Substantial Impact of Post Vaccination Contacts on Cumulative Infections during Viral Epidemics

Nash D. Rochman[1,*], Yuri I. Wolf[1], and Eugene V. Koonin[1,*]

[1]National Center for Biotechnology Information, National Library of Medicine, Bethesda, MD 20894

For correspondence: nash.rochman@nih.gov, koonin@ncbi.nlm.nih.gov

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Abstract:

Background: The start of 2021 will be marked by a global vaccination campaign against the novel coronavirus SARS-CoV-2. Formulating an optimal distribution strategy under social and economic constraints is challenging. Optimal distribution is additionally constrained by the potential emergence of vaccine resistance. Analogous to chronic low-dose antibiotic exposure, recently inoculated individuals who are not yet immune play an outsized role in the emergence of resistance. Classical epidemiological modelling is well suited to explore how the behavior of the inoculated population impacts the total number of infections over the entirety of an epidemic.

Methods: A deterministic model of epidemic evolution is analyzed, with 7 compartments defined by their relationship to the emergence of vaccine-resistant mutants and representing three susceptible populations, three infected populations, and one recovered population. This minimally computationally intensive design enables simulation of epidemics across a broad parameter space. The results are used to identify conditions minimizing the cumulative number of infections.

Results: When an escape variant is only modestly less infectious than the originating strain within a naïve population, there exists an optimal rate of vaccine distribution. Exceeding this rate increases the cumulative number of infections due to vaccine escape. Analysis of the model also demonstrates that inoculated individuals play a major role in the mitigation or exacerbation of vaccine-resistant outbreaks. Modulating the rate of host-host contact for the inoculated population by less than an order of magnitude can alter the cumulative number of infections by more than 20%.

Conclusions: Mathematical modeling shows that optimization of the vaccination rate and limiting post-vaccination contacts can affect the course of an epidemic. Given the relatively short window between inoculation and the acquisition of immunity, these results might merit consideration for an immediate, practical public health response.

Introduction:

The emergence of the novel Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) responsible for the Covid-19 pandemic motivated dramatic public health intervention including recommendations for isolation and quarantine throughout most of 2020[1]. The beginning of 2021 will be marked by widespread vaccine distribution. Optimizing distribution is challenging and subject to a myriad of social and economic constraints[2-4]. The potential emergence of vaccine-resistant variants of the virus[5,6] introduces additional complications. Vaccination applies new selective pressures which can lead to diverse intermediate outcomes even under conditions admitting eventual pathogen eradication[7-13]. The larger the size of the vaccinated population, the greater the pressure towards escape of vaccine-resistant variants.

Escape variants emerge within individual hosts after infection with the originating strain. Naïve, unvaccinated, hosts are more easily infected than vaccinated hosts but mutations conferring resistance are unlikely to provide a selective advantage in the naïve background. Thus, naïve hosts are likely to shed escape variants at very low, likely, negligible rates. The reverse is true for vaccinated hosts. Recently vaccinated, inoculated, hosts that are not yet immune remain highly susceptible to infection with the originating strain, and in these hosts, mutations conferring resistance are more likely to provide a selective advantage. As a result, a substantial fraction or even most of the virus shed by such hosts will be resistant mutants. This situation is analogous to the administration of a low-dose antibiotic regime[14,15]. In both cases, the pathogen is introduced to a susceptible host and subject to elevated selective pressure towards the emergence of resistant (escape) variants.

We sought to establish the constraints imposed by virus escape on optimal vaccine distribution and the role played by the small, but critical, population of inoculated hosts. To this end, we constructed an epidemiological compartment model to simulate vaccination campaigns over a broad parameter regime. This minimally computationally

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70   intensive approach enabled us to simulate many possible scenarios for epidemic

71   evolution, in order to determine the optimal vaccination strategy for each condition.

