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Abstract

Vaccination will change SARS-CoV-2 epidemiology. We used an age stratified compartmental model calibrated to French data to anticipate these changes and determine implications for epidemic control, assuming vaccines reduce the risk of hospitalisation, infection and transmission if infected by 95%, 60% and 50%, respectively. In our baseline scenario (R_0=5; vaccine coverage of 70%-80%-90% among 12-17, 18-59 and ≥60 y.o.), important stress on healthcare is expected without measures. Unvaccinated adults ≥60 y.o. represent 3% of the population but 43% of hospitalisations. Children aged 0-17 y.o. represent a third of infections and are responsible for almost half of transmissions. Unvaccinated individuals have a disproportionate contribution to transmission so that measures targeting them may help maximize epidemic control while minimizing costs for society compared to non-targeted approaches. With the Delta variant, vaccinated individuals are well protected against hospitalization but remain at risk of infection and should therefore apply protective behaviours (e.g. mask wearing). Control strategies should account for the changing SARS-CoV-2 epidemiology.

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]. A number of modelling studies evaluated how vaccination will help mitigate a SARS-CoV-2 epidemic rebound this autumn, highlighting that it might be difficult to fully relax control measures given the high transmissibility and severity of SARS-CoV-2[4–7]. These studies assessed impact on key health metrics (e.g. number of hospitalisations and death) and identified the level of social distancing that would remain necessary as a function of vaccine coverage. A question that has received less attention is that, in this new era where a large part of the population is vaccinated, the epidemiology of SARS-CoV-2 (Who is infected? Who transmits? Who is hospitalized?) will be different from what it was prior to the distribution of vaccines[8]. 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. For example, the expectation that unvaccinated individuals will have a higher contribution to infections, transmissions and hospitalisations has led some countries to introduce control strategies specifically targeting this population. This is the case of France: confronted to a rapid rise in Delta cases and a plateau in vaccinations in June-July 2021, French authorities announced in July that a sanitary pass, i.e. a proof of completed vaccination, recent infection or recent negative test, would be required to access places such as bars, restaurants and cinemas. The announcement led to an important surge in vaccination appointments and in vaccine coverage. A number of European countries introduced similar measures.

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 different control strategies, including repeated testing and non-pharmaceutical measures, targeting the whole population or subgroups such as unvaccinated individuals to optimally mitigate an autumn epidemic rebound. This is also an opportunity to revisit impact assessment accounting for the increased transmissibility and severity of the Delta variant as well as the reduction in vaccine protection against infection associated with this variant. We consider Metropolitan France as a case study.

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=5 and a vaccine coverage of 70%-80%-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 5,200 hospital admissions per day which is larger than the peaks observed in France during the two pandemic waves of 2020.

We anticipate that the roll-out of vaccines will 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 33% 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=1.9 times higher than that of a vaccinated individual among those aged 18-59 y.o (RR=1.3 among 0-17 y.o. and RR=2.1 among over 60; Supplementary Table 1). Overall, unvaccinated individuals represent 29% of the population but 46% of infections. Their contribution to the transmission process is even higher with a risk of transmission from an unvaccinated individual that is 4.3 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 65% 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 30% (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 66% of hospitalisations from that age group (RR: 17.2); and 3% of the general population but 43% of all hospitalisations (RR: 26.7) (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, 28% 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 70%-80%-90% and R_0=5. Weekly testing of 50% of unvaccinated individuals aged ≥12 y.o. could reduce the peak of hospitalisations by 19% (range: 16-23% for 20-30% of the population infected prior to September 1st 2021) if an autotest is used and 22% (19-27%) 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 8% (7%-10%) and 10% (8%-12%), 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 (68% vs 19%; Figure 2A), for a cost that would be 4.5 times lower (0.16 vs 0.72 billion euros; Supplementary Figure S2). Moreover, only vaccination would be able to reduce the peak of hospital admissions below the peaks observed in the 2020 spring and fall waves.

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 39%, 70%, 90% and 97%, respectively (Figure 2B). If these measures were only targeted towards the few unvaccinated individuals (29% of the population), we could still reach 27%, 51%, 72% and 87% peak reductions, respectively. In both scenarios, reducing transmission rates by 20% would be sufficient to make the peak of hospitalisations drop below the levels observed during the second wave of 2020. Given the residual risk of infection in vaccinated individuals with the Delta variant, substantial gains can be made if vaccinated individuals mitigate their risk of infection for example by wearing masks.

Sensitivity analyses

Keeping in mind that 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 3 shows the expected size of the Autumn peak in hospital admissions, for different values of R_0 and vaccine coverages, considering scenarios where control measures can target unvaccinated individuals only or the whole population leading to reductions of transmission rates in the targeted population between 0% (no control) and 40%. 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, we would not anticipate an epidemic rebound for the vaccine coverage expected to be achieved in France. For R_0=4, the peak is expected to be below the ones of 2020 even if measures are fully relaxed. For R_0=5, in the absence of

control measures, the peak could remain below the one of the Autumn 2020, if vaccine coverage was increased to 70% in teenagers, 90% in 18-59 y.o. and 95% in those over 60 y.o.. For R_0=6, increasing the vaccine coverage to these levels would still not allow a full relaxation of control measures and the implementation of control measures would be necessary to further mitigate impact on healthcare. Overall, high vaccination coverage and even limited control of transmission can help mitigate an epidemic rebound. The age distribution of infected and hospitalized individuals depends on vaccine coverage in the different age groups (Figure 4, Figure S3-S4). For example, when vaccine coverage in those over 60 y.o. increases from 90% to 95%, the contribution of this age group to hospitalisations drops from 65% to 55%. Those distributions are relatively robust to a change in R_0 (Supplementary Figure S3-S4).

Comparing our baseline scenario (60% reduction in the risk of infection given Delta) to that with an 80% reduction in the risk of infection that was considered prior to the rise of Delta, we find that the lower protection conferred by vaccines against Delta infection substantially degrades projections, with a peak of hospitalisations that roughly doubles when moving from 80% to 60% protection (Figure 3). This reduction of protection against infection also increases the contribution of vaccinated individuals to infections: they represent 34% of infections with a protection of 80% compared to 54% with a protection of 60% (Figure 4, Figure S6). As a consequence, compared to vaccinated individuals, unvaccinated individuals are 4 and 10 times more likely to transmit in scenarios with a protection against infection of 60% and 80%, respectively, for R_0=5 and a vaccine coverage of 70%-80%-90%.

For 90% protection against hospitalisation instead of 95% in our baseline scenario, we expect a 28% increase in the peak of hospitalisations (Figure 3). This also increases the proportion of vaccinated individuals among those hospitalized from 28% to 44% (Figure 4 , Figure S7).

Comparing our baseline scenario (70% of teenagers vaccinated) to one where teenagers are not vaccinated (Supplementary Figure S8), our results suggest that the vaccination of teenagers may substantially reduce the stress on the healthcare system. For example, if 80% of 18-59 y.o. and 90% of over 60 are vaccinated, the vaccination of 70% of teenagers could reduce the peak of hospitalisations by 66% and 40% for R_0=4 and 5, respectively, compared to a scenario where they are not vaccinated.

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 decreases from 33% to 31% while the proportion among those that cause infection drops from 43% to 36% (Supplementary Figure S5).

Discussion

Countries with partially vaccinated populations enter a new era in the control of the SARS-CoV-2 epidemic. However, given the high transmissibility and severity of the Delta variant and the reduced efficacy of vaccines against infection by this variant, SARS-CoV-2 may continue to generate substantial stress on healthcare in the absence of mitigation measures, even with high vaccine coverage. Nonetheless, the partial vaccination of the population modifies 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[9]. The Alpha variant that is currently dominant in France was found to be about 50% more transmissible than historical lineages[10–12] and the Delta variant that is now dominant might be more than 50% more transmissible than the Alpha variant[13]. 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=5 in our baseline analysis and explored values between 3 and 6 in our sensitivity analyses. For $R_0 \geq 5$ which appears likely for the Delta variant and under our baseline vaccine coverage of 70%-80%-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). Ongoing efforts to control transmission should therefore be maintained. On a more positive note, thanks to vaccination, the intensity of control measures necessary to maintain hospitalisations at manageable levels should be substantially less than what was required before the roll-out of vaccines. Indeed, while lockdowns used in 2020 reduced transmission rates by 70-80%[9], we find that reductions of the order of 20-30% might now be sufficient. Such reductions might potentially be achieved through protective measures (e.g. masks, hand hygiene), a certain degree of social distancing, the sanitary pass and Test-Trace-Isolate.

