

13 **Abstract:** Dramatic variation in SARS-CoV-2 virulence and transmission between hosts has
14 driven the COVID-19 pandemic. The complexity and dynamics of the immune response present
15 a challenge to understanding variation in SARS-CoV-2 infections. To address this challenge, we
16 apply control theory, a framework used to study complex feedback systems, to establish rigorous
17 mathematical bounds on immune responses. Two mechanisms of SARS-CoV-2 biology are
18 sufficient to create extreme variation between hosts: (1) a sparsely expressed host receptor and
19 (2) potent, but not unique, suppression of interferon. The resulting model unifies disparate and
20 unexplained features of the SARS-CoV-2 pandemic, predicts features of future viruses that
21 threaten to cause pandemics, and identifies potential interventions.

22

23 **Main Text:**

24 Variations in virulence and transmission, shorthanded as the dual puzzles of
25 asymptomatic cases and superspreaders, have made SARS-CoV-2 infection and spread difficult
26 to predict and control (1–4). The relationship between pathogen virulence and transmission has
27 been a subject of longstanding speculation and formal study (5–7), and continues to be debated
28 in the context of variation in SARS-CoV-2 infection (3, 8–10). The complexity of the immune
29 response has impeded a unified mechanistic understanding of virulence, transmission, and
30 variation, relevant to SARS-CoV-2 and future emerging viruses (**Figure 1**). Here, we extend
31 techniques from control theory, a mathematical framework that has been used to analyze
32 complex feedback systems in both engineered and biological settings (11–14), to immune
33 biology to analyze SARS-CoV-2 virulence and transmission.

34

35 **Results**

36 *A control-theoretic approach to immune dynamics*

37 We use control theory to uncover mechanisms that lead to variation in virulence and
38 transmission. Informally, we compute the best-case immune response, consolidating unmodeled
39 immune dynamics into a control function K (**Figure 2A**). The best-case immune response
40 minimizes virulence and implicitly suppresses transmission. We implement mechanistic details
41 as constraints on the set of realizable control functions, and in this way identify mechanisms
42 (constraints) for which even a best-case K yields virulence and transmission variation. This best-
43 case K bounds any immune system model that we could have used, allowing us to pose rigorous
44 questions without a detailed model of immune dynamics. Formally, we consider the robust
45 control problem:

$$46 \quad v[t + 1] = A_{\Delta}[t]v[t] + B_{\Delta}[t]u[t] + \delta[t]$$

$$47 \quad u[t] = K(v[1:t])$$

48 v is a vector of viral loads, u is the immune action, and new virus enters the system as δ .

49 A_{Δ} and B_{Δ} are sets of time-varying matrices describing uncertain linearized dynamics. We
50 leverage theorems guaranteeing that the best-case K always corresponds to a convex set, so that
51 the best-case K computed from the set will be the best K over all realizable functions (15).

52

53 *The open-loop problem*

54 We first consider the open-loop dynamics of viral replication, or equivalently $K = 0$. We
55 model viral infection in the individual host as a three-step process: cell entry, replication in the
56 cell, and release of virus from the cell after an eclipse period T_e (16, 17).



59
$$V \xrightarrow{k} \emptyset$$

60
$$C_I \xrightarrow{k_c} \emptyset$$

61
$$C_S \xrightarrow{k_c} \emptyset$$

62 We derive A in terms of α , the number of productively infected cells that result from a
63 single infected cell, where $(1-l/\phi)$ is the fraction of infected cells that constitutively turn over in
64 a single eclipse period.

65
$$A = \begin{bmatrix} 1 - k & k\alpha \\ I_{n-1} & 0 \end{bmatrix}$$

66
$$\alpha = \frac{r\beta}{k\phi} [C_S]$$

67 α scales linearly with $[C_S]$. A small fraction of respiratory epithelial cells are susceptible
68 to SARS-CoV-2 when compared to rhinovirus, respiratory syncytial virus, and influenza (18–
69 22). A small susceptible cell fraction enables large *relative* variation consistent with reported
70 single-cell data (20, 21) (**Figure 2B-C**).

