A quantitative model used to compare within-host SARS-CoV-2, MERS-CoV and SARS-CoV dynamics provides insights into the pathogenesis and treatment of SARS-CoV-2

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Abstract

The scientific community is focused on developing antiviral therapies to mitigate the impacts of the ongoing novel coronavirus disease (COVID-19) outbreak. This will be facilitated by improved understanding of viral dynamics within infected hosts. Here, using a mathematical model in combination with published viral load data, we compare within-host viral dynamics of SARS-CoV-2 with analogous dynamics of MERS-CoV and SARS-CoV. Our quantitative analyses using a mathematical model revealed that the within-host reproduction number at symptom onset of SARS-CoV-2 was statistically significantly larger than that of MERS-CoV and similar to that of SARS-CoV. In addition, the time from symptom onset to the viral load peak for SARS-CoV-2 infection was shorter than those of MERS-CoV and SARS-CoV. These findings suggest difficulty of controlling SARS-CoV-2 infection by antivirals. We further used the viral dynamics model to predict the efficacy of potential antiviral drugs that have different modes of action. The efficacy was measured by the reduction in the area under the viral load curve (AUC). Our results indicated that therapies that block *de novo* infection or virus production are likely to be effective if and only if initiated before the viral load peak (which appears 2-3 days after symptom onset), but therapies that promote cytotoxicity of infected cells are likely to have effects with less sensitivity to the timing of treatment initiation. Furthermore, combining a therapy that promotes cytotoxicity and one that blocks *de novo* infection or virus production synergistically reduces the AUC with early treatment. Our unique modelling approach provides insights into the pathogenesis of SARS-CoV-2 and may be useful for development of antiviral therapies.

Keywords: SARS-CoV-2, MERS-CoV, SARS-CoV, mathematical model, antiviral therapy

Introduction

The ongoing coronavirus disease 2019 (COVID-19) outbreak was first reported in Wuhan, China in late December 2019 [1, 2]. Since then, the causative agent (severe acute respiratory syndrome coronavirus 2, SARS-CoV-2) has been transmitted elsewhere in China and to most other countries and territories around the world. The number of global confirmed cases currently stands at more than 63 million (as of 30 November 2020). Given that 40-45% of patients are asymptomatic [3], and even symptomatic infections are underreported [4], the true number of cases is most likely much higher than this.

Antiviral drugs and vaccines are currently under development to counter this outbreak. The efficacy of these drugs can be evaluated *in vitro* using a cell culture system supporting SARS-CoV-2 infection [5, 6] and in various animal models [7-10].

To aid the development process, characterization of the viral dynamics of SARS-CoV-2 is crucial. Several studies have reported longitudinal viral load data from symptomatic patients collected for over 20 days after symptom onset [8, 11-16]. Mathematical models describing viral dynamics have been used to analyze such data [17-20]. In a recent paper [9], the pathogeneses of SARS-CoV-2, MERS-CoV and SARS-CoV infections were compared in a nonhuman primate model. Here, we analyze and compare longitudinal viral load data of SARS-CoV-2, SARS-CoV, and MERS-CoV in humans. Further, we fit a mathematical model to the viral load data and then use the model with best-fit parameters to predict the effect of potential antiviral treatments on viral dynamics. We do not consider treatments, such as dexamethasone, aimed at reducing the inflammatory response or other downstream events that can lead to the generation of symptoms. The results of our antiviral treatment simulations provide information useful for the development of antiviral agents and treatment

82 strategies for SARS-CoV-2, specifically addressing questions such as the best time to
83 a initiate a therapy given its mode of action. Interestingly, we find that the timing varies
84 depending on the viral-host process targeted by the antiviral drug.
85

Results and Discussion

Characterizing SARS-CoV-2, MERS-CoV, and SARS-CoV infections by analyzing viral load measurements

