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

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Supplementary Material

Overview of developments in intranasal antiviral prophylaxis

Neutralising antibodies against a broad range of respiratory viruses can be administered through the inhaled route for the direct and immediate protection of the susceptible mucosal surface which is the primary route of virus entry [1-4]. Antibody in mucosal secretions may protect the target epithelial cells, prevent infection mainly through immune exclusion and virus neutralisation and reduce upper-airway symptoms [2]. Intranasal administration of neutralising antibodies may also limit the progression of the infection and shorten its duration [2]. Infected cells can be eliminated via antibody-dependent cellular cytotoxicity and cytolytic T cell activity. Some evidence of the prophylactic effectiveness of nasal antibody treatments against respiratory tract infections has been demonstrated in human studies [2].

Rapid boosting of the innate immune response by using intranasal interferon (IFN) administration has also been suggested as a desirable option for prophylaxis or early treatment of emerging respiratory virus infections, but more studies to prove safety and efficacy are required [5-8]. Prophylactic IFN treatments (including intranasal treatments) are being assessed in ongoing clinical trials [8]. Studies have also focused on the formulation of a polysaccharide-based spray which directly contacts the nasal mucosa lining the epithelium. Such nasal sprays can protect the nasal epithelium by trapping the virus within the sprayed layer blocking the entry into the cells, which is then eliminated through natural nasal clearance mechanisms. Viral replication can also be inhibited by the formation of a steric barrier across the cell interface which can block the virus entry into the cells, and/or by adsorption of the polymer to the interface of the virus [9].

Animal studies have shown that intranasal administration of compounds which stimulate protective innate immune responses could also improve the ability of the epithelium to respond quickly when the virus enters the epithelium of the upper respiratory tract. There is a substantial body of evidence that such treatments could serve as suitable antimicrobial or antiviral agents to restrict viral replication in the nasal epithelia, decline viral transmission to the lower respiratory tract that causes severe disease, and suppress excessive virus-induced airway inflammation and tissue damage. The treatments have also been effective in reducing viral transmission between animals [10-13]. The success of such animal models demonstrates the potential for the development of successful intranasal prophylactic treatments in humans to mitigate the impact of respiratory pathogens. A biotechnology company, ENA Respiratory, is conducting Phase II clinical studies of a novel nasal spray that can be self-administered to stimulate the innate immunity in the nose, aiming at the elimination of respiratory viruses before they spread to the lower airways [14]. Vries et al. [15] have developed animal models to show the prophylactic effect of similar intranasal treatments which prevent membrane fusion between the virus and the cells. Administration via the nasal route of novel peptide fusion inhibitors that target conserved regions of the virus surface have been tested in animal models showing highly preventative and protective effect against multiple pathogenic viruses [15, 16]. For example, studies have shown that daily intranasal administration of fusion-inhibitory lipopeptides to ferrets could provide complete protection against SARS-CoV-2 transmission through direct-contact between animals [15]. Table S1 presents some of the studies on intranasal prophylaxis against respiratory virus infections.

Table S1. Overview of studies on intranasal prophylaxis against respiratory virus infections

Code	Technology	Virus	Stage in the development process	Reference
EK1C4	Peptide	SARS-CoV-2, SARS-CoV, MERS-CoV, HCoV-OC43	Animal studies (mice)	[17]
OC43-HR2P, EK1	Peptide	HCoV-OC43, MERS-CoV	Animal studies (mice)	[16]
[SARSHRC-PEG_4]$_2$-chol	Lipopeptide	SARS-CoV-2, SARS-CoV, MERS-CoV	Animal studies (ferrets)	[15]
H5-VHH	Nanobody	Influenza A	Animal studies (mice)	[18]
Nb_{15}-Nb_H-Nb_{15}	Nanobody	SARS-CoV-2	Animal studies (mice)	[19]
TriSb92	Antibody mimetic	SARS-CoV-2	Animal studies (mice)	[20]
CF-401, CF402, CF-403	Antibody	Influenza A and B	Animal studies (mice)	[21]
CR8020, CR6261	Antibody	Influenza A	Animal studies (mice)	[21]
5A7	Antibody	Influenza B	Animal studies (mice)	[21]
IgM-14	Antibody	SARS-CoV-2	Animal studies (mice)	[4]
InvisiMask	Antibody	SARS-CoV-2	Animal studies (mice)	[22]
DZIF-10c	Antibody	SARS-CoV-2	Animal studies (mice)	[23]
F61, H121	Antibody	SARS-CoV-2	Animal studies (mice)	[24]
ftIFN-α	Type I interferon (IFN), IFN-α	Influenza A	Animal studies (ferrets)	[6]
rhIFN-α	Recombinant human interferon alpha	SARS-CoV-2	'Prospective open-label clinical trial'	[7]