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73   **Methods:**

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75   We divided the population into 7 compartments (Fig. 1A). Three compartments are

76   susceptible to infection by either the originating strain or escape mutants: Naïve (N,

77   unvaccinated and fully susceptible to the originating strain and escape mutants),

78   Inoculated (I, recently vaccinated and still partially susceptible to the originating strain,

79   and fully susceptible to escape mutants), and Vaccinated (V, minimally susceptible to

80   the originating strain, but fully susceptible to escape mutants). Two compartments

81   represent ongoing infection with the originating strain and are distinguished by the

82   host's previous compartment: Infected-Naïve (F) and Infected-Inoculated (M). The third

83   infected compartment represents infection by an escape variant, Infected-Escape (E).

84   The remaining compartment, Recovered (R), contains all hosts who were previously

85   infected. Vaccination is represented by a reduction in susceptibility to infection with the

86   originating strain. Naïve hosts are inoculated at rate k_V. Inoculated hosts do not

87   immediately acquire immunity and mature into the vaccinated compartment at rate k_M.

88   All infected hosts recover at rate k_R.

89

90   Within the timescale of the model, recovery is assumed to grant stable immunity, and

91   any variation in population size due to birth/death is assumed to be negligible. It should

92   be noted that, if recovery from the Infected-Naïve or Infected-Inoculated compartments

93   does not confer immunity against escape infection, the key results in this work will have

94   an even greater impact on the vaccination outcome. Hosts come into contact at rate k_C.

95   For simplicity, we assume that contact with an escape-infected host can only produce

96   an escape infection. Also, vaccine efficacy is assumed to be perfect such that

97   vaccinated hosts cannot be infected with the originating strain. The Inoculated-Infected

98   compartment is assumed to represent a symmetric composition of escape and

99   originating infections such that the total probability of a Naïve or Inoculated host being

100   infected after contact with a Naïve-Infected or Inoculated-Infected host is the same.

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101 Finally, we assume that the probability of escape-infection is the same for Naïve and

102 Vaccinated hosts across all three types of infected-susceptible host interactions. This

103 construction yields the following transition probability matrices for Naïve, Inoculated,

104 and Vaccinated hosts:

$$k_C P_N = k_I \begin{bmatrix} 1 & 0 & \alpha \\ 1-\beta & 0 & \alpha+\beta \\ 0 & 0 & \beta \end{bmatrix} ; k_C P_I = k_I \begin{bmatrix} 0 & 1+\alpha & 0 \\ 0 & 1+\alpha & 0 \\ 0 & 0 & \beta \end{bmatrix} ; k_C P_V = k_I \begin{bmatrix} 0 & 0 & \alpha \\ 0 & 0 & \alpha+\beta \\ 0 & 0 & \beta \end{bmatrix}$$

105

106 where k_I represents the rate of infection for Naïve, Infected-Naïve host interactions

107 which is determined both by the contact rate k_C and the infectivity of the originating

108 strain. Rows represent interaction with each of the infected compartments (Infected-

109 Naïve, Infected-Inoculated, and Infected-Escape). Columns represent transitions to

110 each of the infected compartments.

111

112 An escape mutant can emerge within an Infected-Naïve or Infected-Inoculated host.

113 The parameter α represents the infectivity of the escape variant relative to the

114 originating strain when a Naïve host interacts with an Infected-Naïve host. The

115 parameter β represents the infectivity of an escape variant when a Naïve host interacts

116 with an Infected-Escape host relative to the infectivity of the originating strain when a

117 Naïve host interacts with an Infected-Naïve host. Informally, α reflects the ratio of

118 escape variant to originating strain shed by Infected-Naïve hosts, whereas β reflects the

119 fitness of an escape variant relative to the originating strain. Finally, we introduce the

120 parameter q to represent the impact of varying the rate of host-host contact for

121 Inoculated hosts relative to that for the other compartments. $q>1$ represents increased

122 contact, and $q<1$ corresponds to decreased contact. This completes the model

