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BRIEF REPORT

Exploring the Role of Antiviral Nasal Sprays in the Control of Emerging Respiratory Infections in the Community

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ABSTRACT

Introduction: The COVID-19 pandemic has demonstrated that there is an unmet need for the development of novel prophylactic antiviral treatments to control the outbreak of emerging respiratory virus infections. Passive antibody-based immunisation approaches such as intranasal antibody prophylaxis have the potential to provide immediately accessible universal protection as they act directly at the most common route of viral entry, the upper respiratory tract. The need for such products is very apparent for SARS-CoV-2 at present, given the relatively low effectiveness of vaccines to prevent infection and block virus onward transmission. We explore the benefits and challenges of the use of antibody-based nasal sprays prior and post exposure to the virus.

Methods: The classic susceptible-exposed-infectious-removed (SEIR) mathematical model was extended to describe the potential population-level impact of intranasal antibody prophylaxis on controlling the spread of an emerging respiratory infection in the community.

Results: Intranasal administration of monoclonal antibodies provides only a short-term protection to the mucosal surface. Consequently, sustained intranasal antibody prophylaxis of a substantial proportion of the population would be needed to contain infections. Post-exposure prophylaxis against the development of severe disease would be essential for the overall reduction in hospital admissions.

Conclusion: Antibody-based nasal sprays could provide protection against infection to individuals that are likely to be exposed to the virus. Large-scale administration for a long period of time would be challenging. Intranasal antibody prophylaxis alone cannot prevent community-wide transmission of the virus. It could be used

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along with other protective measures, such as non-pharmaceutical interventions, to bridge the time required to develop and produce effective vaccines, and complement active immunisation strategies.

Keywords: COVID-19; Interventions; Intranasal antibody prophylaxis; Passive immunisation; Respiratory infections; SARS-CoV-2; Treatments

Key Summary Points

There is an urgent need for improved preparedness to control the outbreak of emerging respiratory infections.

Intranasal antibody prophylaxis could serve as an additional protective measure for the mitigation of the impact of infectious diseases.

The long-term control of viral transmission in the community with intranasal antibody prophylaxis alone would be challenging, as it would require continuous large-scale administration.

Antibody-based antiviral nasal sprays have the potential to provide immediately accessible universal protection and limit disease severity in vulnerable and high-risk individuals.

INTRODUCTION

The COVID-19 pandemic has had a devastating impact globally with 18.2 million deaths by 31 December 2021, based on excess mortality estimates [1]. It has demonstrated that there is an urgent need for improved preparedness to control the outbreak of pathogenic respiratory viral infections that will emerge in the future.

Non-pharmaceutical interventions (NPIs), such as social distancing, can substantially delay the spread of respiratory infections, but prolonged enforcement of NPIs is not sustainable in most communities [2–4]. Vaccination is currently the most effective pharmaceutical intervention. Rapid vaccine development, trial completion and licensure for SARS-CoV-2 have prevented much of the associated morbidity and mortality, especially in resource-rich countries with high vaccine uptake rates. The situation in resource-poor countries is less encouraging. For example, as of 17 March 2022, full COVID-19 vaccine coverage across Africa was about 15% of the adult population [5], whereas in Europe and the USA it was more than 70%.

As has recently become apparent, vaccine-induced or natural infection-induced immunity alone does not always prevent infection and concomitant infectiousness, but most seem to provide good protection against serious morbidity (hospitalisation) and death [6]. For example, longitudinal studies of human coronaviruses, both seasonal coronaviruses and SARS-CoV-2, suggest that immunity to reinfection is short-lived, perhaps less than 12 months [7], and immunised people may still get infected and transmit the virus to others [8]. This short-lived immunity is attributed to two main factors. The first is continued viral evolution. Antibodies target the receptor-binding domain on the virus spike protein, which is subject to frequent mutations. SARS-CoV-2 variants escape vaccine-elicited immunity, as shown by antigenic cartography [9]. Evolution will always act to increase the transmissibility of the virus via the magnitude of the basic reproduction number R_0. There is often a trade-off between transmissibility and virulence and, as such, this may or may not be associated with decreased pathogenicity to the human host [10]. The second factor is that the SARS-CoV-2 spike protein does not induce lasting B cell memory, neither after natural infection nor after vaccination [7]. This has been observed for all novel SARS-CoV-2 variants of concern, and for all vaccines irrespective of the technology used for development [8, 11]. As such, active immunisation with the current generation of vaccines is insufficient to halt transmission of SARS-CoV-2 virus and will not create herd immunity to infection [6, 8, 12].