Since vaccines reduce the risk of infection and of transmission if infected, our model anticipates that unvaccinated individuals will contribute 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 one third of infections occurring in children and 43% 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 43% 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, gains

achieved thanks to social distancing measures are larger when reducing the contacts of unvaccinated individuals rather than those of vaccinated ones. This suggests that, in this new era, control measures targeting unvaccinated individuals (for example with the use of the sanitary pass) may help maximizing epidemic control. Such a targeting strategy also raises ethical and social issues. From an economic perspective, targeting unvaccinated individuals maximizes 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. However, targeting the unvaccinated leads to forms of discrimination, more or less severely felt. While it is true that discrimination between the vaccinated and unvaccinated is to some extent the result of individual choices, as vaccines are widely available, these choices are nevertheless socially stratified and correlated with age and socioeconomic status. Moreover, the restrictions put in place are not chosen by individuals but defined by the authorities. Choices may therefore be perceived as discrimination, especially by the unvaccinated. in France, while the sanitary pass has been widely accepted, it has also actively mobilized against it minority segments of the population.

Recent data indicate a reduction in vaccine efficacy against infection by the Delta variant and a waning of immunity against infection, with protection against hospitalisation remaining elevated. These changes have important implications for the management of the epidemic since we expect they will facilitate viral circulation even in highly vaccinated populations and eventually increase the stress on the healthcare system. This means that, compared to the first half of 2021, there is a higher risk that vaccinated individuals get infected and transmit the virus. As a consequence, measures reducing the risk of infection and transmission such as the wearing of the mask should apply to vaccinated individuals in situations where transmission is possible (e.g. indoors).

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 remains lower among teenagers due to

later access to the vaccine. While children mostly develop mild SARS-CoV-2 infections, it is essential to secure their 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[14]. 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 yet offered under 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...) and could help mitigate impact[15] 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 uncertainty about the value of R_0 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, however we account for the reduced vaccine efficacy against infection estimated for the Delta variant. We consider a national model for France and do not account for spatial heterogeneities, that are important[16]. We considered a 'leaky' vaccine that exhibits failure in degree, as most SARS-CoV-2 models[5,7,17,18]. This assumption could lead to larger epidemic sizes than models with 'all-or-nothing' vaccines. For this reason, and given the uncertainty on the basic reproductive ratio for Delta, we performed a sensitivity analysis on R_0.

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[19], has been described in detail elsewhere.[9] It accounts for a gradient of severity with age[20], assuming that Delta VOC is 50% more severe than Alpha VOC[21] while Alpha VOC is 40% more severe than previously circulating strains[22]. It has been extended to account for the roll-out of vaccines[4] as well as the deployment of self-administered rapid antigenic tests.[23] A full description of the model and equations is reported in the Supplement.

Scenarios

Vaccine coverages and characteristics

Considering the Delta variant, we assume that vaccines are 95% effective at reducing the risk of hospitalisation[1], 60% at reducing the risk of infection[24] (impact on susceptibility) and 50% at reducing the infectivity of vaccinated individuals[3]. In a sensitivity analysis, we show results if vaccines are 80% effective at reducing the risk of infection[2] (which was the scenario considered prior to the rise of Delta) and 90% effective against hospitalisation. We build several scenarios regarding vaccine coverage achieved in the different age groups by September 1st, 2021: 90% or 95% among those older than 60 years old (y.o.); 60%, 80% or 90% among those aged 18-59 y.o. and 0%, 30% or 70% among the 12-17 y.o. (called teenagers in the following). To give some context, 89% of those older than 60 y.o., 84% of the 18-59 y.o. and 61% of the 12-17 y.o. have received a first dose of vaccines against SARS-CoV-2 by August 25th, 2021. In our baseline scenario that we label 70%-80%-90%,

we assume vaccination coverage will reach 70%, 80% 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 has 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.[9] The emergence of more transmissible variants of concerns (VOC) (such as the Alpha and Delta VOCs)[11–13,25] is expected to increase R_0. We therefore explore scenarios in which R_0 ranges between 3.0 and 6.0 when measures are completely relaxed, considering R_0=5 as our baseline scenario. 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.[19]

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 [9,26]. 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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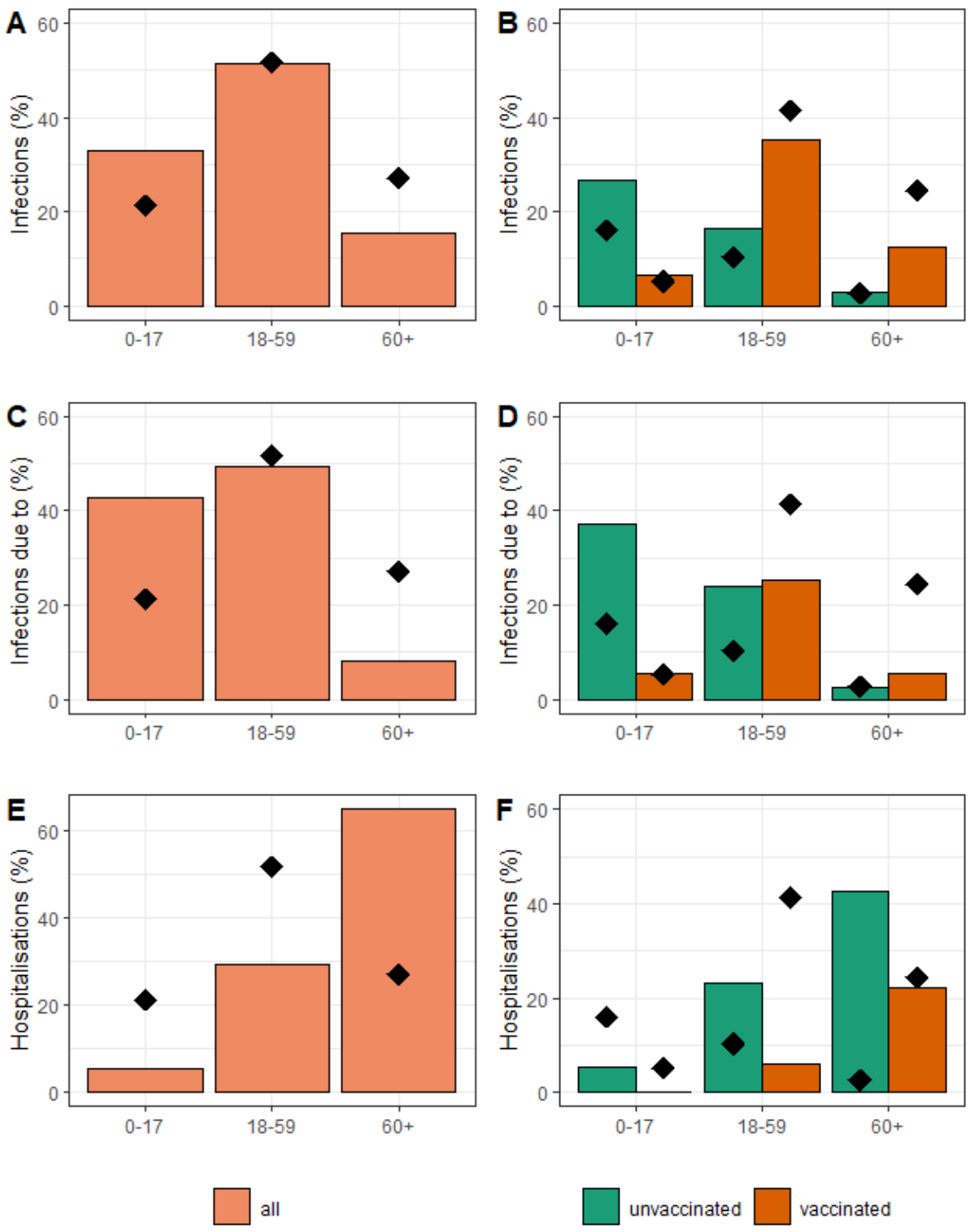

Figure 1: Contribution of groups defined by their age and vaccination status to infections, disease spread and hospital burden, in our baseline scenario with R_0=5 and a vaccine coverage of 70%-80%-90% among 12-17 y.o., 18-59 y.o. and over 60 y.o. Age distribution of new infections **A.** in the entire 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.