123 description and structures the differential equations:

$$N' = - \left(k_V + k_I \left((1 + \alpha)\left(F + M\right) + \beta E\right)\right) N$$

$$I' = k_V N - \left(k_M + q k_I \left((1 + \alpha)\left(F + M\right) + \beta E\right)\right) I$$

$$V' = k_M I - k_I \left(\alpha F + (\alpha + \beta) M + \beta E\right) V$$

$$F' = k_I \left(NF + (1 - \beta) NM\right) - k_R F$$

$$M' = q k_I \left(1 + \alpha\right)\left(F + M\right) I - k_R M$$

$$E' = k_I \left((\alpha F + (\alpha + \beta) M + \beta E)(N + V) + q\beta EI\right) - k_R E$$

$$R' = k_R \left(F + M + E\right)$$

124

125    $k_R = k_M = 1/7$ are fixed across all simulations representing a time to recovery and time

126   between inoculation and the acquisition of immunity of one week. Reducing k_I would

127   prolong the epidemic and reducing k_M would increase the size of the Inoculated

128   compartment.

129

130   k_I is the principal determinant of epidemic magnitude and duration, with larger k_I leading

131   to a greater cumulative number of infections over a shorter period of time (Fig. 1B).

132   However, feedback between the size of the infected population and the rate of host-host

133   contact as well as spatial structure can decouple these variables. Throughout this work,

134   k_I is set to a benchmark value of 0.2 resulting in 50% of the population being infected

135   over a period of approximately 4 months.

136

137   The values of α and β impact the size of the Infected-Escape compartment. Even in the

138   absence of vaccination, large α/β results in the emergence of would-be resistant

139   variants (Fig 1C). In all analyses in this work, α is fixed at the benchmark value of 0.001

140   resulting in a modest number of would-be resistant infections for β close to 1 in the

141   absence of vaccination. Although a larger α would result in a greater total number of

142 escape infections, the fraction of those infections attributable to contact with inoculated

143 hosts would be smaller.

144

145 The solutions of the ODEs were obtained using the MATLAB ode45 method[16].

146 Epidemics are simulated until the size of the Recovery compartment at arbitrarily long

147 times is approached. The principal quantity of interest is the cumulative number of

148 infections. When k_V is selected to minimize this value, minima are found through explicit

149 simulation over a range of rates. In the subsequent analysis, some values are

150 expressed relative to the cumulative number of infections in the absence of vaccination,

151 *R_{Null}~50%.*

152

153 **Results:**

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155 In addition to the rate of vaccination, the outcome of a vaccination campaign depends

156 on how far the epidemic has progressed before vaccination begins, which can be

157 measured by the relative size of the Recovered compartment. The results also depend

158 on β, informally, the fitness of an escape variant relative to the originating strain. We

159 considered two values for β (0.01, low; 0.875, high) and varied both the start and rate of

160 vaccination. When β is low, that is, the escape mutant is much less fit than the

161 originating strain (Fig. 2A), vaccinating earlier and distributing the vaccine faster

162 decreases the cumulative number of infections. If distribution is sufficiently prompt, the

163 cumulative number of infections becomes negligible.

164

165 However, the outcome substantially differs for high β (Fig. 2B). Due to the vaccine

166 escape, at high rates of distribution, the cumulative number of infections remains large.

167 Furthermore, there is an optimal rate of distribution such that exceeding this rate

168 increases the cumulative number of infections. In this regime, the benefit of reducing the

169 size of the population susceptible to infection by the originating strain is outweighed by

170 the cost of increasing the selective pressure for the emergence of escape variants. In all

171 subsequent analysis, the vaccination rate is varied but vaccination is fixed to begin

172 when 1% of the population has recovered from infection.

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173

174   Infections can be mitigated by reducing host-host contact. We sought to determine how

175   perturbing the contact rates for hosts in the Inoculated compartment relative to that of all

176   other compartments, q, affects the outcome. For β ranging between 0.75 and 1, we

177   considered three relative contact rates, $q=[0.2,1,5]$ (Fig. 2C). Increasing the rate of host-

178   host contact only within this compartment has a significant impact on the cumulative

179   number of infections. The optimal vaccination rate is also perturbed. Furthermore, if the

180   optimal vaccination rate it exceeded, reducing q below 1 slows the accumulation of

181   infections (Fig. 2D). The converse is true for increasing q, and the landscape is similar

182   when vaccination falls below the optimal rate (Fig. 2E).