Additional antiviral prophylaxis tools to moderate the impact of emerging respiratory viruses are needed. Passive intranasal immunisation could complement active immunisation and provide more specific antiviral protection than NPIs. It may (1) provide fast protection by preventing viral entry into the epithelial cells in the conducting airways, hampering the diffusion of the virus across the mucosa [13–16], (2) prevent virus replication and transmission in the lower respiratory tract, providing protection against severe respiratory infection, (3) provide protection irrespective of the health and age of the user [17], (4) reduce viral transmission from person to person [14, 15, 18]; for example, the majority of SARS-CoV-2 RNA copies and infectious virions are located in the respiratory tract, and viral load in the upper respiratory tract has been linked to infectiousness and the magnitude of R_0 [19, 20]. In contrast to systemic administration, with intranasal administration active substances are directly deposited at the virus's port of entry, requiring lower doses and typically inducing fewer side effects [13, 16, 17, 21].

Much research has recently focused on non-invasive antivirals that can be easily administered intranasally, and promising preliminary results for their effectiveness against a range of respiratory virus infections have been reported (Supplementary Material, Table S1, [16, 22]). In particular, neutralising monoclonal antibodies that could be administered intranasally [13], for example by nose drops or spray, have recently shown increasing success in animal models and early human studies for the prevention and treatment of respiratory viral infections, including influenza and SARS-CoV-2 infections.

In this study, we explore the benefits of passive immunisation through the intranasal administration of monoclonal antibodies. Employing mathematical models, we illustrate the potential challenges of large-scale administration of intranasal antibody prophylaxis for the control of the spread of emerging respiratory viral infections in the community, focusing on the recent SARS-CoV-2 outbreak at the beginning of the pandemic.

METHODS

A deterministic compartmental model was developed on the basis of a set of differential equations describing the dynamics of infection and treatment states. The transmission model is founded on the classic (mean-field) susceptible-exposed-infectious-removed (SEIR) epidemiological model in a closed homogeneous population which is extended to incorporate the potential effect of intranasal antibody prophylaxis. The possible transitions between states are presented in Fig. 1 (see also the Supplementary Material for details on the mathematical model and analytic derivation of the basic reproduction number, R_0).

The intranasal antibody prophylaxis is assumed to have one, or more, of the following modes of action and properties:

Pre-Exposure Prophylaxis

(i) It protects the host cells and/or neutralises the virus that enters the upper respiratory tract. Thus, it is effective in providing partial protection to susceptible individuals when administered prior to their exposure to the virus, i.e. administration results in the reduction of the probability of a treated susceptible individual becoming infected.

Post-Exposure Prophylaxis

(ii) It is partially effective at the initial stage post-exposure to the virus, before high level virus replication occurs and the exposed individual becomes infectious, by reducing the risk of virus transmission to the lower respiratory tract and, subsequently, reducing the risk of developing severe disease.

At present, there is no evidence that passive immunisation with intranasally administered antibodies could significantly alter the disease process once symptoms have occurred and infection has been established, especially when virus invades the lower respiratory tract and triggers damage to the lungs. We explored the