71

72 *The closed-loop problem*

73 We next consider the effects of immune control with innate extracellular effectors.
74 Higher α requires stronger immune responses to achieve a comparable effect on viral load
75 (**Figure 2D**). The immune response creates symptoms, which enable behavioral measures to
76 avoid infection (23). We use a highly simplified model of avoidance and isolation, emphasizing
77 the consequences of biological variation. We define transmission R_{CL} , where $w(t)$ is a warning
78 signal and $\gamma(t) = \exp(-pw(t))$. Initially, we take $w(t)$ to be a scaled norm of the immune response,
79 so that symptoms promote avoidance and isolation.

80
$$R_{CL} = \alpha_r \omega \int_0^T v(t) \gamma(t) dt$$

81 We extend this simple behavioral model to address a virus with a long presymptomatic
82 period followed by uniformly severe infection (**Figure 3A-B**). Advance warning and isolation
83 measures can contain such a virus. However, fully asymptomatic cases make advance warning
84 more difficult. Fully asymptomatic cases need not be as contagious as presymptomatic-severe
85 cases to have this effect, and low rates of fully asymptomatic cases can be tolerated (**Figure 3C**).

86 Interferon-based control varies less with α than extracellular responses, but interferon-
87 suppressed control varies more. Early interventions with exogenous interferon can potentially
88 reduce the eventual symptom burden in what would otherwise be severe cases (**Figure 3D-E**).

89 Taking these control layers together, we consider virulence and transmission as α varies.
90 Presymptomatic-severe high- α cases take a dominant role in spreading the pathogen, especially
91 where they interact with other high- α individuals (**Figure 4**).

92

93 **Discussion**

94 *Other viruses*

95 HCoV-NL63 and SARS-CoV-1 also bind to ACE2. HCoV-NL63 infection is
96 asymptomatic or cold-like (24), while SARS-CoV-1 infection is typically severe, with some
97 reported asymptomatic cases (4, 25). Viral infection in these cases could be biologically variable
98 with median effects that are too mild or too severe to be evident in clinical outcomes. SARS-
99 CoV-1 exhibits variable transmission, consistent with this interpretation (26). HCoV-NL63's
100 reduced virulence may result from a spike glycoprotein structure that decreases α (27).