183

184   Having demonstrated how q perturbs the optimal vaccination rate and how reducing q

185   below 1 can mitigate or delay the cumulative number of infections even if this rate is not

186   met or, conversely, is exceeded, we sought to establish the impact of q on the

187   cumulative number of infections across a wide range of β at the optimal vaccination rate

188   for each condition (Fig. 3A). The cumulative number of infections is sensitive to q across

189   the entire range of β. Varying q within an order of magnitude can substantially aid or

190   hinder the vaccination campaign, and when $q>>1$, the optimal rate of vaccination is 0.

191   Note that the maximum vaccination rate considered is $k_V=0.03$ representing the

192   inoculation of 3% of Naïve hosts per day. This rate is sufficiently high that the

193   cumulative number of infections at this rate (Fig. 3B) is similar or higher compared to

194   the hypothetical case where the entire Naïve population is immediately inoculated (Fig.

195   3C). Some of these effects are not specific to the inoculated compartment. Increasing

196   the rate of contact for any arbitrary subpopulation can increase the cumulative number

197   of infections. We define the effective k_I, k_{Ieff}, such that the cumulative number of

198   infections for $k_I=k_{Ieff}$ and $q=1$ is equal to the cumulative number of infections for $k_I=0.2$

199   (the benchmark) and arbitrary q. Increasing q within an order of magnitude is equivalent

200   to substantially increasing k_I for the entire population for the entirety of the epidemic

201   (Fig. 3D).

202

203   We additionally consider the cumulative infections added or subtracted relative to the

204   outcome corresponding to $q=1$ and scaled by the fraction of infections due to vaccine

205   escape (Fig. 3E). Varying q within an order of magnitude alters the cumulative number

206   of infections added or subtracted by more than 20% of the cumulative number of

207   infections in the absence of vaccination, R_{Null}, again demonstrating the critical role

208   played by inoculated hosts with respect to vaccine escape. The landscape is similar

209   when then rate of vaccination is fixed (Fig. 3F).

210

211   **Discussion:**

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213   Epidemics can be mitigated through the reduction of host-host contact (quarantines and

214   other similar measures) and vaccination. A reduction in contact carries non-negligible

215   social and economic burdens so that, when vaccination becomes possible, the

216   continuation of such interventions might appear unnecessarily costly. Formulating an

217   optimal vaccination strategy to balance these pressures is challenging and is further

218   complicated by the possibility of vaccine escape. Escape variants emergingas a result

219   of vaccination are not expected to be more infectious than the originating strain,

220   otherwise, such variants would likely already be in circulation prior to vaccination.

221   However, newly emergent variants are not always much less infectious and can be

222   responsible for non-negligible disease incidence[17,18]. Here, we demonstrated that, even

223   when escape variants are modestly less infectious, there exists an optimal vaccination

224   distribution rate such that exceeding this rate increases the cumulative number of

225   infections. This optimal rate depends on the infectivity of the escape variants. Such a

226   prediction is impractical at the time of writing, that is, in the very first days of the

227   vaccination campaign, and the cost of overestimation of the optimal vaccination rate is

228   far less than that of underestimation. However, to our knowledge, this phenomenon,

229   analogous to the evolution of antibiotic resistance, is not widely appreciated and, as

230   such, seems to warrant discussion.

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232   Of more practical concern is the role of inoculated hosts in the emergence of escape

233   variants. Within low-dose antibiotic regimes [14,15], hosts are susceptible to infection with

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234   the originating variant, and in such hosts, the pathogen is subjected to elevated

235   selective pressures towards the emergence of resistance. Similarly, within inoculated

236   hosts, the virus is subjected to gradually increasing selective pressures towards the

237   emergence of resistance while the intra-host population remains sufficiently large to

238   explore a substantial fraction of the mutation space. We demonstrated that moderately

239   increasing or decreasing the host-host contact rates for inoculated hosts only can

240   substantially aid or hinder the vaccination campaign. The time between vaccination and

241   the acquisition of immunity can be readily approximated from clinical endpoints[19,20] and

242   is likely to be short enough that the societal costs of limiting post-vaccination contact

243   would be outweighed by these benefits.

