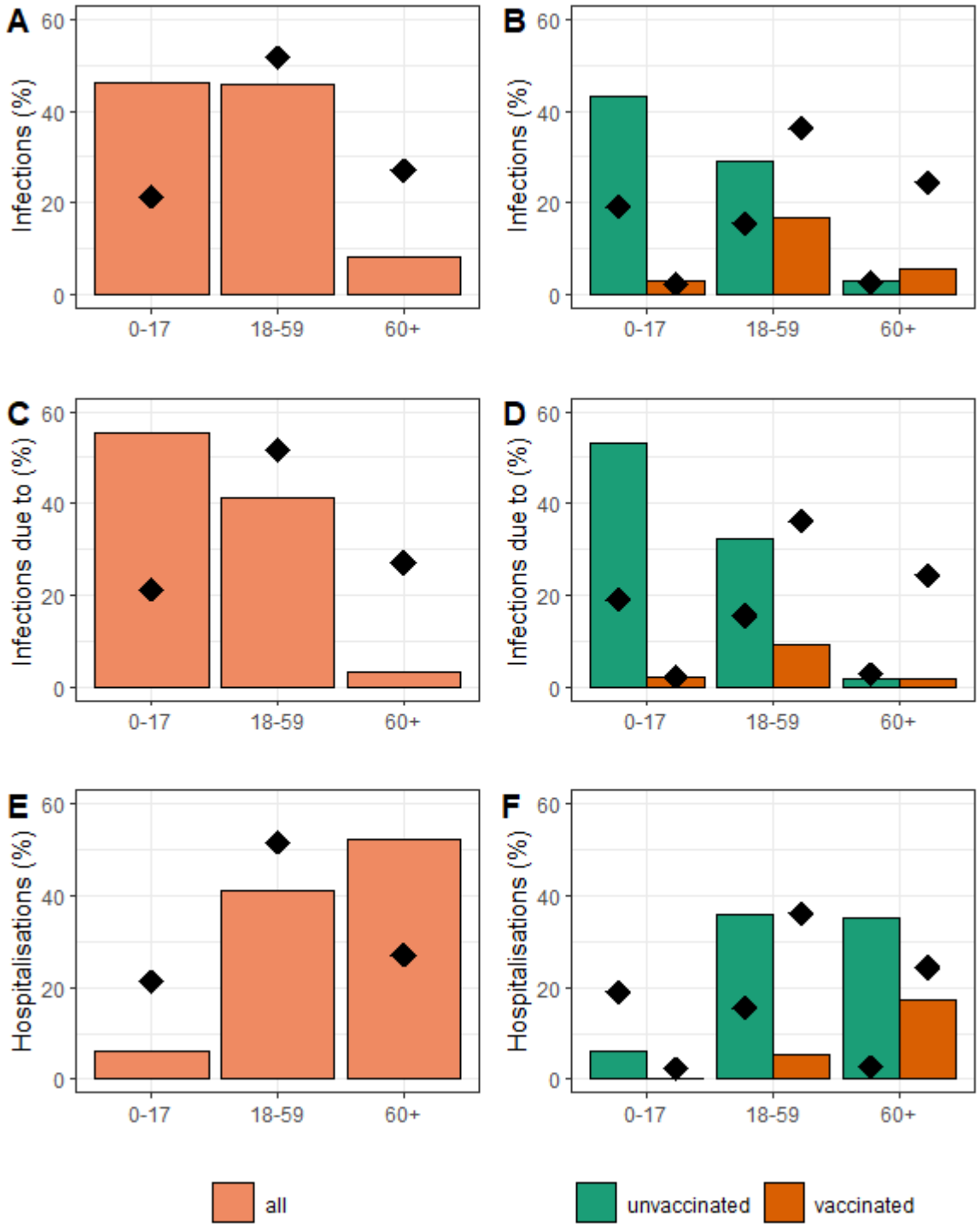

Figure S4: Contribution of groups defined by their age and vaccination status to infections, disease spread and hospital burden in a scenario where children aged 0-9 y.o. are 50% less infectious than adults, in addition to being 50% less susceptible. This is done under our baseline assumptions with R_0=4 and a vaccine coverage of 30%-70%-90% among 12-17 y.o., 18-59 y.o. and over 60 y.o. Age distribution of new infections **A.** in the entire population and **B.** among vaccinated and unvaccinated individuals. Proportion of infections **C.** attributable to different age groups and **D.** attributable to different age groups among vaccinated and unvaccinated individuals. Age distribution of hospitalisations **E.** in the entire population and **F.** among vaccinated and unvaccinated

individuals. In all panels, the diamonds indicate the age distribution of the different groups in the population.