101

102 *Interferon signaling*

103 Clinical and experimental studies have shown that early exogenous interferon
104 administration can reduce coronavirus infection severity (28–32). Our results suggest that
105 presymptomatic interferon could be particularly beneficial in averting severe outcomes.
106 Conversely, our results suggest a mechanism for harm from early immunosuppression in patients
107 with SARS-CoV-2, consistent with clinical trial evidence (33). Because of the ubiquity of
108 interferon suppression strategies in respiratory viruses, studies of control-guided interventions
109 could facilitate responses to future emerging viruses.
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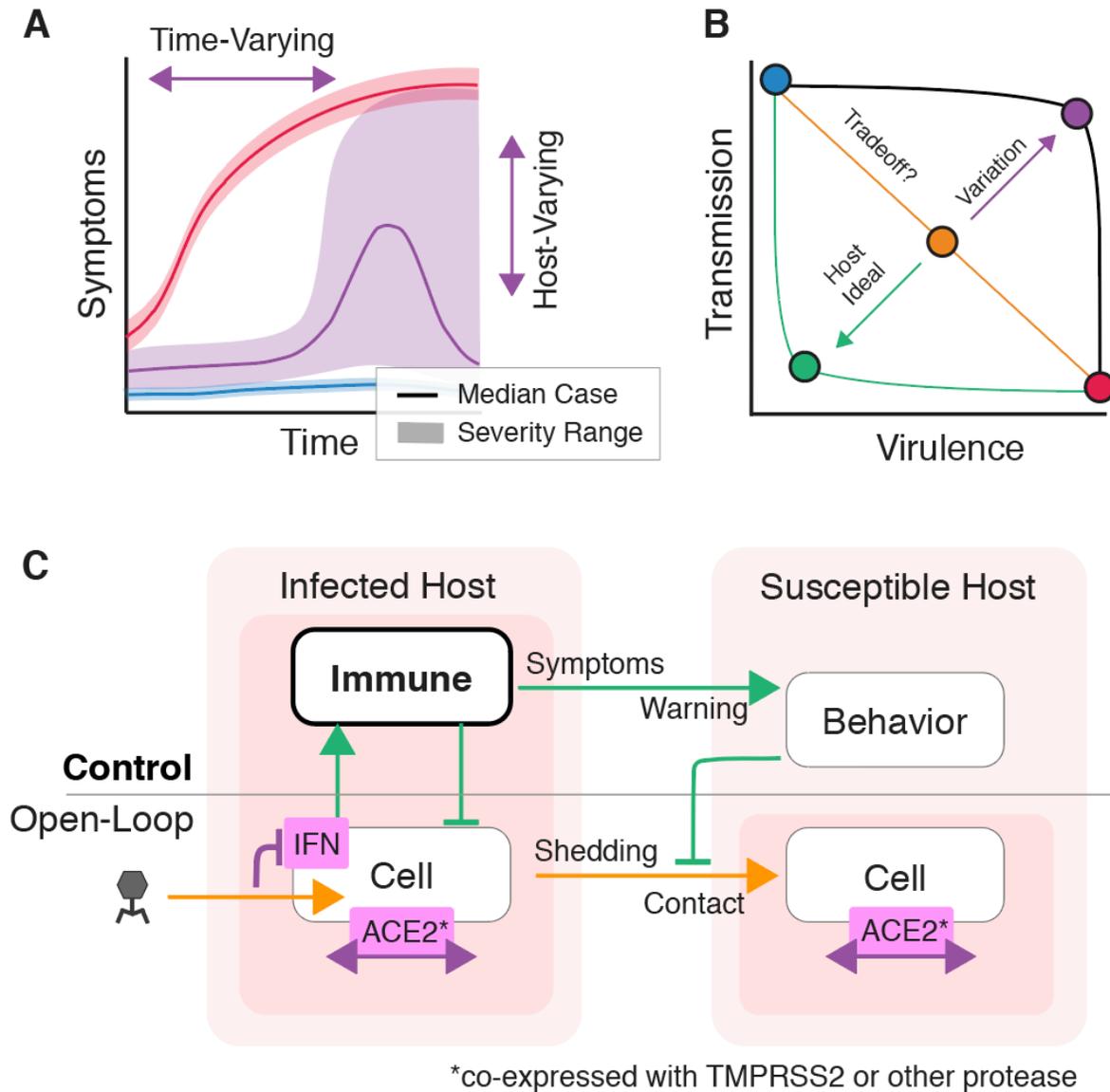
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213 **Fig. 1. A control theory framework to analyze virulence and transmission.**

214 (A) Schematic time-series representations of symptoms for three viruses. The red and blue cases

215 have relatively low variation across hosts and across time. The purple case, schematically like

216 SARS-CoV-2, varies across hosts and across time, suggesting variation in host immune

217 responses.

218 (B) An apparent tradeoff between virulence and transmission can result from host immune
219 responses. However, this tradeoff depends on host control mechanisms, and can be made more
220 favorable to the host population or more favorable to the virus.