Pam2Cys	Toll-like receptor-2 agonist	Influenza A	Animal studies (mice)	[10]
INNA-X	TLR2-mediated activation of innate responses	Influenza A (Udorn)	Animal studies (mice)	[11]
INNA-X	TLR2-mediated activation of innate responses	Rhinovirus	Animal studies (mice)	[12]
INNA-051	TLR2/TLR6 agonist	SARS-CoV-2	Animal studies (ferrets)	[13]
INNA-051	TLR2/TLR6 agonist	Influenza A	A single centre, prospective, randomised, double-blind, placebo-controlled study, Phase IIa trial	[14]
pHOXWELL	A combination of natural virucides	SARS-CoV-2	A randomised, double-blind, placebo-controlled study - Phase II/III trial	[25]
NONS	Nanomolecule	SARS-CoV-2	Phase III trial	[26]

The deterministic mathematical model

Model compartments

Susceptible, S: Individuals susceptible to infection.
Partially protected susceptible, S_p: Susceptible individuals receive the intranasal treatment, with rate q_S, and become partially protected; they can still get exposed to the virus and become infected but with a lower probability (the treatment reduces the infection rates from $\beta_{s_1}, \beta_{m_1}, \beta_{m_2}$ to $\beta_{sp_1}, \beta_{mp_1}, \beta_{mp_2}$, respectively). The treatment effect lasts for $1/l_S$ days.

Exposed, E: Individuals that have been exposed to the infection but are not yet infectious.
Partially protected (Exposed), E_p: Exposed individuals can still receive the treatment, with rate q_E. This reduces the risk of developing severe infection from $1 - p_E$ to $1 - p_{E_p}$. Partially protected susceptible individuals, S_p, that get exposed to the virus also move to this class. The treatment can provide protection to exposed individuals for $1/l_E$ days.

Infectious (mild), I_m: Individuals that become infected and infectious with mild symptoms.
Infectious (severe), I_s: Individuals that become infected and infectious with severe symptoms.
Treated Infectious (mild), I_{mp}: Individuals that become infected and infectious with mild symptoms and have received the treatment, with rate q_{I_m}. Individuals that are in the E_p class also move to the I_{m_p} class. The intranasal treatment could potentially reduce the infectious period from $1/\gamma_m$ to $1/\gamma_{mp}$ and the probability of transmitting the virus to other individuals (reducing the infection rates from β_{m_1} and β_{mp_1} to β_{m_2} and β_{mp_2}, respectively). The treatment is effective for $1/l_{I_m}$ days.

Hospitalised, H_s: Severely infected individuals that are admitted to the hospital.
Intensive care unit (ICU), C: Hospitalised individuals that are transferred to ICU.
Hospitalised post ICU, H_{pc}: Individuals that leave ICU and move to general ward until recovery.

Dead, D: Hospitalised individuals ($H_s + C$) that die from the infection.

Recovered, R: Individuals that recover from the disease. As we are interested in the effect of the treatment within a short period of time, we assume that recovered individuals are immune to re-infection for this duration.

Vaccinated, V: When a vaccine is available, susceptible, exposed and recovered individuals can be vaccinated.

The ordinary differential equation model

Let X denote the population in compartment X, $X \in \{S, S_p, E, E_p, I_m, I_{mp}, I_s, H_s, C, H_{pc}, R, D\}$. Due the short-term infection dynamics, we do not model the aging processes, as well as birth and deaths. The dynamical changes of the different compartments are consistent with the following equations:

$$\frac{dS}{dt} = -\beta_{s_1} S I_s - \beta_{m_1} S I_m - \beta_{m_2} S I_{mp} - q_s S - v\varepsilon_v S + l_s S_p$$

$$\frac{dS_p}{dt} = q_s S - \beta_{sp_1} S_p I_s - \beta_{mp_1} S_p I_m - \beta_{mp_2} S_p I_{mp} - l_s S_p - v\varepsilon_v S_p$$