244

245   **Limitations:**

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247   In this study, we leveraged classical modelling techniques to elucidate the factors that

248   could substantially impact the outcome of any vaccination campaign. Although these

249   results are broadly applicable, they are not necessarily instrumental for predicting

250   quantitative outcomes for the current SARS-CoV-2 pandemic or any other particular

251   epidemic. Similarly, the model presented in this study is not designed to forecast long-

252   term outcome, a topic that has been thoroughly addressed for the case of SARS-Cov-2

253   and more generally[7-13,21-23].

254

255   The results presented here appear to be of immediate interest in relation to the

256   vaccination campaign against SARS-Cov-2 that is beginning at the time of this writing.

257   However, although diversification of the virus is apparent[24-26] and the potential for

258   escape is being actively investigated[5,6,27,28], it cannot be ruled out that all escape

259   variants have a substantially reduced infectivity, represented by $\beta << 1$, in which case the

260   highest possible vaccination rate will be optimal and the benefits specific to post-

261   vaccination contact limitation could be negligible.

262

263   **Conclusions:**

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265 Depending on the infectivity of escaping, vaccine-resistant mutants, the optimal

266 vaccination rate with respect to the cumulative number of infections can be lower than

267 the maximum rate. Contact rates for inoculated hosts can have a substantial impact on

268 the outcomes of vaccination campaigns. Even a brief and moderate limitation of

269 contacts in this well-defined population can potentially mitigate epidemics. These results

270 might merit consideration for an immediate, practical public health response.

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272 **Author Contributions:**

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274 NDR, YIW, and EVK conceived of the study; NDR constructed the model; NDR, YIW,

275 and EVK analyzed data; NDR and EVK wrote the manuscript that was edited and

276 approved by all authors.