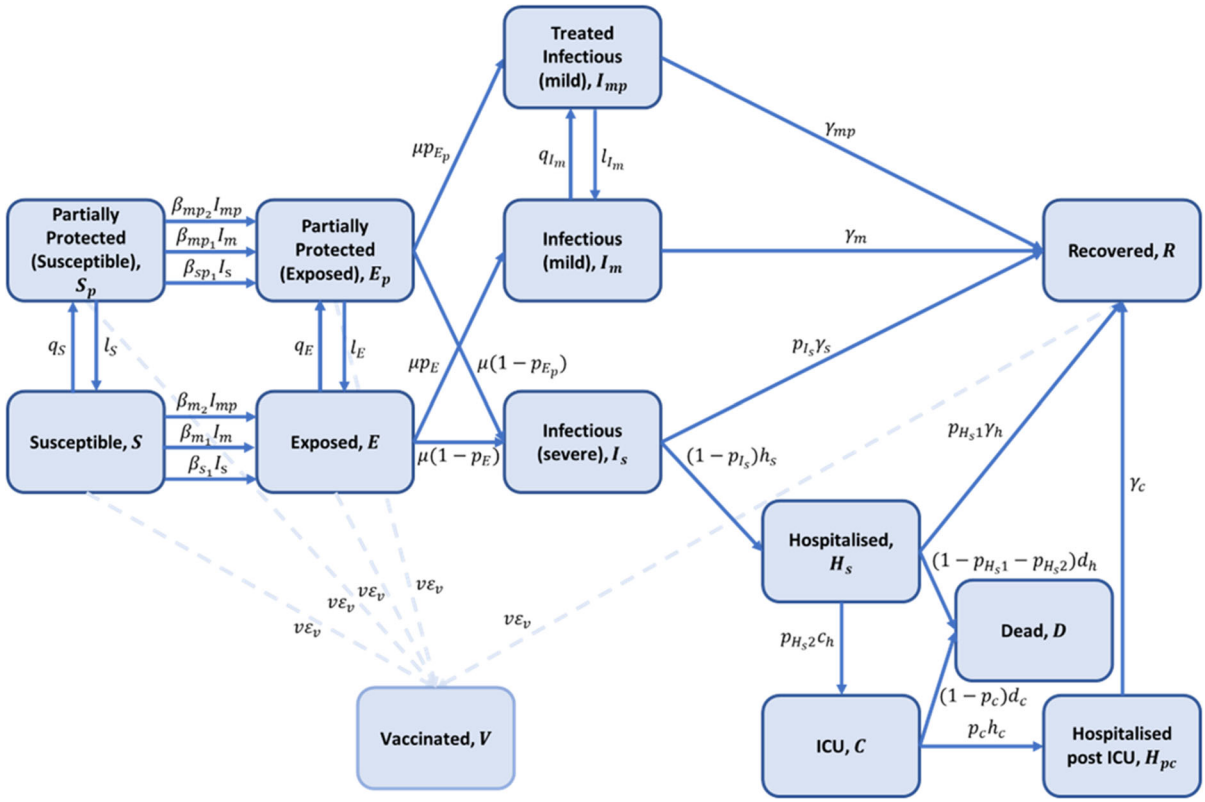

Fig. 1 Schematic diagram showing the possible transitions of individuals between the different health and disease states. This flow chart is defined precisely in a set of differential equations

possibility of the intranasal antibody prophylaxis being effective when received by a mildly infected individual in the following ways:

(iii) It decreases the infectious period.
(iv) It decreases the probability of viral transmission to other individuals.

On the basis of the duration of protection that the current generation of intranasally administered active substances confer, which ranges from a few hours to a few days [17], in all the aforementioned cases it was assumed that the intranasal antibody prophylaxis provides only a short duration of protection, i.e. the treated individuals are not protected after a limited duration of time post-administration, unless they receive consecutive doses in a timely manner. In the numerical examples that have been studied, the treatment efficacy is constant over the duration of administration and there is an immediate protective response, i.e. the treatment is effective as soon as it is taken.

Parameter Values

To illustrate the potential population-level impact of intranasal antibody prophylaxis on controlling the spread of an emerging respiratory virus, we focused on the SARS-CoV-2 outbreak at the beginning of the pandemic when an effective vaccine was not available (see Table S2 in the Supplementary Material for the estimates of the model parameters used). The case of a higher basic reproduction number ($R_0 = 5$) which could occur with more transmissible strains, like Delta and Omicron, has also been considered (Supplementary Material, Fig. S1).

Statement of Ethics Compliance

This article does not contain any new studies with human participants or animals performed by any of the authors. Ethics approval and consent to participate in this study are not applicable.

RESULTS

Intranasal antibody prophylaxis that provides a short-term protection against infection could delay the spread of the infection in the community for as long as consecutive doses were administered to susceptible individuals (Fig. 2). As antibodies administered intranasally do not induce long-lasting immunity, the long-term epidemic control by antibody-based nasal sprays would be challenging in the absence of any other interventions.