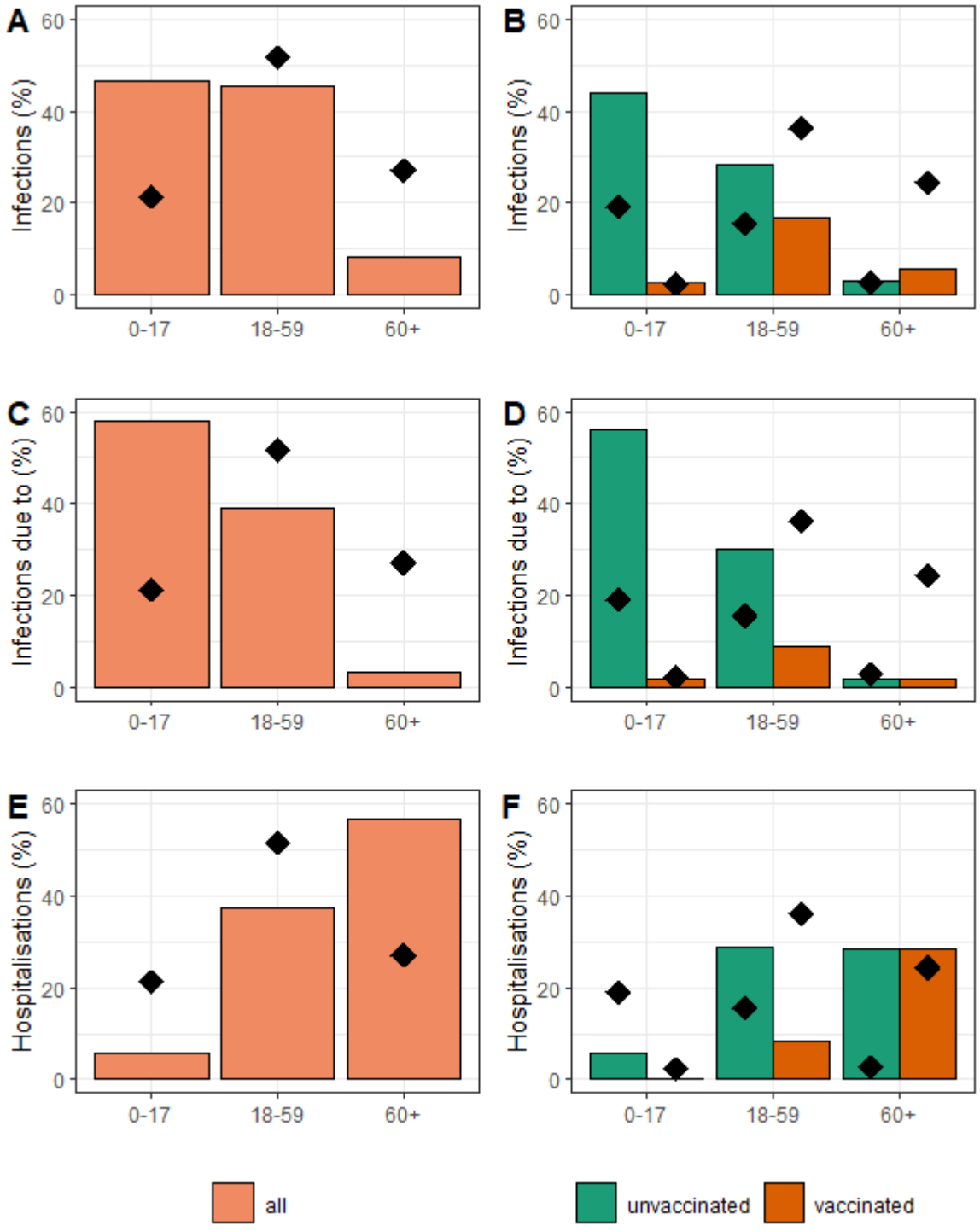

Figure S5: Contribution of groups defined by their age and vaccination status to infections, disease spread and hospital burden in a scenario where the efficacy of the vaccines against hospitalisation is set to 90%. This is done under our baseline assumptions with R_0=4 and a vaccine coverage of 30%-70%-90% among 12-17 y.o., 18-59 y.o. and over 60 y.o. Age distribution of new infections **A.** in the entire population and **B.** among vaccinated and unvaccinated individuals. Proportion of infections **C.** attributable to different age groups and **D.** attributable to different age groups among vaccinated and

unvaccinated individuals. Age distribution of hospitalisations **E.** in the entire population and **F.** among vaccinated and unvaccinated individuals. In all panels, the diamonds indicate the age distribution of the different groups in the population.