We analyzed longitudinal SARS-CoV-2 viral load data reported in [11-14], MERS-CoV viral load data reported in [21, 22] and SARS-CoV viral load data reported in [23] using a viral dynamic model (see **Methods**). Further details about the data sources are described in the **Supplemental Information** and summarized in **Table S1**. A nonlinear mixed-effect modeling approach was employed in which we fit the model to all of the patient data simultaneously to estimate parameters (see **Methods**). The estimated population parameters are listed in **Table 1**, and estimated individual parameters for each patient are listed in **Table S2**. Comparing population parameters between SARS-CoV-2 and the other two coronaviruses, the maximum rate constant for viral replication (γ) of SARS-CoV-2 was significantly larger than that of MERS-CoV ($p < 2.2 \times 10^{-16}$) but similar to that of SARS-CoV. The rate constant for virus infection (β) of SARS-CoV-2 was significantly larger than that of both MERS-CoV and SARS-CoV ($p = 1.0 \times 10^{-8}$ and $p = 1.3 \times 10^{-12}$, respectively). Moreover, the viral load at symptom onset ($V(0)$) of SARS-CoV-2 was similar to that of SARS-CoV, but less than that of MERS-CoV ($p < 2.2 \times 10^{-16}$, respectively). Based on the individual parameters, the best-fit viral load curves for each subject are plotted along with the observed data in **Fig S1** for SARS-CoV-2, MERS-CoV, and SARS-CoV. We further calculated and compared the following quantities, which are derived from the estimated parameters or available by running the model (**Table 1**); the mean duration of virus production from an infected cell ($L = 1/\delta$), the within-host reproductive number at symptom onset ($R_{S0} = \gamma/\delta$), which is the average number of newly infected cells produced by a single infected cell at symptom onset (c.f.[24]), the time from symptom onset to the viral load

peak (T_p), and the critical inhibition level ($C^* = 1 - 1/R_{S0}$) that needs to be reached by antivirals or vaccines to ensure that the viral infection is driven to extinction [25-27].

R_{S0} of SARS-CoV-2 was statistically significantly larger than that of MERS-CoV ($p < 2.2 \times 10^{-16}$) and no different from that of SARS-CoV (**Table 1**). Further, according to our model, SARS-CoV-2 hit its viral load peak 2.0 days after symptom onset (i.e., T_p), which is earlier than that of MERS-CoV and SARS-CoV, which peaked at 12.2 days and 7.2 days after symptom onset, respectively, however the difference was statistically significant only between that of SARS-CoV-2 and SARS-CoV ($p = 2.24 \times 10^{-6}$, **Fig 1** and **Table 1**).

Both the larger R_{S0} value of SARS-CoV-2 than that of MERS-CoV and the earlier peak in viral load for SARS-CoV-2 than the other coronaviruses suggests that the virus more effectively replicates and spreads within-host than MERS-CoV and SARS-CoV. In other words, treating SARS-CoV-2 infection may require more potent therapies and therapies given earlier than for the other coronaviruses. Further, the shorter T_p of SARS-CoV-2 suggests that treating SARS-CoV-2 infection following symptom onset is more challenging because effective antiviral treatment should be initiated before the viral peak, as we demonstrate in the next section. Given that the mean time from symptom onset to hospitalization observed in China was 4.6 days [28], symptom-based diagnosis combined with antiviral treatment might not be an effective treatment strategy if treatment needs to be given in a hospital setting. In the next section, we provide a detailed analysis of anti-SARS-CoV-2 therapy varying the drug efficacy and timing of treatment initiation.

Evaluation of anti-SARS-CoV-2 therapies

Based on our mathematical model and estimated parameter values (**Table 1**), we conducted *in silico* experiments of possible anti-SARS-CoV-2 therapies to investigate the expected outcome under hypothetical drug therapies (or vaccine use) possessing different antiviral mechanisms of action (**Fig 2**). Specifically, drug efficacy (10% to 100%, i.e., $0.1 \leq \varepsilon, \eta, \theta \leq 1$) and timing of therapy initiation after symptom onset (i.e., $0 \leq t^* \leq 4$ days) were varied and their influence on outcomes was investigated (see **Methods**) (**Fig 2**). We used reduction in the area under the viral load curve (AUC) and the fraction of target cells that remain uninfected 4 weeks after symptom onset as outcome measures. Without treatment, the AUC was 8.2×10^5 copies·day/mL and almost no target cells remained after the course of infection (e.g., **Fig 2** and **Fig 3**).