Continuous large-scale administration of highly efficacious intranasal antibody prophylaxis would be required to contain the number of severe infections and hospitalisations (Fig. 3a, b). Stopping the intranasal administration of monoclonal antibodies when the proportion of susceptible individuals is still very high would lead to a surge of cases of infection. The larger the proportion of susceptible individuals, the larger the epidemic wave that the population will experience (Figs. 2, 3b). Speedy rollout of intranasal antibody prophylaxis campaigns at the start of the epidemic would be important, especially in cases where the reproduction number is large and, concomitantly, the infection spreads at a high rate (Fig. 3c, Supplementary Material Fig. S1). It should be noted that in a small, closed population (e.g. a household during the self-isolation period or a small care home which is isolated from the community) where most, or all, members that are exposed to the virus receive intranasal prophylaxis continuously, blocking the transmission and preventing severe infections until the elimination of the virus within the group could be feasible. This would depend on the efficacy of the prophylaxis (e.g. see Fig. S2 in the Supplementary Material).

To evaluate the importance of the different mechanisms of action of antibody-based nasal sprays when they are used continuously by a certain proportion of the population, we considered the potential impact of each of them, separately, on severe cases, hospitalisations and ICU admissions. Preventing the infection would be the most important and efficient mechanism when aiming to delay the spread of the disease and control the rate of severe diseases (Fig. 4). Antiviral prophylaxis that prevents the development of severe disease would not be as effective for controlling severe diseases, unless a larger proportion of exposed individuals could be identified and treated in a timely manner. However, this mechanism of action would enable the reduction of the overall number of severe infections, hospitalisations and ICU admissions. Similarly, reducing the infectious period, or the probability to transmit the virus to other individuals, in the case of mild disease would not be as effective. This is especially the case where the probability of developing a severe infection is high in certain categories within the population, as for COVID-19 in the absence of vaccination and other interventions.

DISCUSSION

The use of antibody-based antiviral nasal sprays could provide fast-acting and timely antiviral prophylaxis to an individual that is exposed to a respiratory virus. Acting directly at the nasal mucosa, the primary entry site of respiratory viruses, they could potentially prevent both disease and becoming infectious to others much faster than systemic interventions.

In the early stage of an infectious disease outbreak within a community, intranasal antibody prophylaxis may provide a stand-alone approach for a short delay of the spread of the disease and prevent significant morbidity (requiring hospitalisation) and mortality. It could therefore help bridge the time needed to develop and produce effective vaccines for active immunisation, or drugs for antiviral treatment. Developing a mathematical model to describe the potential population-level