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278 **Acknowledgements:**

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Figure legends

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Figure 1. The Model. A. Schematic of the 7 compartment model with three susceptible, three infected, and one recovered compartments. **B.** Simulated epidemics for $k_I=[0.15,0.175,0.2$(solid line)$,0.225,0.25]$, $\alpha=0.001$, $\beta=0.01$ **C.** The ratio of cumulative escape infections to all cumulative infections for an epidemic over a range of α. $\beta=[0.5,0.67,0.83,1]$, darker color indicates higher value, $k_I=0.2$. The dotted line specifies the benchmark value of $\alpha=0.001$.
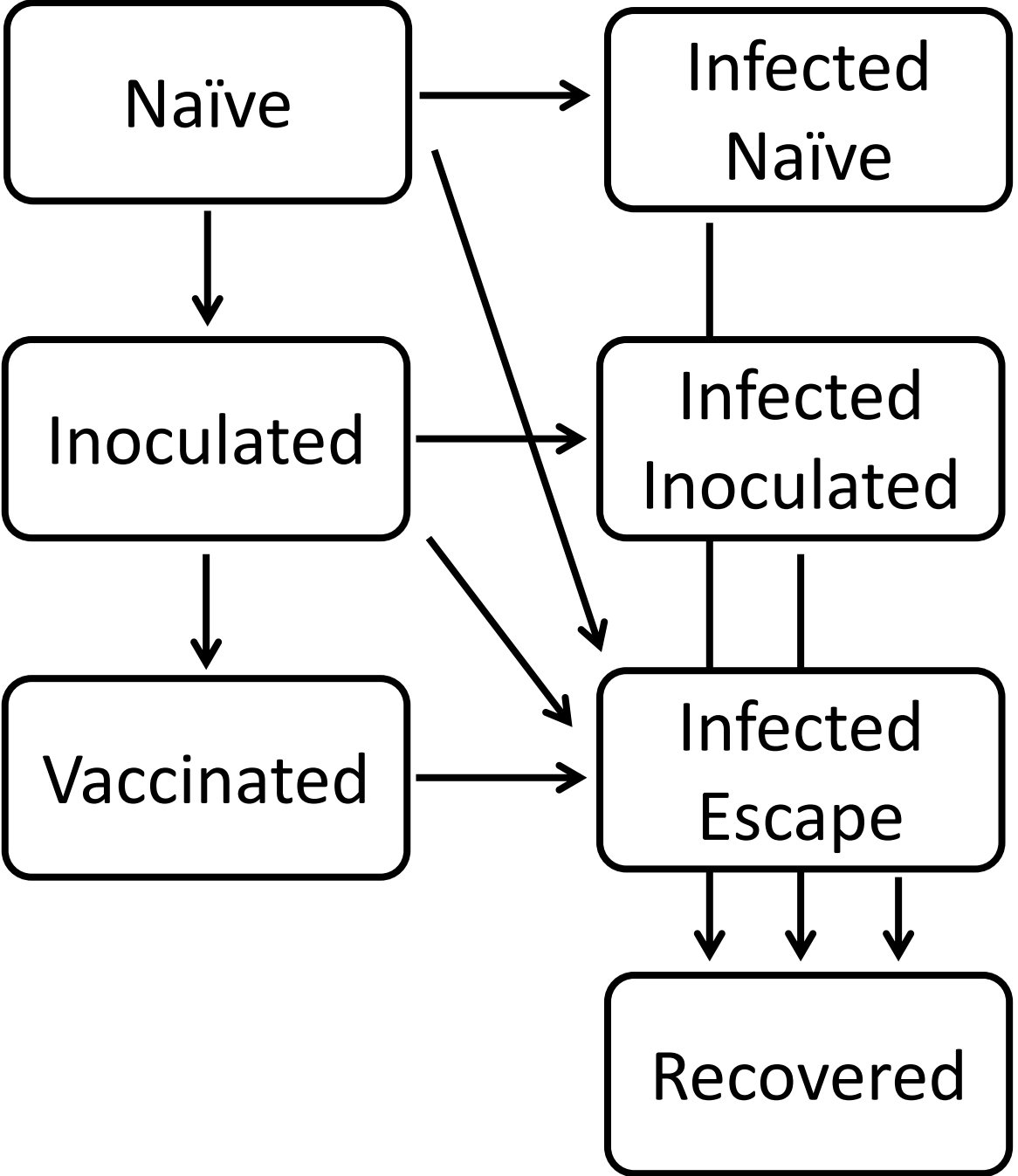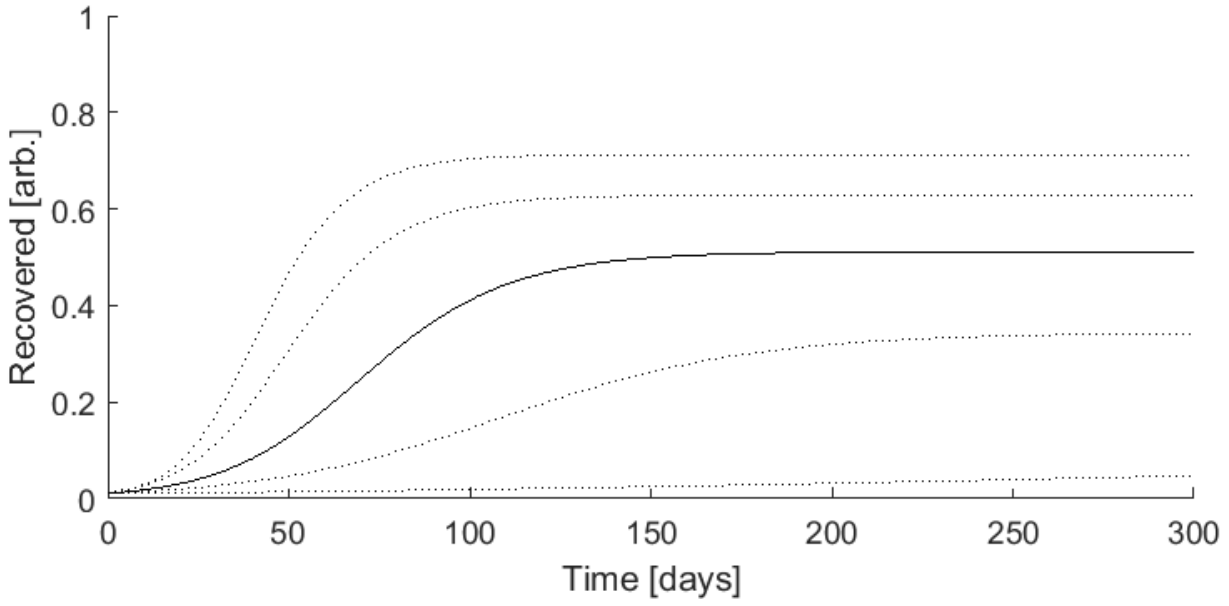
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Figure 2. Optimal Vaccine Distribution. A. The cumulative number of infections relative to no vaccination, R_{Null}, for a range of vaccine initiations and distribution rates. Here β is low, 0.01. **B.** The cumulative number of infections relative to no vaccination, R_{Null}, for a range of vaccine initiations and distribution rates and a large β (0.875). **A/B.** 3840 values were computed for each panel and 4x by 4x bilinearly interpolated points are displayed. **C.** The cumulative number of infections relative to no vaccination, R_{Null}, for $\beta=[0.75$(dotted)$,0.875$(dashed)$,1$(solid)$]$ and three relative contact rates, $q=[0.2$(brown)$,1$(black)$,5$(gray)$]$. **D.** Simulated epidemics comparing a high fixed rate of vaccination, $k_V=0.03$ (solid) representing the inoculation of 3% of Naïve hosts per day, and the optimal vaccination rate for each condition (dashed). $\beta=0.875$ is fixed and $q=[0.2$(brown)$,1$(black)$,5$(gray)$]$. **E.** Same as D. with a low fixed rate of vaccination, $k_V=0.01$. **C/D/E.** The minima for the dashed lines in C correspond to the dashed lines in D/E.