(i) Blocking *de novo* infection

One of the major mechanisms of action for antivirals is blocking *de novo* infection. This can be induced by drugs including human neutralizing antibodies either in convalescent plasma or given as monoclonal antibodies, viral entry-inhibitors and/or antibodies raised by vaccination [5, 29]. For example, a SARS-CoV-specific human monoclonal antibody bamlanivimab has received emergency use authorization by the US FDA for the treatment of SARS-CoV-2 [30].

Higher drug efficacy and earlier treatment initiation is associated with better outcomes: according to our model the AUC was reduced by 73% and 74% of target cells remained uninfected after the course of infection when treatment was initiated 1 day after symptom onset and the antiviral effectiveness was 90% (Fig. 2). Very early treatment initiation is the key for better outcomes when using antiviral therapies.

According to our model, using a drug that blocks infection with 95% efficacy initiated 4 days after symptom onset, the AUC was reduced by only 14%, and only 2% of uninfected cells remain (**Fig 2AD**). This occurs because only a very small fraction of target cells remains uninfected after the viral load peak. After infection abates target cells will replenish but here we ignore this as are evaluating the potential effects of therapy in preserving them. Note that viral shedding may last longer with treatment than without treatment if the antiviral efficacy is below 100% and initiated early. This is because substantial numbers of uninfected target cells remain at the time of treatment initiation and the infection is driven by those uninfected cells but at a slower rate than without treatment.

We observed the same trends for MERS-CoV and SARS-CoV (see **Fig S2AD** and **S3AD**), except that treatment initiated a few days after symptom onset may be efficacious. As we observed in **Fig 1**, the viral load peak comes later for MERS-CoV and SARS-CoV than for SARS-CoV-2. Thus, even if treatment is initiated at 4 days after symptom onset (which is before viral load peak for those two viruses), improvement in the outcomes can be expected.

(ii) Blocking virus production

Most antiviral drugs inhibit intracellular virus replication. Lopinavir/ritonavir (HIV protease inhibitors), remdesivir (anti-Ebola virus disease candidate), and other nucleoside analogues as well as interferon have the potential to suppress SARS-CoV-2 replication [31, 32]. Similar to the findings for drugs blocking *de novo* infection, higher efficacy and earlier treatment is associated with better outcomes. According to our model the AUC was reduced by 76% and 36% of the target cells remained uninfected

after the course of infection when treatment initiated at 1 day after symptom onset and the antiviral effectiveness was 90% (**Fig 2BE**).

In contrast, if treatment was started after the viral load peak, improvement in the outcomes cannot be expected even with 100% inhibition rate. Similar trends were observed for MERS-CoV and SARS-CoV (**Fig S2BE** and **S3BE**). However, as 4 days after symptom onset is still before the viral load peak for these two viruses, substantial improvement in the outcomes are expected with treatment initiated 4 days after symptom onset for these two viruses (**Fig S2BE** and **S3BE**).

(iii) Promoting cytotoxicity

Another possible antiviral mechanism is to promote cytotoxic effects. This could be done by stimulating adaptive immunity including responses mediated by cytotoxic T lymphocytes and NK cells by immunotherapy or vaccination, but the effect would not be immediate. To be consistent with the other modes of drug action discussed above in which we assume the drug takes effect immediately after administration, we envision a drug such as a viral-specific monoclonal antibody conjugated to a toxin as used in cancer therapy [33] or a non-neutralizing viral specific monoclonal antibody that could induce infected cell death by complement-mediated lysis or antibody-dependent cellular cytotoxicity. A neutralizing antibody with these effector functions could be considered the equivalent of combination therapy which is discussed below. Compared with the other two therapeutic mechanisms of action (blocking *de novo* infection and virus production), the induction of cytotoxicity directly removes infected cells which produce viruses, and therefore it enhances the rate of viral load decay. After the viral peak, target cells are depleted and cytotoxicity inducing therapy leads to noticeably more rapid declines in viral load (**Fig 2C**).