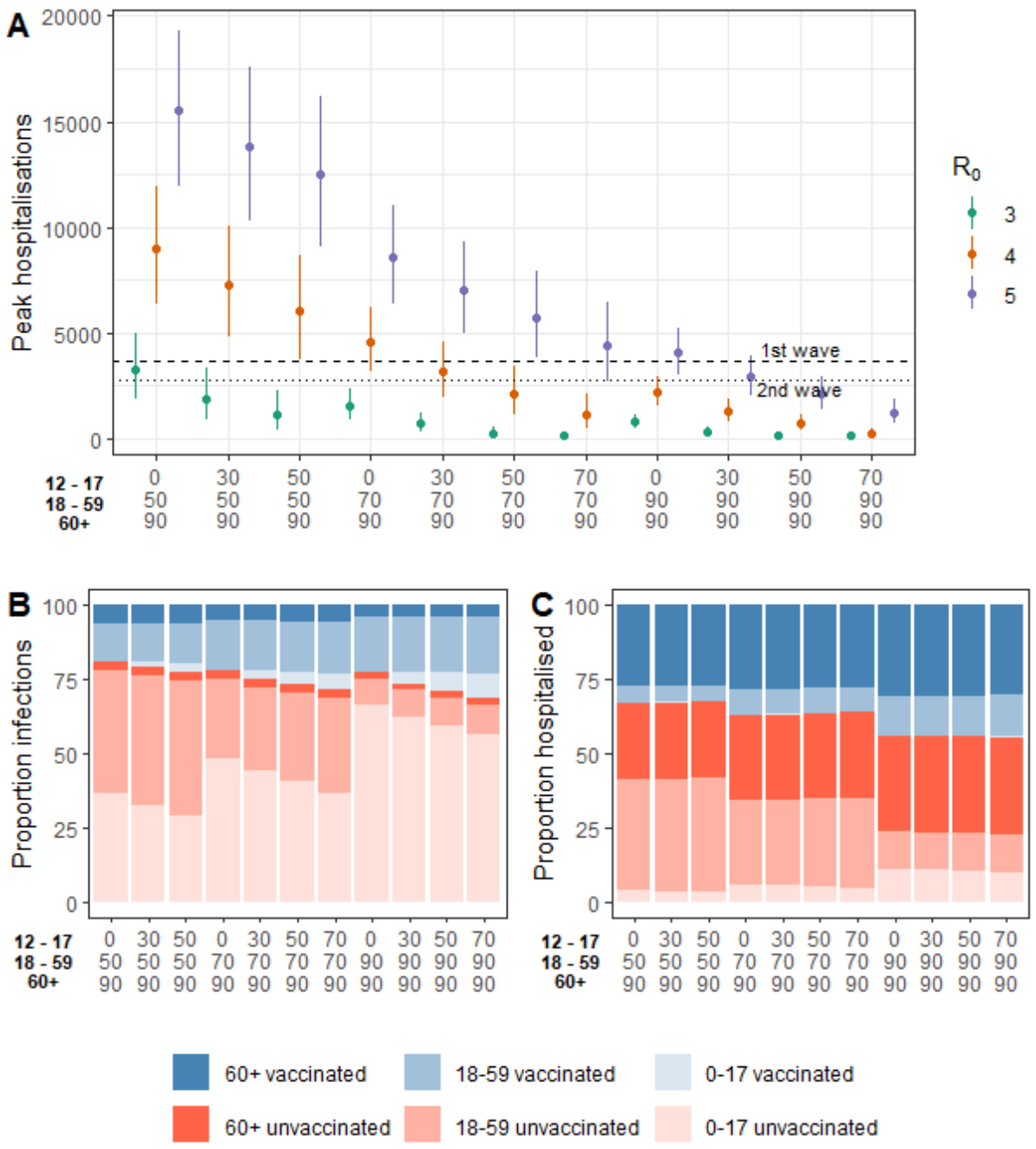

Figure S6: Projections in the absence of control measures, as a function of the basic reproduction number R_0 and vaccine coverage, in a scenario where the efficacy of the vaccines against hospitalisation is set at 90%. A. Peak in daily hospital admissions in the absence of control measures. **B.** Distribution of infections between groups defined by their age and vaccination status. **C.** Distribution of hospitalizations between groups defined by their age and vaccination status. In (B-C), the distribution is reported for infections and hospitalizations occurring between September 1st, 2021 and March 20th, 2022 (end of the study period) and for R_0=4.0. We assume 25% of the population has acquired protection through natural infection (range 20%-30% corresponding to the vertical bars in A).