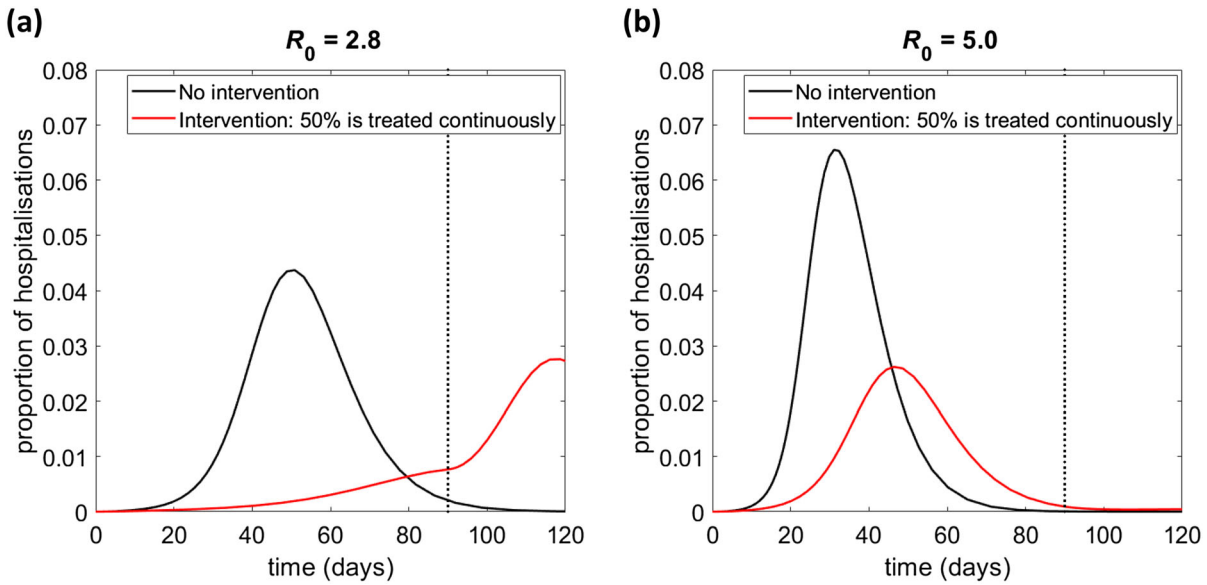

Fig. 2 Proportion of hospitalisations over time in a defined population in the case where there is no intervention (black line) and the scenario where 50% of the susceptible population is continuously receiving prophylaxis of efficacy equal to 0.7 ($f_1 = f_2 = f_3 = 0.7$, $f_4 = 0$) for the first 90 days of the epidemic (red line). $\beta_{s_1} = \beta_{m_1} = \beta_{m_2}$, $\beta_{sp_1} = \beta_{mp_1} = \beta_{mp_2}$. Initially, a proportion 0.0001 with mild infection is introduced into a wholly susceptible population. **a** $R_0 = 2.8$. **b** $R_0 = 5$. These values of R_0 have been chosen to mimic the original SARS-CoV-2 variant that spread widely in Europe in 2020 and the Delta variant that spread in 2021, respectively. In all cases, intranasal prophylaxis starts before and continues after the exposure to the virus and during a mild infection

impact of intranasal antibody prophylaxis, we showed that even when consecutive doses of highly effective intranasal prophylaxis are administered to a substantial proportion of the population, the long-term control of disease transmission would be challenging. This is due to the nature of intranasal antibody prophylaxis providing only short-term (partial) protection to the mucosal surface. The development of antibody-based nasal sprays that could also provide effective post-exposure prophylaxis for the prevention of severe infections (resulting in the reduction of the area under the curve of severe infections) would therefore be particularly important, especially in the absence of effective vaccines and therapeutic treatments. In fact, if the nasal spray only reduces the probability of infection then, depending on the effectiveness, the use of nasal sprays would have a similar, or the same, effect as some of the NPIs, such as wearing face masks or reducing the number of contacts relevant to infectious disease spread between individuals.

Nevertheless, there will always be an individual benefit for those who use nasal sprays (e.g. see Fig. S3 in the Supplementary Material which shows the relative risk of developing severe infection). Their contribution in reducing the risk of infection would be important in many cases. Intranasal antibody prophylaxis could be an effective measure (1) against infection in those unvaccinated, (2) where vaccines do not protect against infection with new variants, (3) when waning of immunity occurs and the risk of reinfection increases, (4) within a household or other small group after a member has tested positive for a virus, (5) prior to attending a large gathering of people, such as a football match [13]. This would be particularly important if NPIs are not introduced.