Thus, with a 50% effective cytotoxicity promoting antiviral, which by our definition (see Methods) causes the death rate of infected cells to double, initiated at day 1 results in an only slightly slower viral growth rate and an only slightly delayed time of the viral load peak, but more rapid decay in viral load than other two therapeutic modes of action (blocking *de novo* infection & virus production) (**Fig 2, yellow curves**). Moreover, cytotoxicity induction initiated after the viral load peak can still reduce the AUC. A 95% effective cytotoxicity promoting antiviral initiated at 4 days after symptom onset reduces the AUC by 13%, however, only 2% of target cells remain uninfected because the most of the target cells were already infected by the viral load peak (**Fig 2CF, blue curves**). We confirmed much later treatment initiation (13 days after symptom onset) with this type of antiviral still increases the rate of viral load decay (**Fig S4A**).

Overall, compared with the effects of the other two types of antivirals, the effect of promoting cytotoxicity on the AUC is less dependent on the magnitude of the antiviral effect and the timing of treatment initiation, although earlier treatment and more efficacy is positively associated with an increased reduction in the AUC.

We confirmed a similar trend in the treatment effect on MERS-CoV and SARS-CoV infection (**Fig S2CF** and **S3CF**). Given that their viral load peak comes later than that of SARS-CoV-2, treatment initiated at 4 days after symptom onset is predicted to still reduce the AUC and save uninfected target cells (see below).

To evaluate the effect of promoting cytotoxicity initiated long after the viral load peak, we compared the effect of a 50% effective treatment initiated at 1 day and 13 days after symptom onset on all three coronaviruses (**Fig S4**). The therapy initiated at 1 day delayed the time of the viral load peak particularly for MERS-CoV and SARS-CoV. When the treatment was initiated at 13 days, which is after the viral load peak,

233 the viral load declined rapidly compared with treatment initiated at 1 day, because few
234 target cells remain and thus new infection is limited.

235 The analysis of the treatment effect of drugs with three different modes of action
236 revealed that the treatment strategy should be different for each type of drug. For
237 example, using drugs that block *de novo* infection or virus production can avoid
238 substantial target cell reduction if initiated before the viral load peak. Using a drug that
239 promotes cytotoxicity is less time sensitive and treatment initiated after the viral peak
240 still can reduce the AUC. These findings suggest the possibility of a synergistic effect
241 of combining drugs with different modes of action.

242

243 **(iv) Combination therapy**

244 In this section, we describe the effect of combining two different drugs among
245 the three described in the section above. In general, combinations of antiviral therapies
246 are considered preferable when it synergistically enhances the antiviral effects,
247 reduces the needed individual drug dose, and reduces the side effects compared with
248 the cases of monotherapy [6, 27, 34-36]. Here, we focus on the synergistic antiviral
249 effect on the model outcomes (i.e., reduction in the AUC and saving target cells from
250 infection).

251 The three possible two drug combination therapies (i.e., blocking *de novo*
252 infection & virus production, blocking *de novo* infection & promoting cytotoxicity,
253 blocking virus production & promoting cytotoxicity in **Fig 3AD, BE** and **CF,**
254 respectively) were simulated using the same assumptions as for the single drug
255 therapies. All three combination therapies improved the antiviral effects when
256 compared to the corresponding monotherapies. As we expected, combining the drugs
257 with distinct modes of action, especially with a drug promoting cytotoxicity being one

of them, more effectively reduced the AUC and saved target cells from infection. With monotherapy, the AUC was reduced by 13%, 44%, and 54% with the drugs blocking *de novo* infection, blocking virus production, and promoting cytotoxicity with a 50% antiviral effect initiated at 1 day after symptom onset (**Fig 2DEF**), whereas it was reduced by 58% or greater under combination therapy (**Fig 3DEF)**. Notably, combining a drug promoting cytotoxicity with one of the other two types of drugs compensated the "weakness" of each treatment: no clear effect is expected from the drugs blocking *de novo* infection or virus production if initiated after the viral load peak.