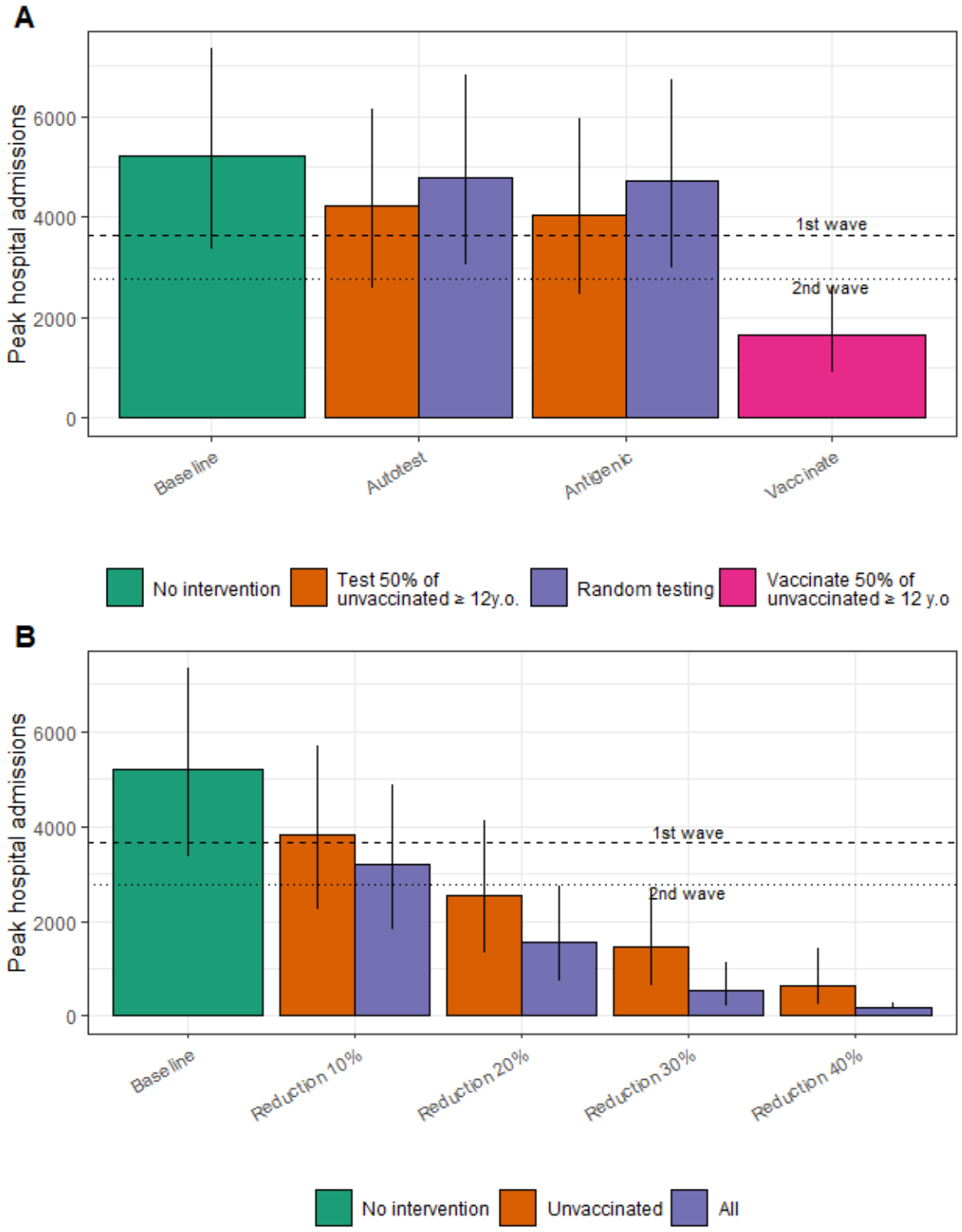

Figure 2: Comparison of the impact of control strategies targeting the entire population vs unvaccinated individuals only, in our baseline scenario with R_0=5 and a vaccine coverage of 70%-80%-90% among 12-17 y.o., 18-59 y.o. and over 60 y.o. A. Peak in daily hospital admissions under different testing 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).

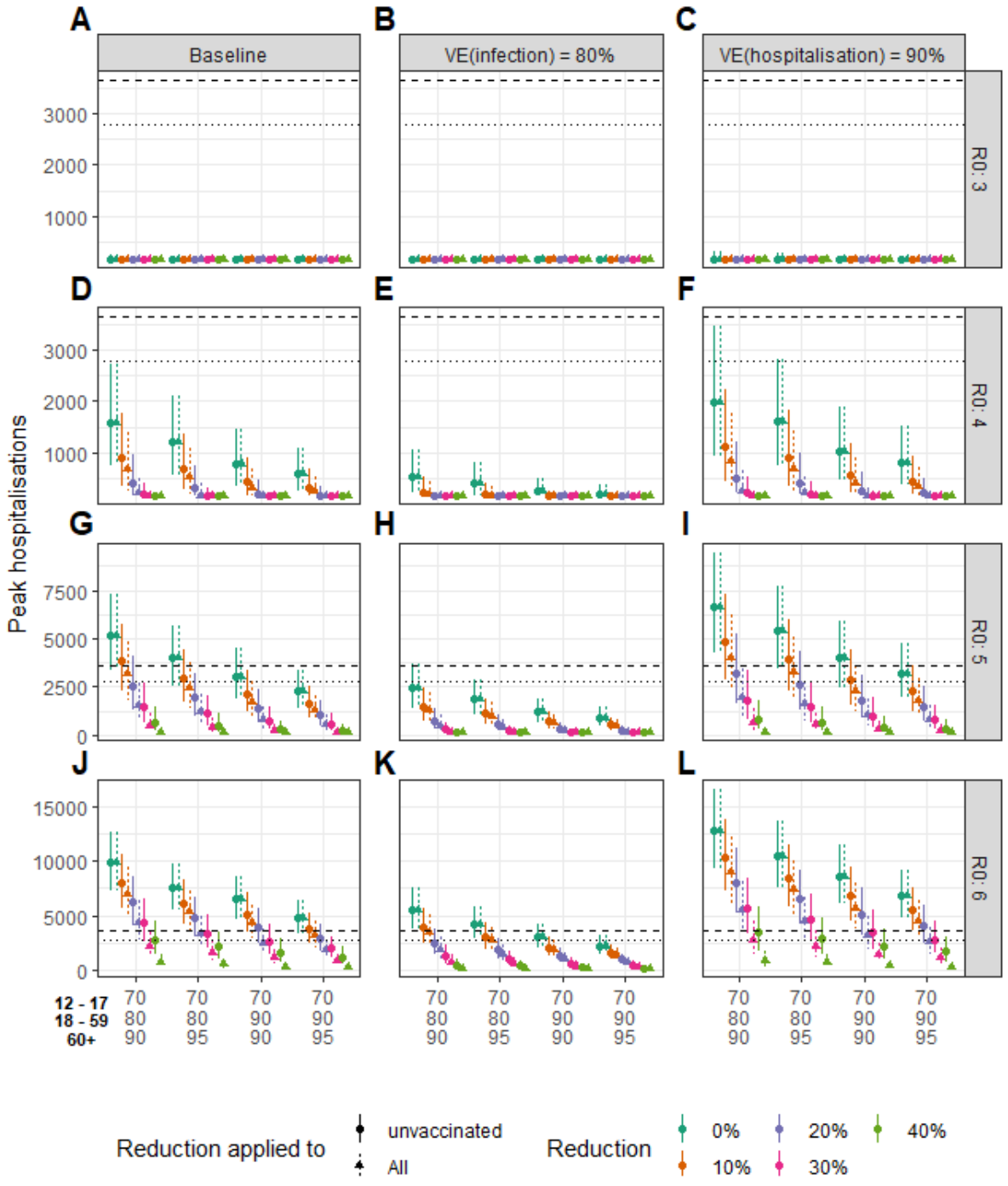

Figure 3: Expected size of the peak of hospitalisations when non-pharmaceutical interventions target unvaccinated individuals only or the whole population, as a function of the basic reproduction number R_0, vaccine coverage in the 12-17 y.o., 18-59 y.o. and over 60 y.o. and for different efficacy of the vaccine against the risk of infection or hospitalisation. Non-pharmaceutical interventions reduce the transmission rate of unvaccinated individuals (points) or the whole population (triangles) by 0%, 10%, 20%, 30%, 40%. R_0 takes the values 3.0 (top row, A-B-C), 4.0 (D-E-F), 5.0 (G-H-I), and 6.0 (bottom row, J-K-L). In the baseline scenario (left column) we assume that the vaccines are 95% effective at reducing the risk of hospitalisation, 60% at reducing the risk of infection and 50% at reducing the infectivity of vaccinated individuals. In sensitivity analyses, we consider an 80% reduction against infection (middle column) and 90% reduction against

hospitalisation (right column). We assume 25% of the population has acquired protection through natural infection (range 20%-30% corresponding to the vertical bars). Horizontal lines indicate the peak of daily hospital admissions observed during the first (dashed line) and the second (dotted line) epidemic wave of 2020.