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Figure 3. Post-vaccination contacts. A. The cumulative number of infections relative to no vaccination, R_{Null}, for a range of β and q, optimizing k_V for each condition. **B.** Same as in A. for fixed $k_V=0.03$ representing the inoculation of 3% of Naïve hosts per day. **C.** Same as in A. for the case where all Naïve hosts are immediately inoculated. **D.** Log of the effective k_I, k_Ieff, relative to $k_I=0.2$, the benchmark, vs. log of q for $\beta=[0.5$ (dotted line)$, 0.7$ (dashed line)$, 1$ (solid line)$]$. **E.** The cumulative number of infections relative to R_{Null} and $q=1$ scaled by the fraction of infections due to vaccine escape,

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372    $\sum Escape(q)/\sum Infections(q)(\sum Infections(q)-\sum Infections(q=1))/R_{Null}$, for a range of β and q,

373   optimizing k_v for each condition. **F.** Same as in E for fixed $k_v=0.03$. **A-C/E/F.** 961 values

374   were computed for each panel and 4x by 4x bilinearly interpolated points are displayed.

375

A

Naïve → Infected Naïve

Naïve → Inoculated

Inoculated → Infected Inoculated

Infected Naïve → Infected Inoculated

Naïve → Infected Escape

Inoculated → Infected Escape

Inoculated → Vaccinated

Vaccinated → Infected Escape

Infected Inoculated → Infected Escape

Infected Escape → Recovered

B

Recovered [arb.] vs Time [days]

C

Σ Escape/Σ Infections [arb.] vs α

A Σ Infections/R_{Null}

B Σ Infections/R_{Null} *k_V fixed

C Σ Infections/R_{Null} *Immediate Inoculation

D $\log(k_i\text{eff}/k_i)$ vs $\log(q)$

F Effect of Contact *k_V fixed

E Effect of Contact