From a biological point of view, promoting cytotoxicity is distinct from the other two mechanisms. Both blocking *de novo* infection and virus production limit ongoing *de novo* infection, whereas promoting cytotoxicity enhances virus and infected cell removal independent of target cell availability. A broadly neutralizing antibody with potent effector functions that induced infected cell death would be a good therapeutic option as it induces two modes of action in one molecule. Antibodies of this type are being explored for HIV [37, 38]. SARS-CoV-2 neutralizing antibodies are also in clinical development, and the role of their effector functions in providing protective activity are being examined [39]. Our analysis also implies that, if antiviral drugs induce immunomodulation as a bystander effect, even if the treatment is initiated after the viral load peak, they might be able to reduce viral load. We confirmed the same trends for MERS-CoV and SARS-CoV (**Fig S5BE** and **S6BE**, respectively).

Conclusions

To aid the development of antiviral drugs and treatment strategies for SARS-CoV-2 infection, we characterized the viral dynamics of SARS-CoV-2 and the related viruses, SARS-CoV and MERS-CoV, using a mathematical model. We further introduced the effect of antivirals with different modes of action in the model and explored the influence of the drug efficacy and timing of treatment initiation on the outcomes (viral load AUC and the fraction of target cells that remain uninfected). We found that R_{S0} is larger for SARS-CoV-2 compared with MERS-CoV, and the difference in viral load peak timing was significantly different between SARS-CoV-2 and SARS-CoV. Some studies suggested that viral load peaks occur before the onset of symptoms [40, 41], while other studies suggest that the viral load peaks occur within the first week of symptom onset [14, 42-44]. Although it is difficult to accurately determine whether the peak is before or after symptom onset since there is little viral load data available before the onset of symptoms, an earlier viral peak for SARS-CoV-2 is consistent with recent findings [14, 40-44]. The larger R_{S0} and earlier viral peak suggest it may be more difficult to treat SARS-CoV-2 infection than SARS-CoV and MERS with drug therapy that blocks viral production or *de novo* infection, because for these types of drugs, treatment initiation before the viral load peak is important to reduce viral load and save target cells from infection. The variations in parameter estimates among the individuals studied do not change our results on the importance of initiating antiviral therapy before the viral load peak (**Fig S7**). The modelling of antivirals with different drug efficacies highlighted the importance of early initiation of treatments blocking *de novo* infection and virus production. In contrast, a treatment promoting cytotoxicity reduces AUC even when treatment is initiated after the viral load peak. Due to the uniqueness of the drugs promoting cytotoxicity compared with

304 the other two types of drugs, combination therapy promoting cytotoxicity and one of
305 the two other drugs more effectively reduced the AUC and saved target cells from
306 infection because the combination compensated for the weakness of each drug.

307 We used the area under the viral load curve and the fraction of target cells
308 remaining uninfected as outcomes rather than the length of hospital stays, clinical
309 improvement, severity, and mortality, which have been more commonly used as
310 primary outcomes in clinical studies [45-52]. However, the outcomes should be
311 determined case-by-case basis. For example, if the objective is to find or assess the
312 effectiveness of a lifesaving treatment, then mortality should be used as a primary
313 outcome. However, if the objective is to assess the effectiveness of antiviral treatment,
314 the degree of viral load reduction might be a primary outcome. Indeed, viral load
315 related outcomes have been used in multiple clinical studies for antivirals [15, 46, 53-
316 57]. Further, viral load outcomes are particularly important for SARS-CoV-2 because
317 many patients experience mild or no symptoms (i.e., asymptomatic cases) and yet are
318 still isolated. To determine ending isolation, it is frequently necessary to have a
319 negative PCR test as well as disappearance of symptoms [14]. This is sensible as a
320 strong association between viral load and infectiousness has been suggested [19].