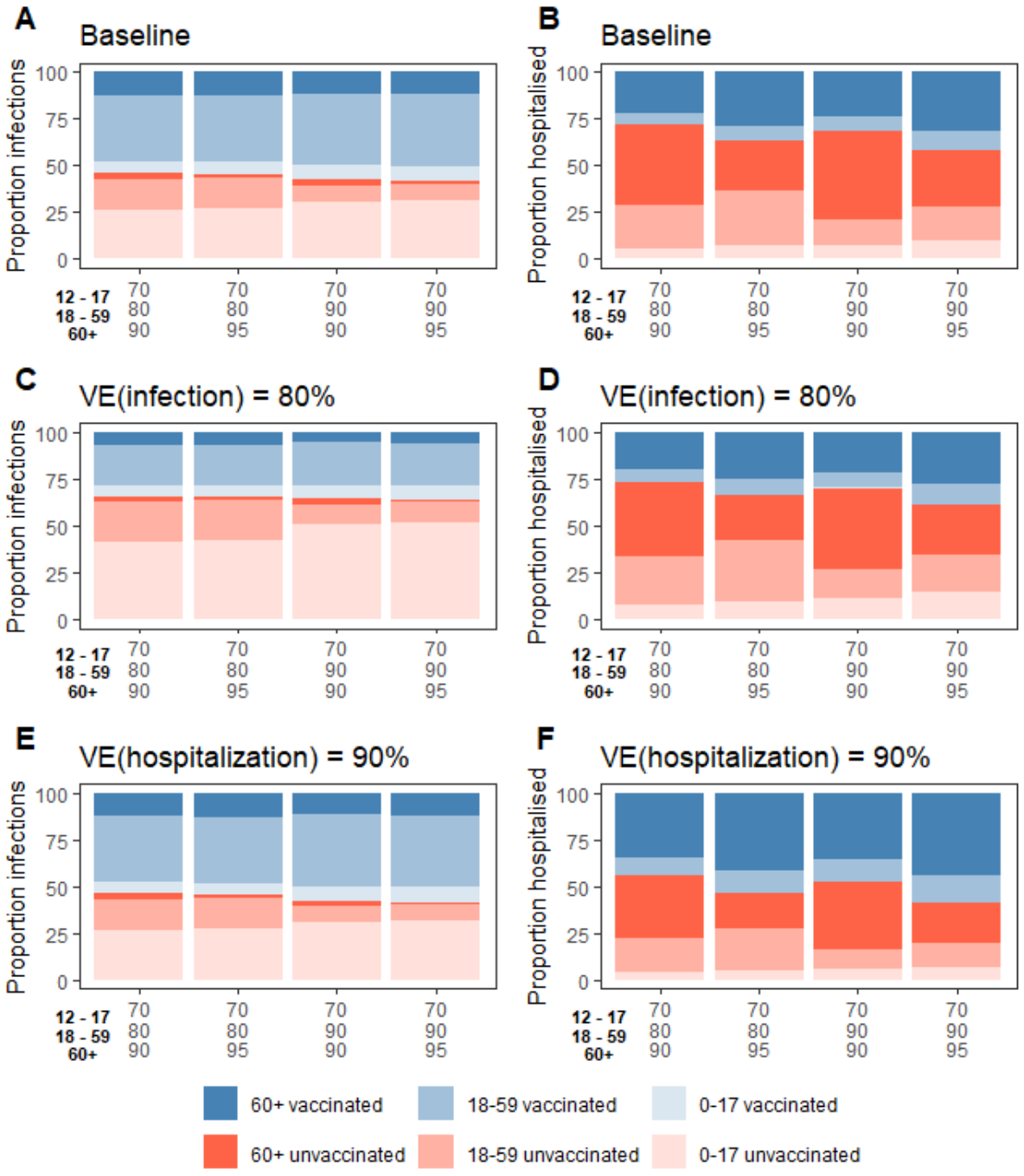

Figure 4: Proportion of infections (A,C,E) and hospitalizations (B,D,F) among groups defined by their age and vaccination status as a function of the vaccine coverage in the 12-17 y.o., 18-59 y.o. and over 60 y.o.. In the baseline scenario **(A-B)** we assume that vaccines are 95% effective at reducing the risk of hospitalisation, 60% at reducing the risk of infection and 50% at reducing the infectivity of vaccinated individuals. In **(C-D)**, we assume a vaccine efficacy at reducing the risk of infection of 80%. In **(E-F)**, we assume a vaccine efficacy at reducing the risk of hospitalisation of 90%. 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=5.0. We assume 25% of the population has acquired protection through natural infection.

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[2] as well as the deployment of self-administered rapid antigenic tests[3]. 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[4,5]. The model is implemented with the R software using the *odin* package[6].

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 infected people who will need to be admitted to the hospital is age-dependent and accounts for the increased severity associated with the Delta variant. Specifically, Delta VOC is assumed to be 50% more severe than Alpha VOC[7], whereas Alpha VOC is assumed to be 40% more severe than historical strains[8]. The age-dependent probability of hospitalization for the historical strains is obtained from Lapidus et al[9]. 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 [2].

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:

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

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

$$dS^v_i/dt =$$

$$-(1-VE_{susc})S^v_i \beta(\Sigma_j C_{ij}((1-\rho_{int})(E2_j + I_j^{mild} + I_j^{hosp} + (1-\rho_{iso})(E2iso_j + Iiso_j^{mild} + Iiso_j^{hosp}))$$

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

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

$$+ (1-\rho^v_{int})(1-VE_{inf})(E2^v_j + I^v_j{}^{mild} + I^v_j{}^{hosp} + (1-\rho_{iso})(E2iso^v_j + Iiso^v_j{}^{mild} + Iiso^v_j{}^{hosp})))/N_j)$$
$$- g_1 \cdot E1_i$$

$$dE1^v_i/dt =$$

$$(1-VE_{susc})S^v_i \beta(\Sigma_j C_{ij}((1-\rho_{int})(E2_j + I_j^{mild} + I_j^{hosp} + (1-\rho_{iso})(E2iso_j + Iiso_j^{mild} + Iiso_j^{hosp}))$$

$$+ (1-\rho^v_{int})(1-VE_{inf})(E2^v_j + I^v_j{}^{mild} + I^v_j{}^{hosp} + (1-\rho_{iso})(E2iso^v_j + Iiso^v_j{}^{mild} + Iiso^v_j{}^{hosp})))/N_j)$$
$$- g_1 \cdot E1^v_i$$

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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 15th 2021[1] (Figure S1). 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% or 95% among those older than 60 years old (y.o.)
- 60%, 80% or 90% among those aged 18-59 y.o.
- 0%, 30% or 70% among the 12-17 y.o.

In our baseline scenario we assume a vaccination coverage of 70%, 80% and 90% among 12-17 y.o., 18-59 y.o. and over 60 y.o. respectively on September 1st, 2021.