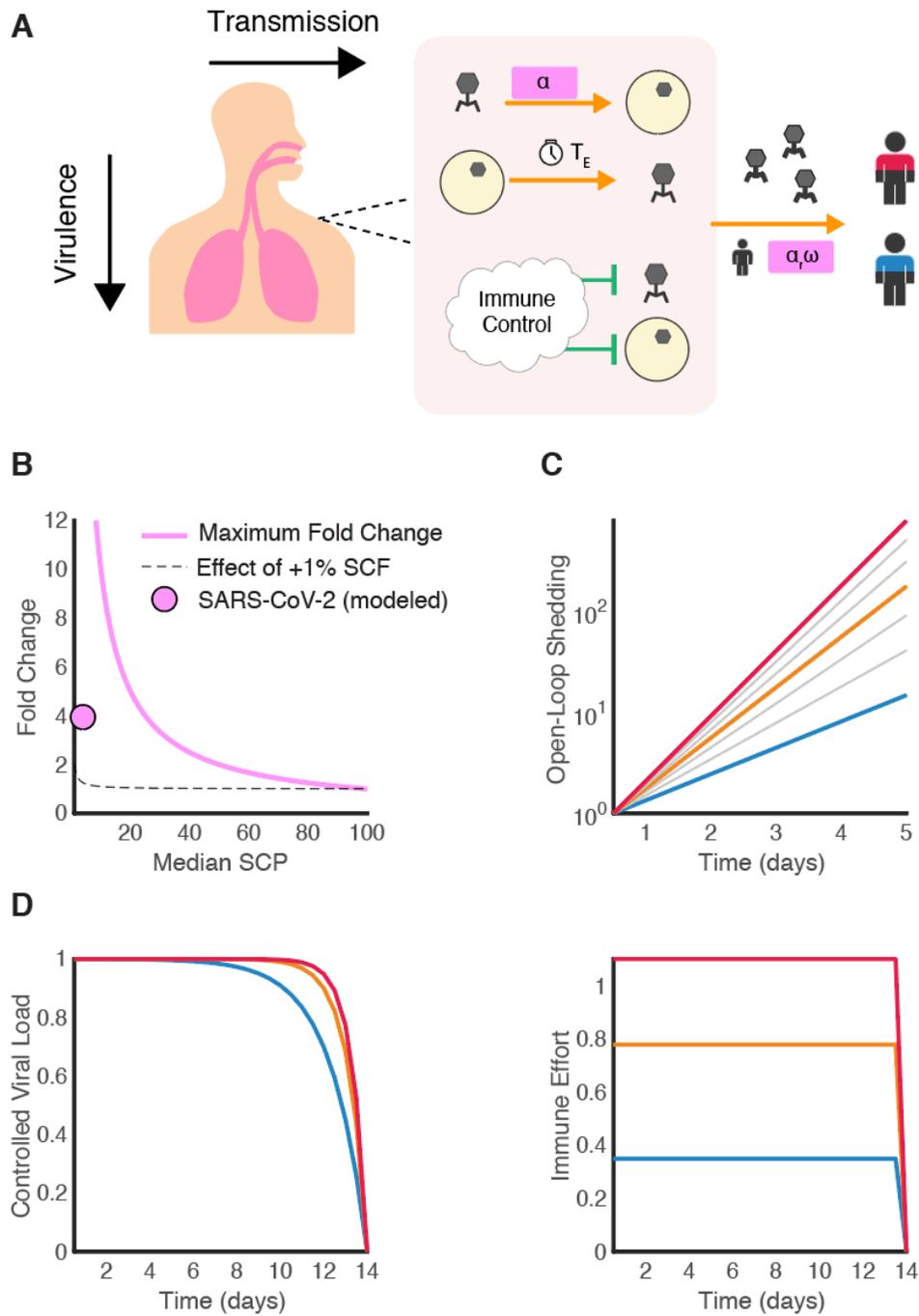
221 (C) A block diagram shows the relationships between virulence and transmission control in two
222 hosts, one infected with SARS-CoV-2 and one susceptible. The dynamics without control are
223 shown in the lower half of the diagram, and the control responses in the upper half. Immune
224 responses suppress shedding, create symptoms, and allow behavioral responses.

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230 **Fig. 2. Host dynamics shape virulence and transmission.**