321 Drug repurposing – reusing drugs already approved for specific purposes for
322 other (new) purposes – is currently the major approach for rapidly deploying antiviral
323 drugs for SARS-CoV-2. A number of drugs such as lopinavir and ritonavir [47, 55],
324 chloroquine [48], favipiravir [46], interferon beta-1b, lopinavir-ritonavir and ribavirin [58],
325 a nebulized form of interferon beta-1a [59] and remdesivir [49, 50] have been tested
326 in clinical studies. However, the findings from such trials are not consistent: some
327 claim a significant effect but the others do not for the same drug. One of the major
328 issues is that of poor study design [60]. Beyond that, we suspect the treatment was

not initiated early enough and may have yielded null findings even though the drug is effective as we demonstrated *in silico* in this study for drugs blocking *de novo* infection and virus production. Indeed, the mean interval between symptom onset and hospitalization was 4.6 days during the COVID-19 epidemic in Shenzhen, China [28], which is longer than the interval between symptom onset and viral load peak for SARS-CoV-2 (2.9 days), suggesting that therapy is commonly started well after the viral load peak in hospitalized patients.

A limitation of our analysis is the simplicity of our mathematical model. However, this model is flexible and extendable. For example, we did not consider heterogeneity of target cells and we assumed the death rate of infected cell, δ, is constant. However, models with multiple types of target cells could be developed and δ can be made time-dependent as was done in the case of HIV where there was extensive viral load data [61, 62]. Alternatively, equations can be introduced to explicitly model effector cell responses [63, 64]. These approaches could be reflected in extended versions of our model if relevant data and supporting evidence becomes available. Indeed, several more complex models have been proposed to describe SARS-CoV-2 viral dynamics [17, 18]. However, these complex mathematical models yielded similar conclusions about the need to initiate therapy with a typical antiviral that blocks viral production early as the simple model we employed.

Development or identification of effective antiviral drugs is urgently needed. We believe our theoretical framework can at least partially explain why such drugs have not been identified (late treatment initiation) and could help design clinical studies and treatment strategies by assessing their potential effect on viral load related outcomes.

Methods

Study data

The longitudinal viral load data were extracted from clinical studies of SARS-CoV-2 [11-14], MERS-CoV [21, 22] and SARS-CoV [23]. Only the data from individuals with more than three data points above the detection limit were included in the analysis. The data from patients who received antiviral treatment during infection were excluded. We confirmed that ethics approval was obtained from the ethics committee at each institution, and that written informed consent was obtained from the patients or their next of kin in the original studies. The data were extracted from images in those publications using the program datathief III (version 1.5, Bas Tummers, www.datathief.org). We converted cycle threshold (Ct) values reported in the above papers to viral RNA copies number values (copies/mL), where these quantities are inversely proportional to each other [65]. The following formula was used to convert Ct values (y) to viral RNA copies (x in copies/mL): $\log_{10}(x) = ay + b$ with $a = -0.32$ and $b = 14.11$ [23]. **Table S1** summarized the data. The likelihood function accounted for censored data (i.e., data points under the detection limits) [66].

Mathematical model

We used a simple target cell limited model to describe SARS-CoV-2, SARS-CoV and MERS viral dynamics [20, 24, 67]. Target cell limited models have proved very valuable in understanding infection dynamics and therapy for chronic viral infections such as HIV [61, 68], HCV [69], and HBV [70] and for acute infections such as influenza [71], West Nile virus [72] Zika virus [73] and SARS-CoV-2 [17, 74, 75]. Although the model does not explicitly describe immune responses the effects of immune responses are implicitly included in model parameters such as the infection

rate, which can be influenced by innate responses and the death rate of infected cells, which can be influenced by adaptive immune responses. Because of the simplicity of the model these parameters can be estimated and compared among the three different coronaviruses. The form of the model that we use was first introduced to model influenza infection [71] and is given by