$$\frac{dE}{dt} = \beta_{s_1} S I_s + \beta_{m_1} S I_m + \beta_{m_2} S I_{mp} + l_E E_p - q_E E - \mu E - v\varepsilon_v E$$

$$\frac{dE_p}{dt} = \beta_{sp_1} S_p I_s + \beta_{mp_1} S_p I_m + \beta_{mp_2} S_p I_{mp} + q_E E - l_E E_p - \mu E_p - v\varepsilon_v E_p$$

$$\frac{dI_s}{dt} = (1 - p_E)\mu E + \left(1 - p_{E_p}\right)\mu E_p - p_{I_s}\gamma_s I_s - \left(1 - p_{I_s}\right)h_s I_s$$

$$\frac{dI_m}{dt} = p_E \mu E + l_{I_m} I_{mp} - \gamma_m I_m - q_{I_m} I_m$$

$$\frac{dI_{mp}}{dt} = p_{E_p}\mu E_p + q_{I_m} I_m - \gamma_{mp} I_{mp} - l_{I_m} I_{mp}$$

$$\frac{dH_s}{dt} = \left(1 - p_{I_s}\right)h_s I_s - p_{H_s 1}\gamma_h H_s - p_{H_s 2} c_h H_s - \left(1 - p_{H_s 1} - p_{H_s 2}\right)d_h H_s$$

$$\frac{dC}{dt} = p_{H_s 2} c_h H_s - p_C h_c C - (1 - p_C) d_c C$$

$$\frac{dH_{pc}}{dt} = p_C h_c C - \gamma_c H_{pc}$$

$$\frac{dR}{dt} = \gamma_m I_m + \gamma_{mp} I_{mp} + p_{I_s}\gamma_s I_s + p_{H_s 1}\gamma_h H_s + \gamma_c H_{pc} - v\varepsilon_v R$$

$$\frac{dD}{dt} = \left(1 - p_{H_s 1} - p_{H_s 2}\right)d_h H_s + (1 - p_c) d_c C$$

$$S + S_p + E + E_p + I_s + I_m + I_{mp} + H_s + C + H_{pc} + R + D + V = 1.$$

We assume that

$$\beta_{sp_1} = (1 - f_1)\beta_{s_1},\ \beta_{mp_1} = (1 - f_1)\beta_{m_1}, \beta_{mp_2} = (1 - f_1)(1 - f_4)\beta_{m_2}, f_1, f_4 \in [0,1],$$

$$p_{E_p} = p_E + f_2(1 - p_E), f_2 \in [0,1],$$

$$\gamma_{mp} = \frac{1}{1 - f_3}\gamma_m, f_3 \in [0, 1),$$

$$\beta_{m_2} = (1 - f_4)\beta_{m_1}, f_4 \in [0,1],$$

where f_1 and f_2 describe the effectiveness of the treatment in reducing the transmission rate and the probability of developing severe infection, respectively. f_3 describes the effectiveness of the treatment in reducing the infectious period γ_m. f_4 describes the effectiveness of the treatment in reducing the probability of virus transmission from a mildly infected individual that has received the prophylaxis.

Basic reproduction number, R_0

At the disease-free steady state, before the outbreak, we have:

$$\frac{dS}{dt} = 0 => -q_s S^* + l_s S_p^* - v\varepsilon_v S^* = 0 => S^* = \frac{l_s}{q_s + v\varepsilon_v} S_p.$$

$$\frac{dS_p}{dt} = 0 => q_s S^* - l_s S_p^* - v\varepsilon_v S_p^* = 0 => S_p^* = \frac{q_s}{l_s + v\varepsilon_v} S^*.$$

$$S^* + S_p^* = 1 => S^* = \frac{l_s}{l_s + q_s + v\varepsilon_v}, S_p^* = \frac{q_s + v\varepsilon_v}{l_s + q_s + v\varepsilon_v}.$$

Let p_p be the proportion of susceptible individuals that take the prophylaxis at the disease-free steady state.