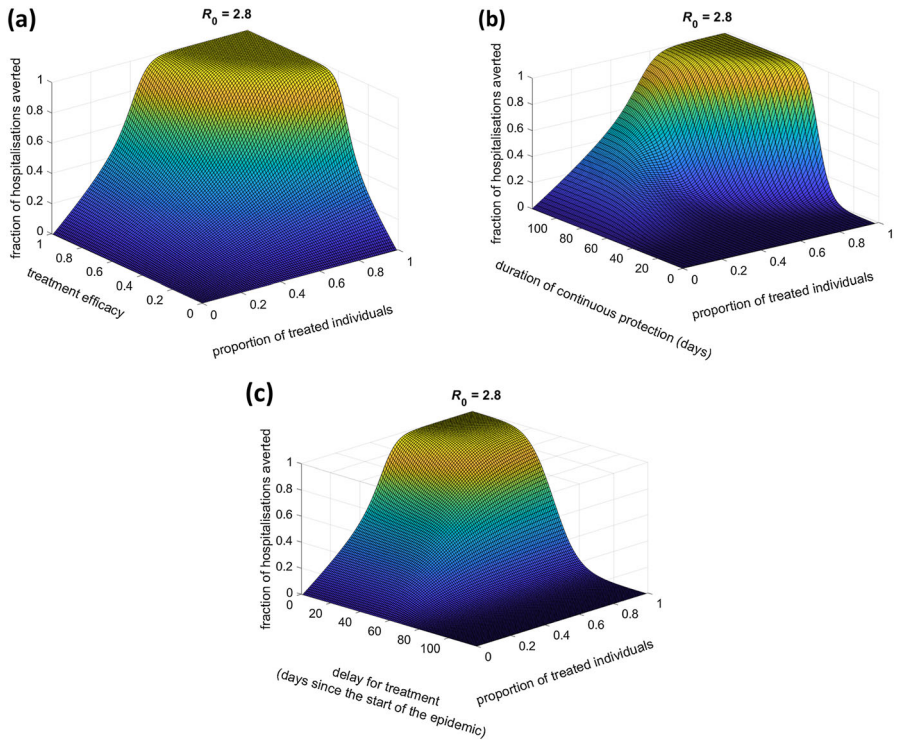

Fig. 3 The fraction of hospitalisations averted within 120 days as a function of the proportion of the population that continuously receives intranasal prophylaxis and **a** the treatment efficacy (treatment initiates at day 0 and continues up to day 120), **b** the duration of continuous administration from the beginning of the outbreak, **c** the delay in treatment initiation (when treatment administration begins, it is continuous up to day 120). Initially, a proportion 0.0001 with mild infection is introduced into a wholly susceptible population. $R_0 = 2.8$. $\beta_{s_1} = \beta_{m_1} = \beta_{m_2}, \beta_{sp_1} = \beta_{mp_1} = \beta_{mp_2}$. In a, $f_1 = f_2 = f_3, f_4 = 0$. In b and c, $f_1 = f_2 = f_3 = 0.7$, $f_4 = 0$. In all cases, intranasal prophylaxis starts before and continues after the exposure to the virus and during a mild infection

CONCLUSION

Intranasal antibody prophylaxis has the potential to provide immediately accessible protection to individuals that are likely to be exposed to the virus. The use of antibody-based nasal sprays could replace some of the non-pharmacological prevention and control measures, including self-isolation and the use of face mask, reducing some of the associated adverse consequences of such measures. If exposure to the virus is prolonged, the use of nasal sprays with short duration of protection would become less effective. Intranasal prophylaxis alone cannot act to prevent community-wide transmission of the virus. It could constitute an additional protective measure to vulnerable people, such as the elderly, those that are unvaccinated, people with comorbidities and the immunocompromised, or those visiting crowded places. In any case, individual behaviour in terms of compliance to repeated treatment would be one of the most important factors for this to succeed, as continuous self-administration would be required.