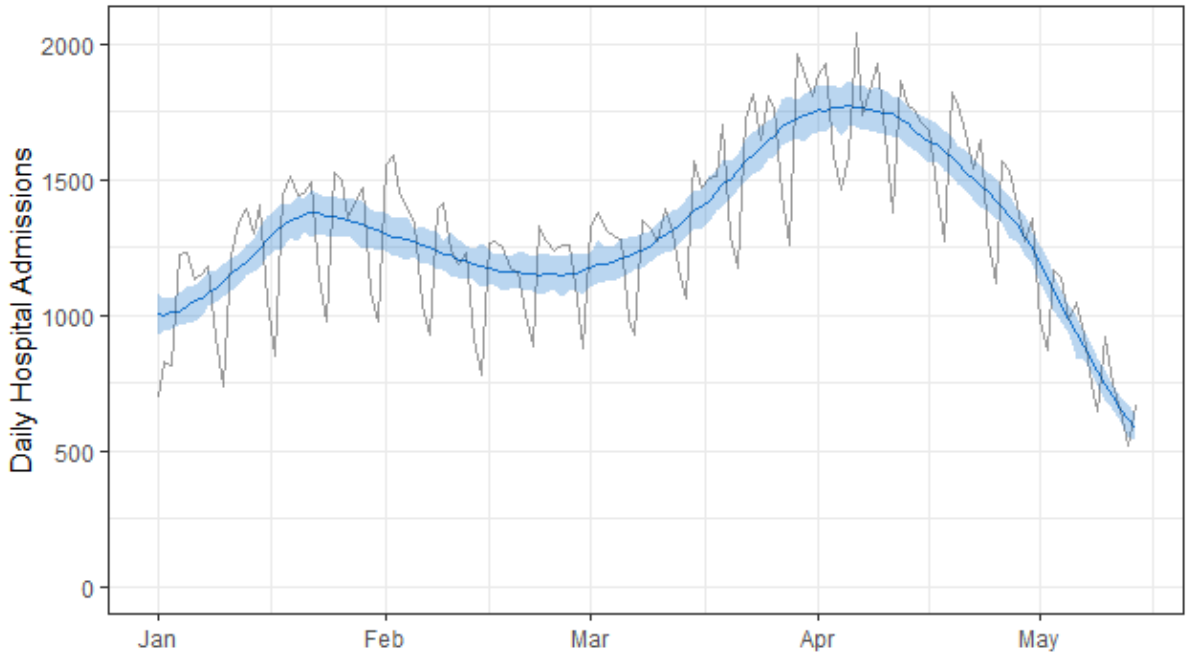

Figure S1: Fit to the data. Daily hospital admissions through time. The blue line and area correspond to model posterior mean and 95% credible intervals, while the grey line corresponds to data.

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=5 and a vaccine coverage of 70%-80%-90% among 12-17 y.o., 18-59 y.o. and over 60 y.o.

Age group	Infection	Transmission	Hospitalisation
0-17	1.3	2.2	18.9
18-59	1.9	3.8	15.0
60+	2.1	4.3	17.3
All	2.0	4.3	6.1

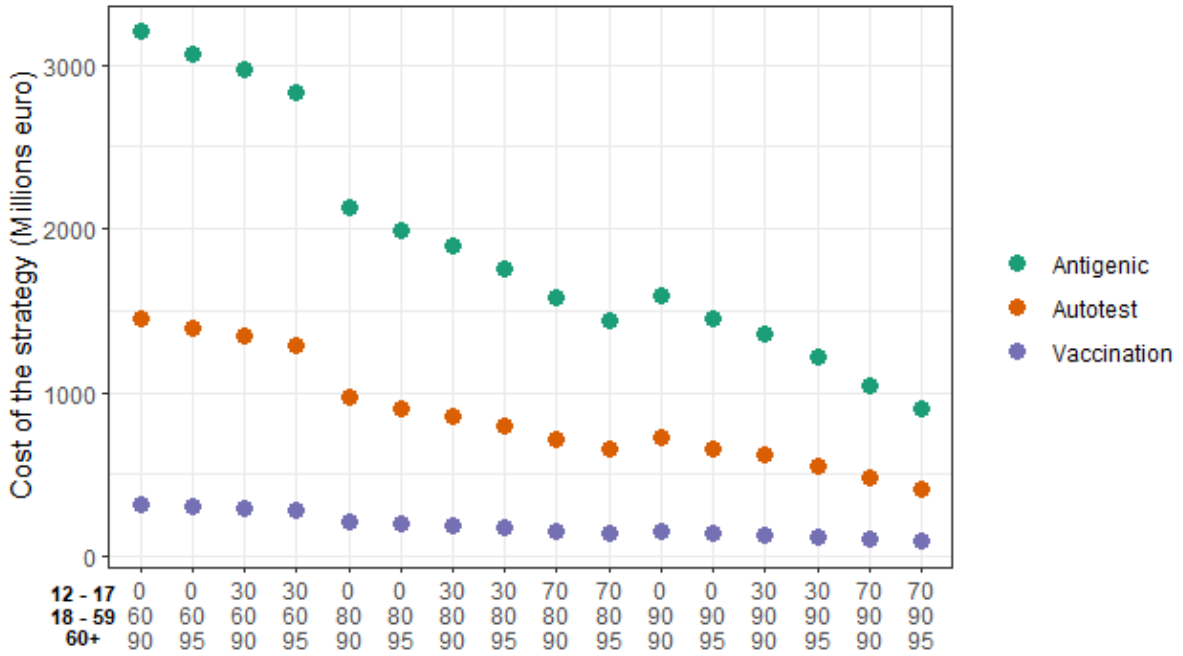

Figure S2: Comparison of the costs of different strategies. Costs of strategies targeting 50% of the unvaccinated individuals older than 12 y.o. as a function of the vaccine coverage reached in different groups. The 3 strategies are: weekly testing with an antigenic test performed by a professional ("antigenic"), weekly testing with an antigenic test performed by the individual ("autotest"), vaccination.