The basic reproduction number is the dominant eigenvalue of the next-generation matrix, FV^{-1}, where

$$F=\begin{bmatrix} 0 & 0 & \beta_{s_1}(1-p_p) & \beta_{m_1}(1-p_p) & \beta_{m_2}(1-p_p) \\ 0 & 0 & \beta_{sp_1}p_p & \beta_{mp_1}p_p & \beta_{mp_2}p_p \\ 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 \end{bmatrix},$$

$$V=\begin{bmatrix} -(q_E+\mu+v\varepsilon_v) & l_E & 0 & 0 & 0 \\ q_E & -(l_E+\mu+v\varepsilon_v) & 0 & 0 & 0 \\ (1-p_E)\mu & (1-p_{E_p})\mu & -(p_{I_s}\gamma_s+(1-p_{I_s})h_s) & 0 & 0 \\ p_E\mu & 0 & 0 & -(\gamma_m+q_{I_m}) & l_{I_m} \\ 0 & p_{E_p}\mu & 0 & q_{I_m} & -(\gamma_{mp}+l_{I_m}) \end{bmatrix}.$$

The determinant of V, $|V|$, is given by

$$|V|=-(\mu+v\varepsilon_v)(p_{I_s}\gamma_s+(1-p_{I_s})h_s)(q_E+l_E+\mu+v\varepsilon_v)[\gamma_m(\gamma_{mp}+l_{I_m})+\gamma_{mp}q_{I_m}],$$

and $V^{-1}=\frac{adj(V)}{|V|}$, where $adj(V)$ is the adjoint of a V. We get that:

$$R_0 = \frac{\mu}{(\mu+v\varepsilon_v)(q_E+l_E+\mu+v\varepsilon_v)}\left(\frac{\beta_{s_1}\left[(1-p_p)\left[q_E\left(1-p_{E_p}\right)+(1-p_E)(l_E+\mu+v\varepsilon_v)\right]+(1-f_1)p_p\left((q_E+\mu+v\varepsilon_v)\left(1-p_{E_p}\right)+l_E(1-p_E)\right)\right]}{p_{I_s}\gamma_s+(1-p_{I_s})h_s}\right.$$
$$+\beta_{m_1}\left[(1-p_p)\left[q_E l_{I_m}p_{E_p}+p_E(l_E+\mu+v\varepsilon_v)(\gamma_{mp}+l_{I_m})\right]+(1-f_1)p_p\left((q_E+\mu+v\varepsilon_v)l_{I_m}p_{E_p}+p_E l_E(\gamma_{mp}+l_{I_m})\right)\right]+$$
$$\left.+\frac{+\beta_{m_2}\left[(1-p_p)\left[q_E(\gamma_m+q_{I_m})p_{E_p}+p_E q_{I_m}(l_E+\mu+v\varepsilon_v)\right]+(1-f_1)p_p\left((q_E+\mu+v\varepsilon_v)(\gamma_m+q_{I_m})p_{E_p}+p_E q_{I_m}l_E\right)\right]}{\gamma_m(\gamma_{mp}+l_{I_m})+q_{I_m}\gamma_{mp}}\right).$$

If $f_1=1$, then

$$R_0=\frac{\mu(1-p_p)}{(\mu+v\varepsilon_v)(q_E+l_E+\mu+v\varepsilon_v)}\left(\frac{\beta_{s_1}(1-p_E)(l_E+\mu+v\varepsilon_v)}{p_{I_s}\gamma_s+(1-p_{I_s})h_s}\right.$$
$$\left.+\frac{\beta_{m_1}[q_E l_{I_m}+p_E(l_E+\mu+v\varepsilon_v)(\gamma_{mp}+l_{I_m})]+\beta_{m_2}[q_E(\gamma_m+q_{I_m})+p_E q_{I_m}(l_E+\mu+v\varepsilon_v)]}{\gamma_m(\gamma_{mp}+l_{I_m})+q_{I_m}\gamma_{mp}}\right).$$

In the absence of treatment, R_0 becomes

$$R_0=\frac{\mu}{(\mu+v\varepsilon_v)}\left(\frac{\beta_{s_1}(1-p_E)}{(p_{I_s}\gamma_s+(1-p_{I_s})h_s)}+\frac{\beta_{m_1}p_E}{\gamma_m}\right).$$