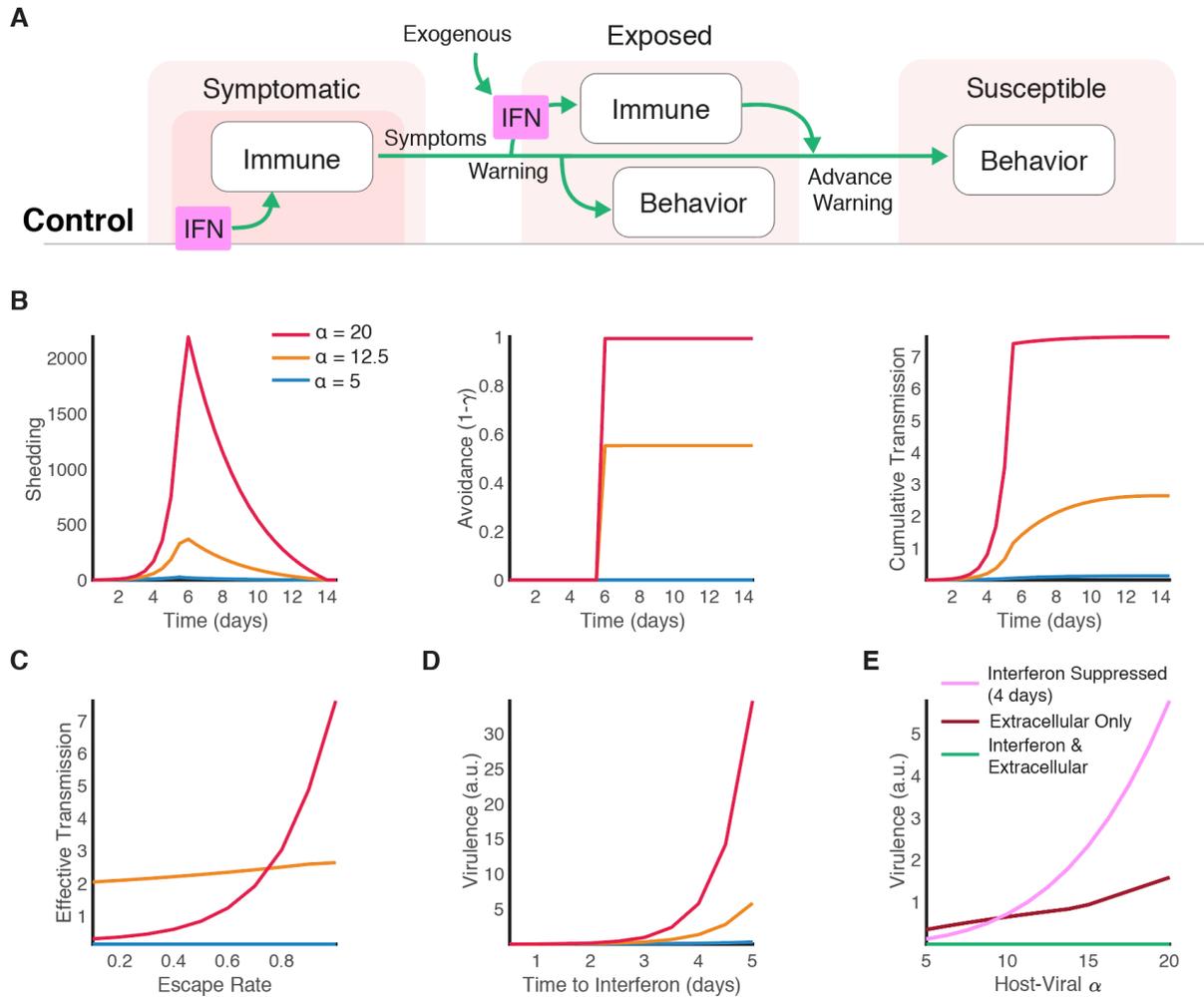
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232 (A) Within each host, well-characterized kinetics govern viral replication. Viruses enter cells,
233 replicate, exit after a delay, and degrade in the extracellular space. These kinetics are coupled to
234 immune responses, for which we compute best-case bounds with control theory.

235 (B) A low susceptible cell percentage (SCP) in the host enables variation. The maximum fold-
236 change deviation from the median and the effect of a small fluctuation both grow as the median
237 SCP approaches 0%.

238 (C) An open-loop model removes all control elements and considers the underlying dynamics.
239 Open-loop variation in viral shedding varies dramatically on relevant time-scales, amplifying
240 variations in SCP.

241 (D) Ideal extracellular immune control can create similar, low-variation viral load trajectories
242 between hosts, but these similar trajectories require differing immune effort. The underlying
243 open-loop dynamics directly shape virulence.