$$\frac{dT(t)}{dt} = -\beta T(t)V(t), \qquad (1)$$

$$\frac{dI(t)}{dt} = \beta T(t)V(t) - \delta I(t), \qquad (2)$$

$$\frac{dV(t)}{dt} = pI(t) - cV(t), \qquad (3)$$

where the variables $T(t)$, $I(t)$, and $V(t)$ are the numbers of uninfected target cells, infected target cells, and the amount of virus at time t (note; we used time after symptom onset as the time-scale), respectively. Symptom onset is defined slightly differently between papers, but it essentially means when any coronavirus related symptoms (fever, cough, and shortness of breath) appear [76]. The parameters β, δ, p, and c represent the rate constant for virus infection, the death rate of infected cells, the per cell viral production rate, and the per capita clearance rate of the virus, respectively. Since the clearance rate of the virus is typically much larger than the death rate of the infected cells *in vivo* [27, 67, 77], we made a quasi-steady state (QSS) assumption, $dV(t)/dt = 0$, and replaced Eq.(3) with $V(t) = pI(t)/c$. Because data on the numbers of coronavirus RNA copies, $V(t)$, rather than the number of infected cells, $I(t)$, were available, $I(t) = cV(t)/p$ was substituted into Eq.(2) to obtain

$$\frac{dV(t)}{dt} = \frac{p\beta}{c}T(t)V(t) - \delta V(t). \qquad (4)$$

Furthermore, we replaced $T(t)$ by the fraction of target cells remaining at time t, that is, $f(t) = T(t)/T(0)$, where $T(0)$ is the initial number of uninfected target cells. Note $f(0) = 1$. Accordingly, we obtained the following simplified mathematical model, which we employed to analyze the viral load data in this study:

$$\frac{df(t)}{dt} = -\beta f(t)V(t), \qquad (5)$$

$$\frac{dV(t)}{dt} = \gamma f(t)V(t) - \delta V(t), \qquad (6)$$

where $\gamma = p\beta T(0)/c$ corresponds to the maximum viral replication rate under the assumption that target cells are continuously depleted during the course of infection. Thus, $f(t)$ is equal or less than 1 and continuously declines.

In our analyses, the variable $V(t)$ corresponds to the viral load for SARS-CoV-2, MERS-CoV, and SARS-CoV (copies/mL). Because all of them cause acute infection, loss of target cells by physiological turnover can be ignored, considering long lifespan of the target cells.

The nonlinear mixed effect model

The nonlinear mixed effect modeling was used to fit the model to the longitudinal viral load data. The model includes both fixed effects (i.e., population parameters) and random effects. The random effects represent the difference among patients. The parameter values for patient k is ϑ_k $(= \vartheta \times e^{\pi_k})$, which is a product of a fixed effect, ϑ, and a random effect, e^{π_k}. π_k is assumed to follow the normal distribution: $N(0, \Omega)$. This approach allows us to estimate the parameters for patients with limited time point data, because the population parameters are estimated from not only his/her data, but all the patients' data. We used the viral type as a categorical covariate in estimating the parameters γ, β and $V(0)$ which provide the lowest BICc.

Fixed effects and random effects were estimated using the stochastic approximation expectation-maximization algorithm and the empirical Bayes' method, respectively. The statistical differences of covariate for γ, β and $V(0)$ were tested by the Wald test. Fitting was implemented using MONOLIX 2019R2 (www.lixoft.com) [78]. The estimated (fixed and individual) parameters and the initial values are listed in **Table 1** and **Table S2**. The viral load curve using the best fit parameter estimates for each individual patient is shown with the data in **Fig S1**. Note that the mixed model approach has been used elsewhere in longitudinal viral load data analysis [17, 73].

In silico experiments for antiviral therapies

Based on the parameterized model for each virus, we investigated the antiviral effects of drugs with the following different mechanisms of action: (i) blocking *de novo* infection; (ii) blocking virus production; and (iii) promoting cytotoxicity on two outcomes: the reduction in the area under the viral load curve (AUC) (i.e., $\int_0^{28} V(s)ds$) and the remaining fraction of target cells after the course of infection (i.e., $f(28)$). Note that we used 28 days after symptom onset as the upper bound for observation, because most of viral load is below the detection limit by this time and some previous clinical studies used health conditions (e.g., mortality) at 28 days (4 weeks) as a primary outcome [79]. In the simulation, the best fit population parameters estimated by fitting the model to the data were used. We varied the time of treatment initiation after symptom onset, t^*, and the antiviral efficacy, ε, η, and θ to assess the dependency of them on the outcomes. Note that $t^* = 0$ corresponds to therapy initiated immediately after symptom onset.