Parameter values

Table S2: Model parameter values

Virus	SARS-CoV-2
Basic reproduction number, R_0	2.8 [27]
Transmission rates when in contact with infectious individuals, $\beta_{s_1} = \beta_{m_1} = \beta_{m_2}$	Calculated from R_0 (see formula)
Probability of developing mild/asymptomatic infection, p_E	0.45 [27]
Probability of severely infected individuals being hospitalised, $1 - p_{I_s}$	0.49 [27]
Probability of ICU admission if hospitalised, $p_{H_s 2}$	0.27 [27]
Probability of death during hospitalisation, $1 - p_{H_s 1} - p_{H_s 2}$	0.33 [27]
Probability of death when in ICU, $1 - p_c$	0.63 [27]
Mean incubation period, $\frac{1}{\mu}$	3.4 days [27]
Mean duration of mild infection before recovery, $\frac{1}{\gamma_m}$	2.9 days [27]
Mean duration of severe infection before recovery, $\frac{1}{\gamma_s}$	5.7 days [27]
Mean duration of severe infection before hospitalisation, $\frac{1}{h_s}$	5.7 days (assumed) [27]
Mean duration of hospitalisation before recovery, $\frac{1}{\gamma_h}$	10.7 days [27]
Mean duration of hospitalisation before ICU, $\frac{1}{c_h}$	2.5 days [27]
Mean duration of hospitalisation before death, $\frac{1}{d_h}$	10.3 days [27]
Mean duration in ICU before returning to a general ward, $\frac{1}{h_c}$	15.6 days [27]
Mean duration in ICU before death, $\frac{1}{d_c}$	11.8 days [27]
Mean duration of hospitalisation in a general ward post ICU until recovery, $\frac{1}{\gamma_c}$	12.2 days [27]

The fraction of hospitalisations averted: $R_0 = 5.0$

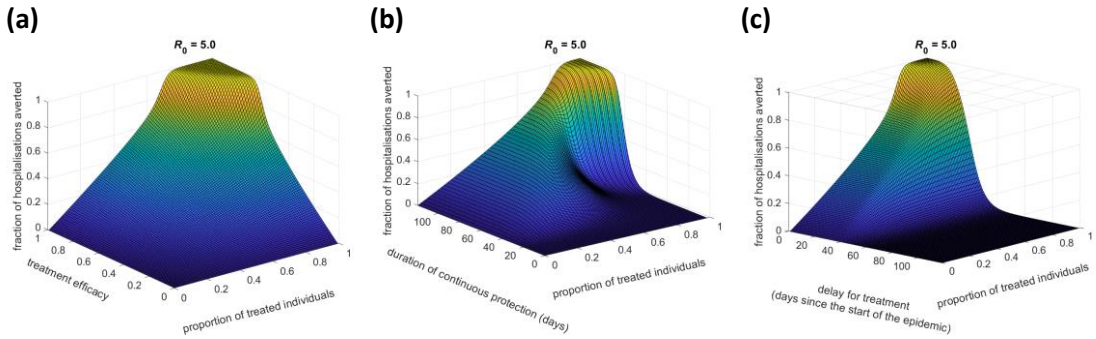

Fig. S1 The fraction of hospitalisations averted within 120 days as a function of the proportion of the population that continuously receives intranasal prophylaxis and **a** the treatment efficacy (treatment initiates at day 0 and continues up to day 120), **b** the duration of continuous administration 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. $R_0 = 5.0$. $\beta_{s_1} = \beta_{m_1} = \beta_{m_2}, \beta_{sp_1} = \beta_{mp_1} = \beta_{mp_2}$. 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