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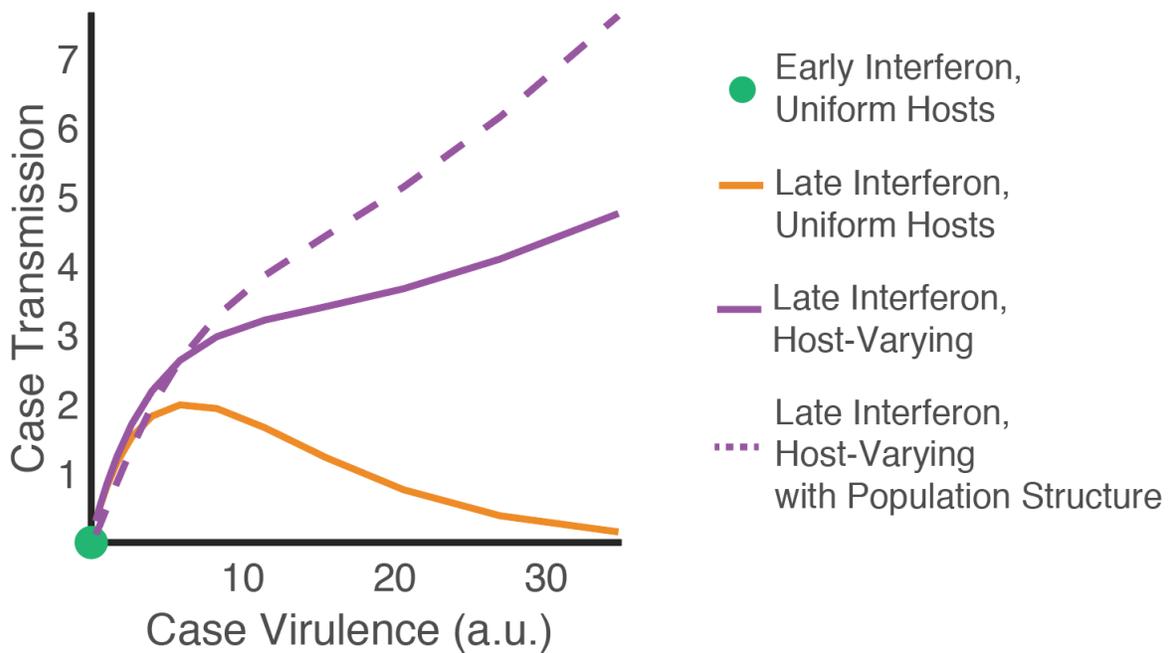
245 **Fig. 3. Layered control of virulence, transmission, and variation.**

246 (A) When all infected hosts are eventually symptomatic, advance warning allows isolation and
 247 potentially treatment measures in pre-symptomatic individuals.

248 (B) Interferon-suppressed responses allow an extended period of viral replication and shedding
 249 during which avoidance behaviors are not possible (without advance warning). Transmission can
 250 be computed from the viral and immune trajectories.

251 (C) Advance warning can reduce the effective transmission rate of presymptomatic individuals,
 252 but asymptomatic cases facilitate escape. As the rate of escape increases, the effective
 253 transmission from presymptomatic-severe individuals increases sharply.

- 254 (D) Timing is a crucial determinant of interferon efficacy. Presymptomatic exogenous interferon
255 administration can potentially reduce the eventual symptom burden in an individual who would
256 otherwise experience severe disease.
- 257 (E) Extracellular immune responses vary more with α than interferon-based immune responses,
258 but interferon-suppressed responses vary most.



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260

261 **Fig. 4. Virulence and transmission depend on host control strategies.**

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263 The relationship between virulence and transmission depends on control conditions in individual

264 hosts. If immune control is ideal for the host, replication is quickly blocked by interferon and

265 neither serious symptoms nor substantial transmission occur. With interferon suppression,

266 transmission peaks at low virulence. With interferon suppression and host variation, however,

267 transmission is higher and peaks at higher virulence. This effect is amplified when high- α

268 individuals interact, leading to both high presymptomatic shedding and high susceptibility.