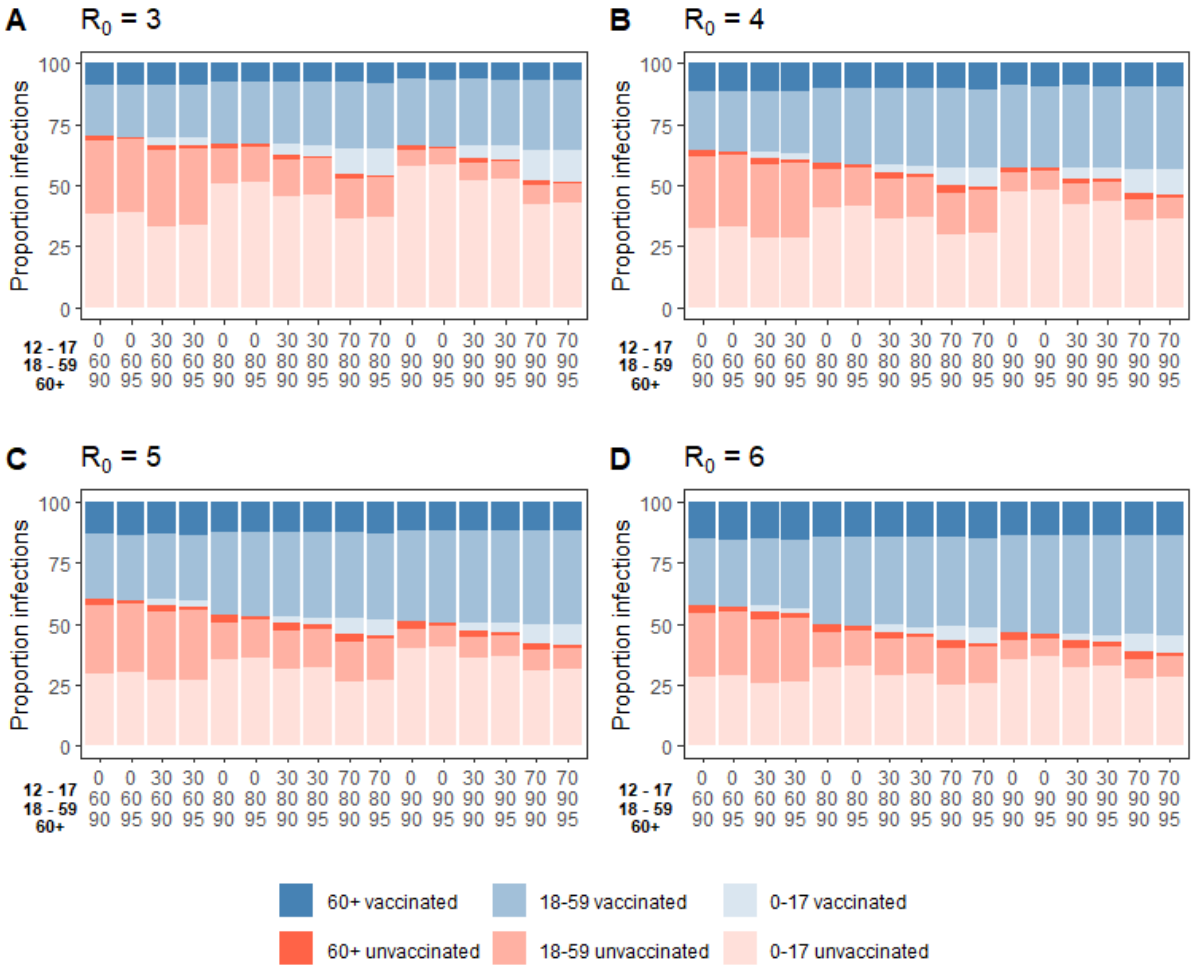

Figure S3: Distribution of infections between groups defined by their age and vaccination status. A. for R_0 = 3. **B.** for R_0 = 4. **C.** for R_0 = 5. **D.** for R_0 = 6. The distribution is reported for infections occurring between September 1st, 2021 and March 20th, 2022 (end of the study period) and as a function of the vaccine coverage reached in the 12-17 y.o., 18-59 y.o. and over 60 y.o.

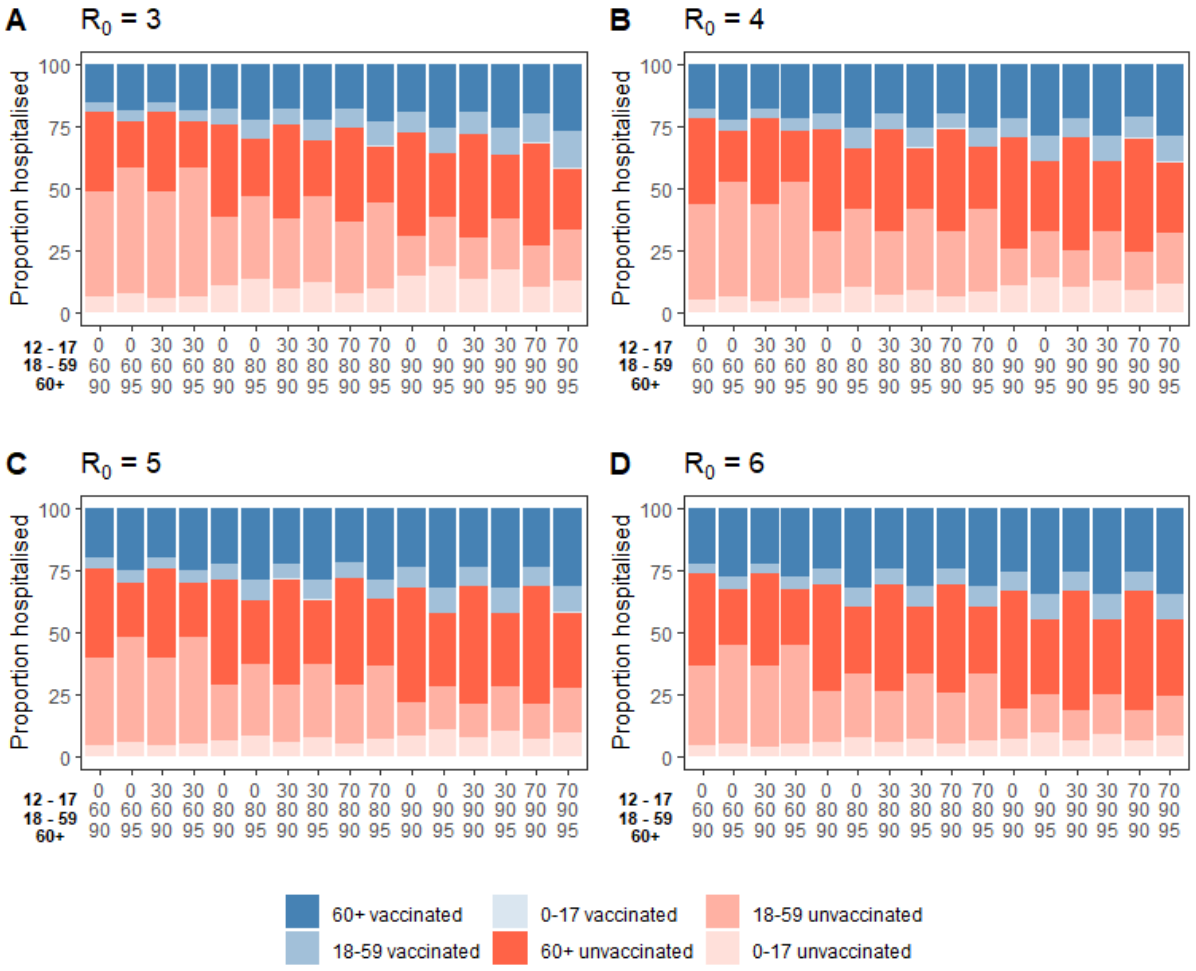

Figure S4: Distribution of hospitalisations between groups defined by their age and vaccination status. A. for R_0 = 3. **B.** for R_0 = 4. **C.** for R_0 = 5. **D.** for R_0 = 6. The distribution is reported for hospitalizations occurring between September 1st, 2021 and March 20th, 2022 (end of the 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.