Effect of intranasal antibody prophylaxis in a small closed population

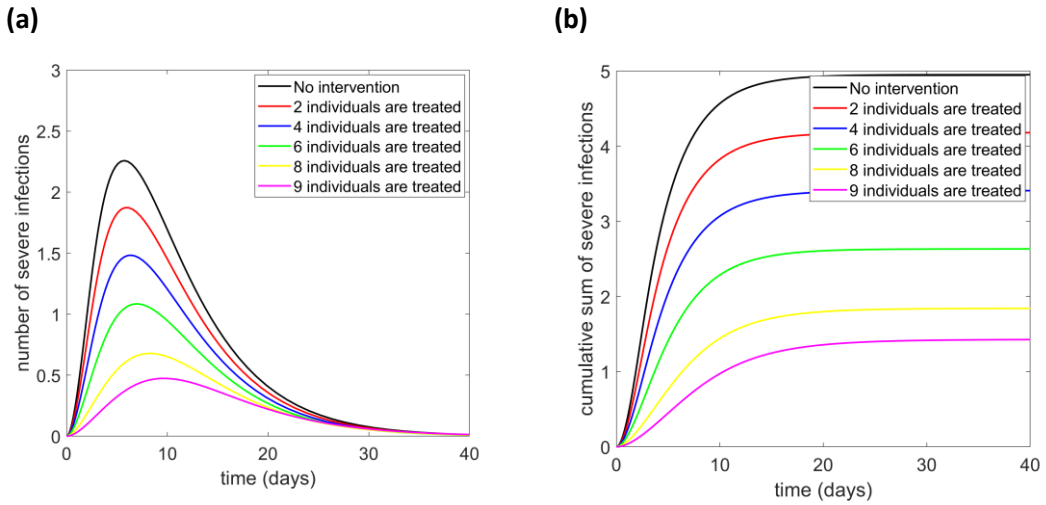

Fig. S2 **a** The number, and **b** the cumulative sum, of severe infections in a small group of 10 individuals. In such cases, a large proportion of the group could take intranasal antibody prophylaxis continuously until the elimination of the virus within the group. It is assumed that the group is isolated from the community (e.g., it may represent the members of a household during the self-isolation period when some of them have been infected). In this example, one individual of the group has initially been mildly infected. $R_0 = 2.8$. $f_1 = f_2 = f_3 = 0.7$. $\beta_{s_1} = \beta_{m_1} = \beta_{m_2}, \beta_{sp_1} = \beta_{mp_1} = \beta_{mp_2}$. In all cases, intranasal prophylaxis starts before and continues after the exposure to the virus and during a mild infection

Relative risk

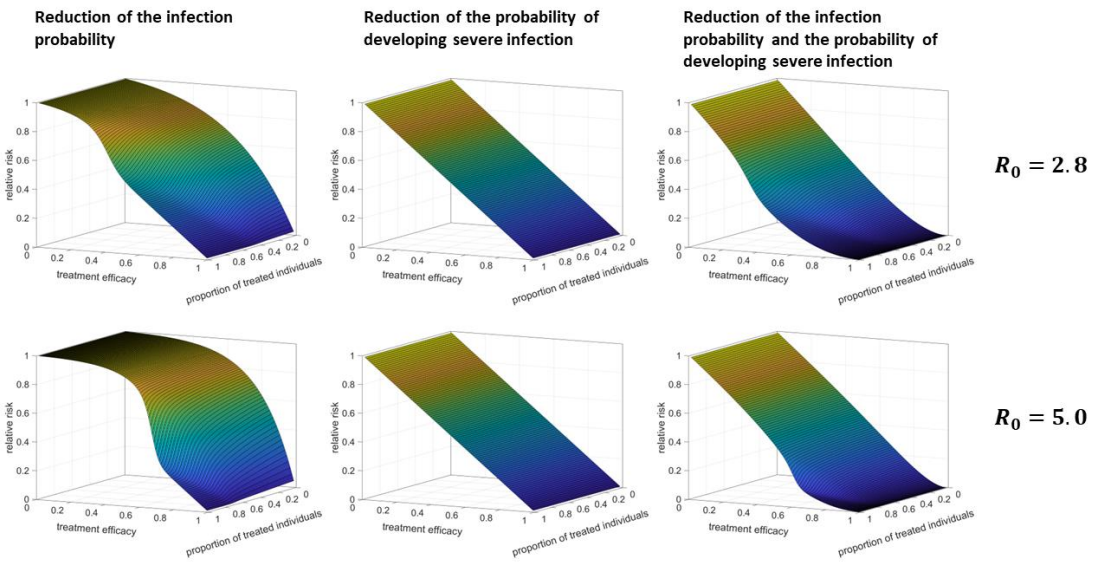

Fig. S3 The relative risk of developing severe infection by day 120 for intranasal antibody prophylaxis with different mechanisms of action. The efficacy of intranasal prophylaxis and the initial proportion of individuals that receive the prophylaxis continuously for 120 days are varying. Initially, a proportion 0.0001 with mild infection is introduced into a wholly susceptible population. $\beta_{s_1} = \beta_{m_1} = \beta_{m_2}$, $\beta_{sp_1} = \beta_{mp_1} = \beta_{mp_2}$

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