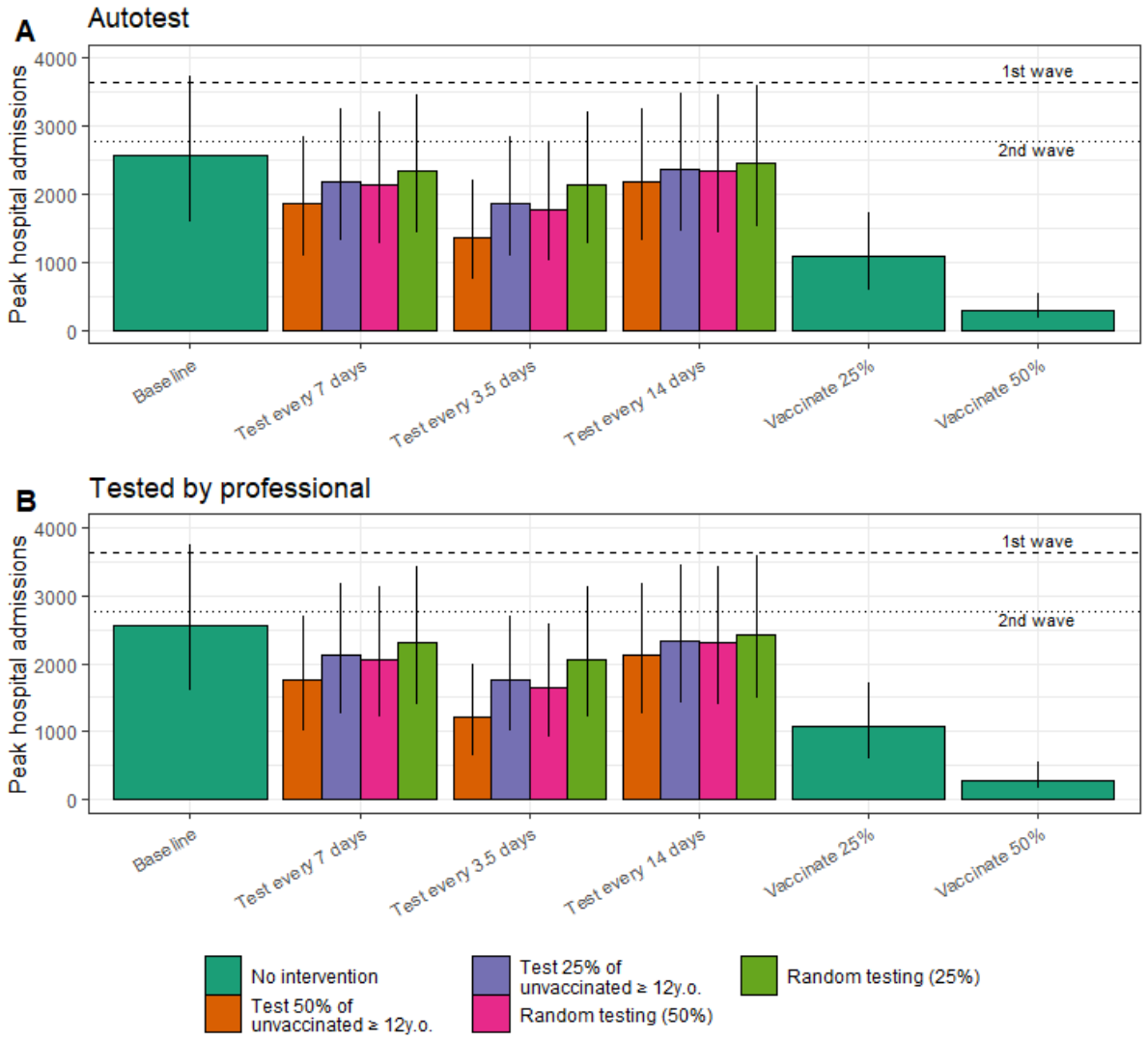

Figure S7: Peak in daily hospital admissions under different testing strategies. A. For self testing (sensitivity: 75%) **B.** For tests performed by a professional (sensitivity: 90%). The following interventions are explored: *Baseline* - no intervention; *Test every x days unvaccinated* - 50% or 25% of the unvaccinated individuals older than 12 y.o. are tested every x days; *Random* - the same number of individuals are tested but in the population of individuals older than 12 y.o. irrespective of vaccination status; *Vaccinate x%* - x% of the unvaccinated individuals older than 12 y.o. are vaccinated. Results are displayed for R_0=4.0. We assume 25% of the population has acquired protection through natural infection (range 20%-30% corresponding to the vertical bars).