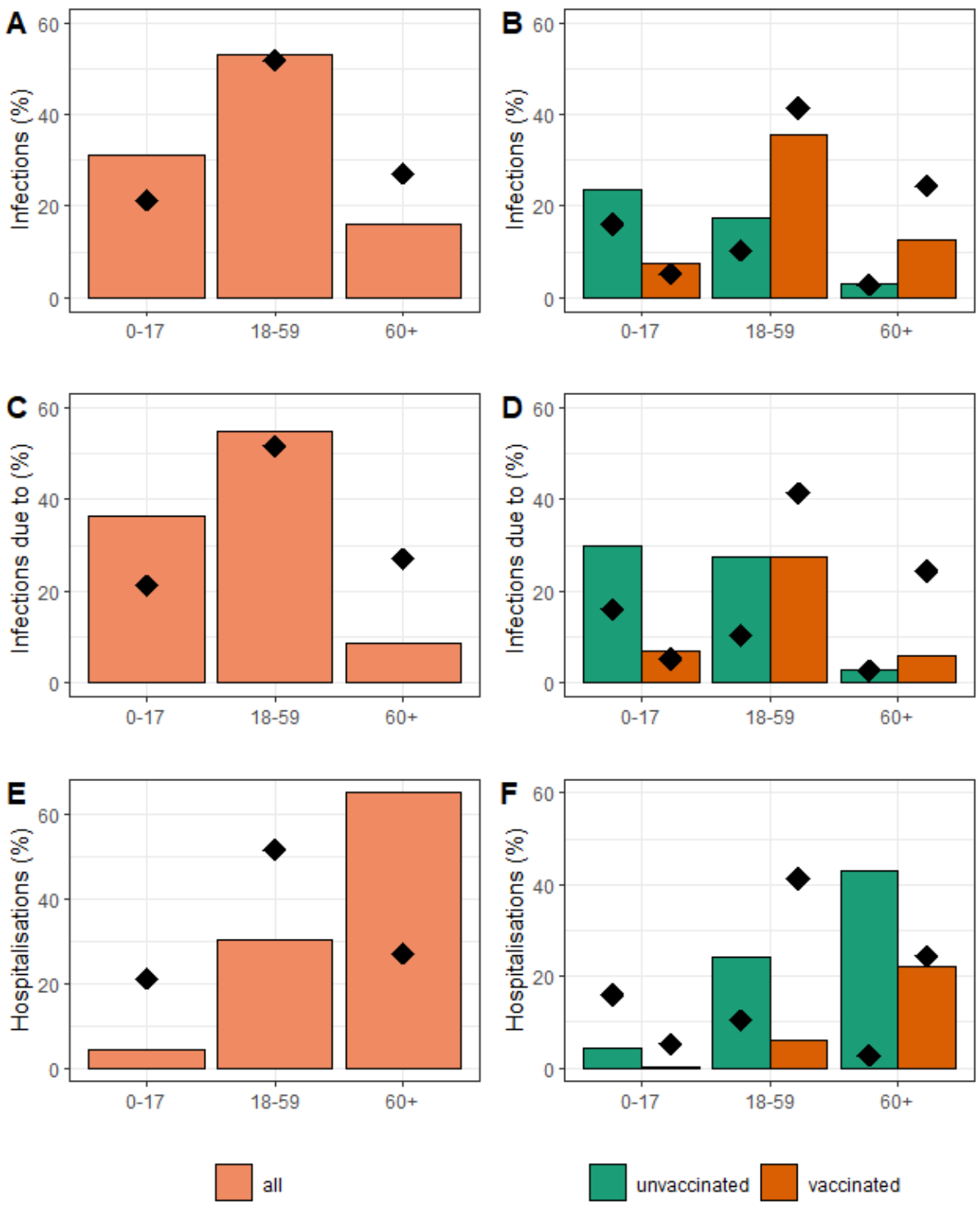

Figure S5: Contribution of groups defined by their age and vaccination status to infections, disease spread and hospital burden in a scenario where children aged 0-9 y.o. are 50% less infectious than adults, in addition to being 50% less susceptible. This is done under our baseline assumptions with R_0=5 and a vaccine coverage of 70%-80%-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.

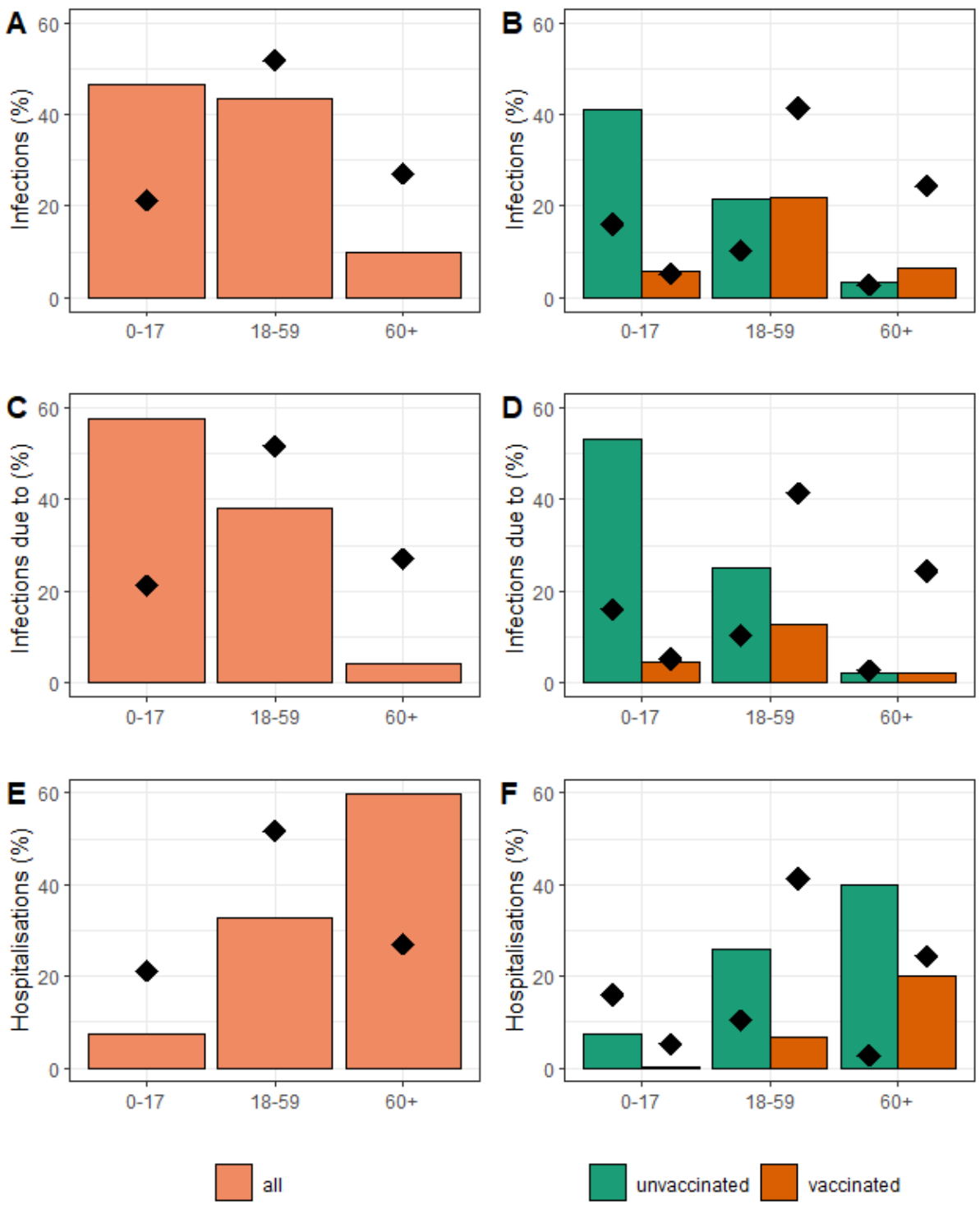

Figure S6: Contribution of groups defined by their age and vaccination status to infections, disease spread and hospital burden in a scenario where the efficacy of the vaccines against infection is set to 80%. This is done under our baseline assumptions with R_0=5 and a vaccine coverage of 70%-80%-90% 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.