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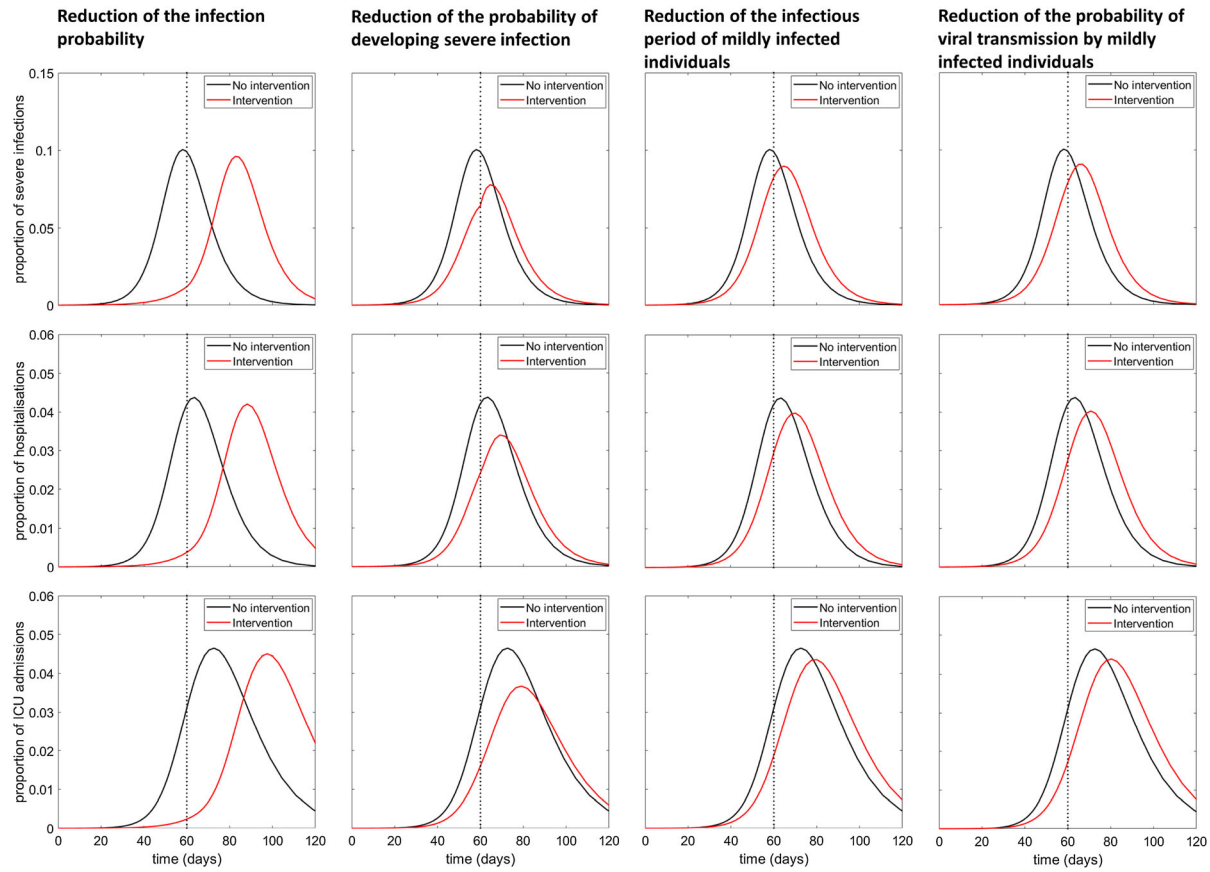

Fig. 4 The impact of intranasal antibody prophylaxis with each of the four different mechanisms of action, as described in the "Methods" section, on the proportion of severe infections, hospitalisations and ICU admissions. No intervention (black line) and the scenario where 40% of the population continuously receives the prophylaxis during the first 60 days of the epidemic (red line) are illustrated. In each case the efficacy is equal to 0.7. Initially, a proportion 0.0001 with mild infection is introduced into a wholly susceptible population. For the first three mechanisms, $\beta_{s_1} = \beta_{m_1} = \beta_{m_2}$ and $\beta_{sp_1} = \beta_{mp_1} = \beta_{mp_2}$. For the fourth mechanism, $\beta_{s_1} = \beta_{m_1} = \beta_{sp_1} = \beta_{mp_1}$ and $\beta_{m_2} = \beta_{mp_2}$. $R_0 = 2.8$

Author Contributions. All authors contributed to the study conception and design. Material preparation, data collection, model development and analysis were performed by Christoforos Hadjichrysanthou. The first draft of the manuscript was written by Christoforos Hadjichrysanthou. All authors reviewed and interpreted the data, and commented on previous versions of the manuscript. All authors read and approved the final manuscript.

Disclosures. Christoforos Hadjichrysanthou, Roy M. Anderson, and Frank De Wolf have no relevant financial or non-financial interests to disclose. Anna Beukenhorst, Clarissa Koch and Jaap Goudsmit have disclosed that they are employees of Leyden Laboratories with stock options in this company. Galit Alter is the founder of and equity holder in Seromyx Systems Inc., is an employee of and equity holder in Leyden Labs, and has collaborative agreements with Sanofi, Pfizer, BioNtech, Merck, GSK, Medicago, BMS.

Compliance with Ethics Guidelines. This article does not contain any new studies with human participants or animals performed by

any of the authors. Ethics approval and consent to participate in this study are not applicable.

Data Availability. The mathematical model and data that have been used are included in this article.

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