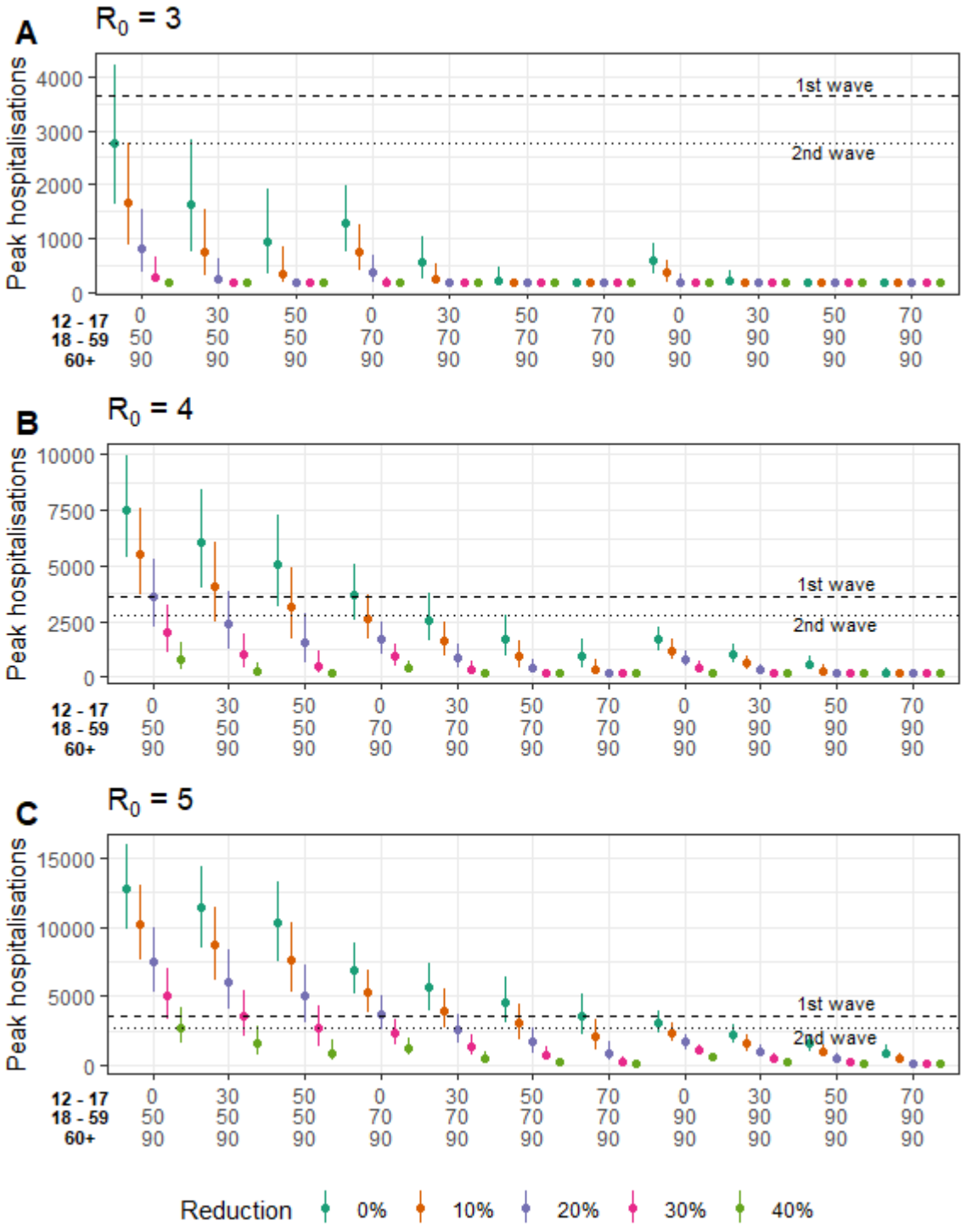

Figure S8: Impact of the intensity of non-pharmaceutical interventions targeting the general population on the peak of hospitalizations. Peak in daily hospital admissions as a function of the vaccination coverage reached in different groups and the intensity of non-pharmaceutical interventions reducing the overall transmission rate by 0-40%. For a R_0 of **A.** 3.0, **B.** 4.0, and **C.** 5.0. We assume 25% of the population has acquired protection through natural infection (range 20%-30% corresponding to the vertical bars).

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