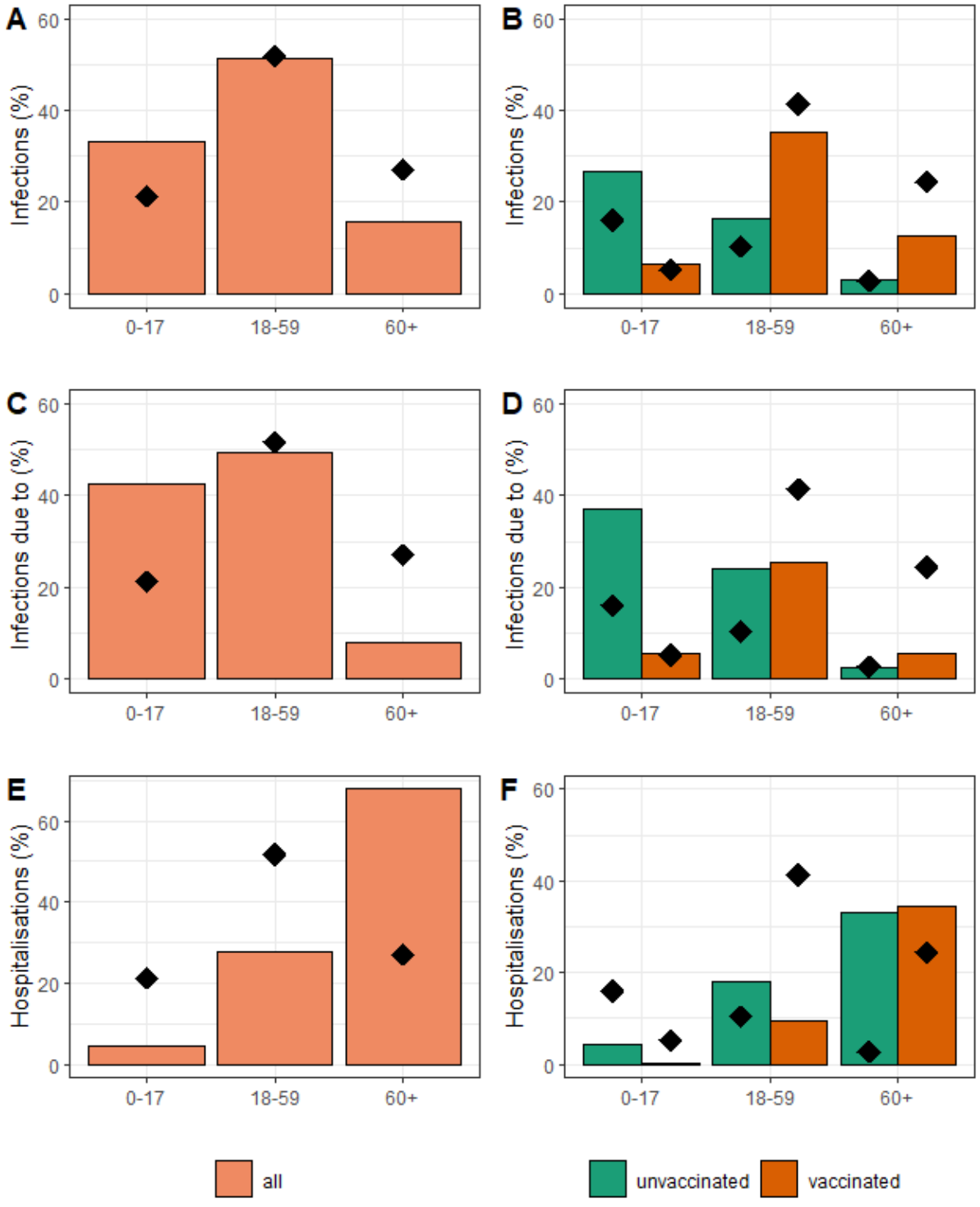

Figure S7: Contribution of groups defined by their age and vaccination status to infections, disease spread and hospital burden in a scenario where the efficacy of the vaccines against hospitalisation is set to 90%. This is done under our baseline assumptions with R_0=5 and a vaccine coverage of 70%-80%-90% 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.

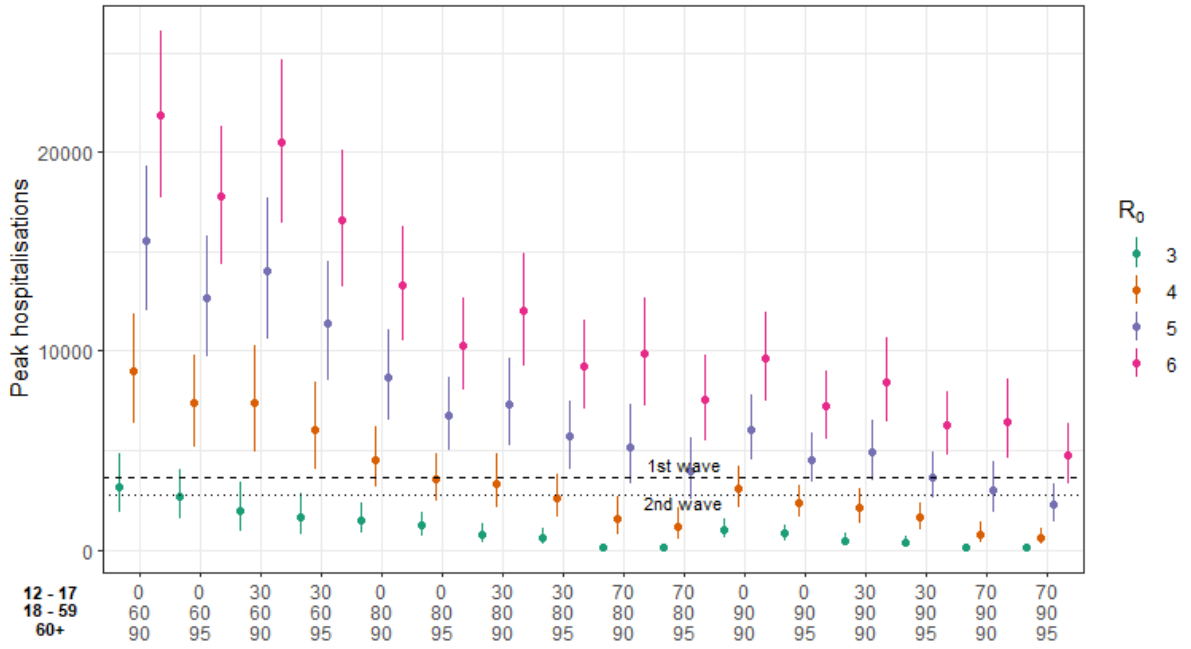

Figure S8: Projections in the absence of control measures, as a function of the basic reproduction number R_0 and vaccine coverage. Peak in daily hospital admissions in the absence of control measures.

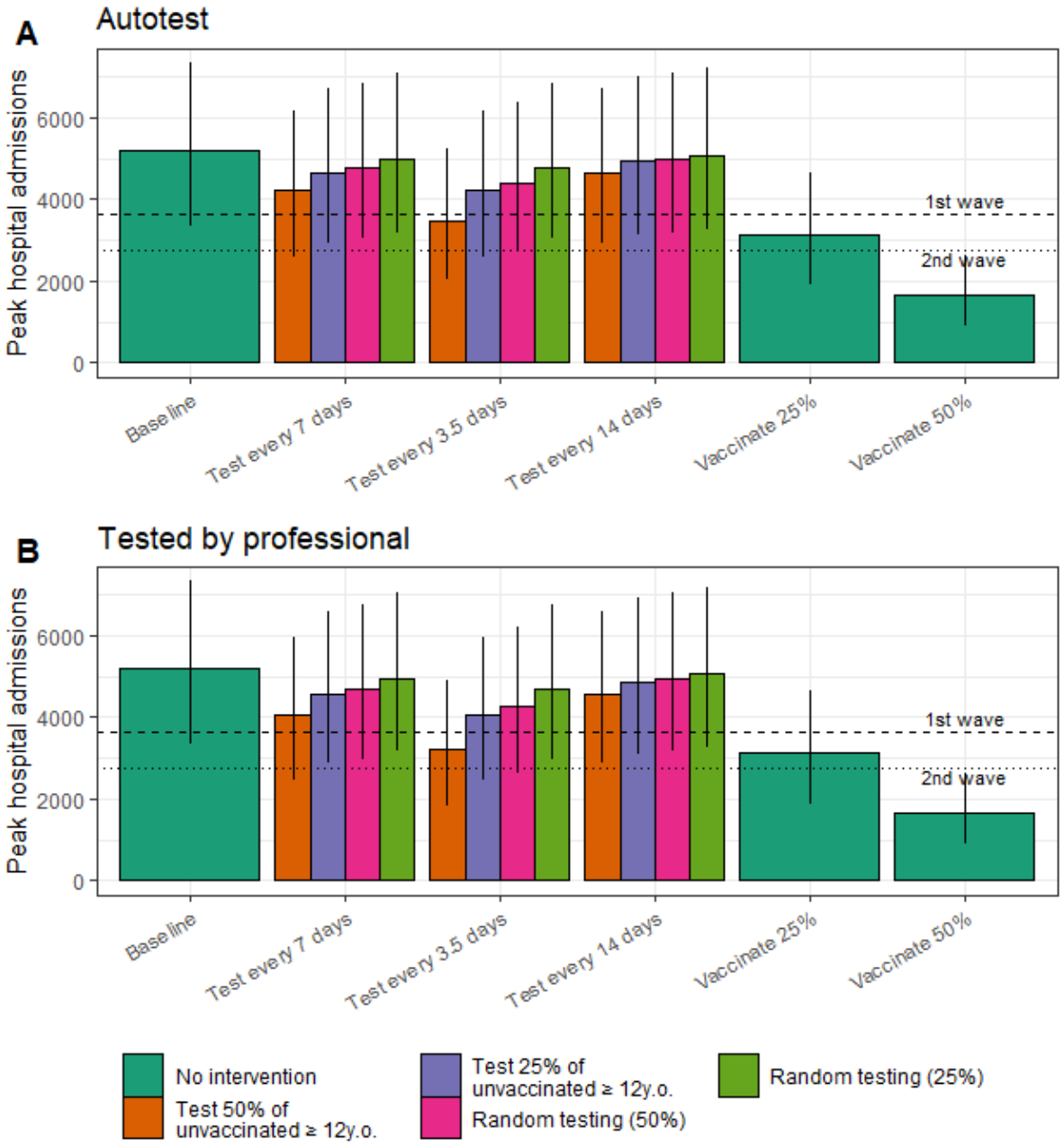

Figure S9: Peak in daily hospital admissions under different testing strategies. A. For self testing (sensitivity: 75%) **B.** For tests performed by a professional (sensitivity: 90%). The following interventions are explored: *Baseline* - no intervention; *Test every x days unvaccinated* - 50% or 25% 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=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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