We modeled viral load dynamics under antiviral treatment with the three different mechanisms of action as follows:

(i) Blocking *de novo* infection. The viral dynamics under antiviral treatment for blocking *de novo* infection is modeled as follows:

$$\frac{df(t)}{dt} = -\big(1 - \varepsilon H(t)\big)\beta f(t)V(t), \qquad (7)$$

$$\frac{dV(t)}{dt} = \big(1 - \varepsilon H(t)\big)\gamma f(t)V(t) - \delta V(t), \qquad (8)$$

where $H(t)$ is the Heaviside step function defined as $H(t) = 0$ if $t < t^*$: otherwise $H(t) = 1$. t^* is the time of treatment initiation and ε is the treatment efficacy: $0 < \varepsilon \leq 1$. $\varepsilon = 1$ implies *de novo* infection is 100% inhibited.

(ii) Blocking virus production. The virus dynamics under treatment for blocking virus production is modeled as follows:

$$\frac{dV(t)}{dt} = \big(1 - \eta H(t)\big)\gamma f(t)V(t) - \delta V(t), \qquad (9)$$

where η is the treatment efficacy: $0 < \eta \leq 1$. $\eta = 1$ indicates that virus production from infected cells is fully inhibited. Note that the difference between blocking *de novo* infection and virus production is that the drugs in the former model reduce β, whereas the drugs in this model reduce p in the full model, that is, Eqs. (1-3).

(iii) Promoting cytotoxicity. The virus dynamics under the antiviral treatment of promoting cytotoxicity (or increasing the death rate of infected cells) is modeled as follows:

$$\frac{dV(t)}{dt} = \gamma f(t)V(t) - \left(\frac{1}{1 - \theta H(t)}\right)\delta V(t), \qquad (10)$$

where θ is the treatment efficacy: $0 < \theta \leq 1$. $\theta = 1$ indicates that the drug is 100% effective and causes the immediate death of an infected cell. No drug is expected to be 100% effective. A 50% effective drug would cause a 2-fold increase in the death rate and a 90% effective drug would cause a 10-fold increase.

(iv) Combination therapy. The virus dynamics under therapies combining all the three types of drugs is modeled as follows:

$$\frac{df(t)}{dt} = -\big(1 - \varepsilon H(t)\big)\beta f(t)V(t), \tag{11}$$

$$\frac{dV(t)}{dt} = \big(1 - \varepsilon H(t)\big)\big(1 - \eta H(t)\big)\gamma f(t)V(t) - \left(\frac{1}{1 - \theta H(t)}\right)\delta V(t). \tag{12}$$

In the simulation, we assumed any of two therapies are combined (thus one of the three parameters is set as zero).

Computation of L, R_{S0}, C^*, and T_p and statistical test for the difference between viruses

Based on the estimated parameters, we calculated several quantities for each virus: the duration of virus production ($L = 1/\delta$), the reproduction number ($R_{S0} = \gamma/\delta$) at symptom onset and the critical inhibition level ($C^* = 1 - 1/R_{S0}$). Further, the time from symptom onset to the viral load peak (T_p) was calculated by running the model using estimated (fixed and individual) parameters and the initial values. The difference in T_p was tested by the Jackknife test [80, 81]. To evaluate statistical differences for R_{S0} and C^* we applied the Wald test as well.

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515 ## Competing interests

516 The authors declare that they have no competing interests.
517

518 ## Authors' contributions

519 Conceived and designed the study: KE RNT ASP SI. Analysed the data: KSK
520 KE SI HO YK SN SI. Wrote the paper: KSK KE KW KA ASP RNT SI. All authors read
521 and approved the final manuscript.
522

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These antibodies are being produced for human clinical trials but have not been licensed to any commercial entity. No other disclosures were reported.
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826 ## Figure legends
827

828 **Figure 1. Comparison of SARS-CoV-2, MERS-CoV, and SARS-CoV dynamics**.
829 Expected viral load trajectories for SARS-CoV-2, MERS-CoV and SARS-CoV infection
830 are shown. The solid curves give the solution of Eqs. (5-6) using estimated parameters
831 (the best fit population parameters) and the shaded regions correspond to 95%
832 predictive intervals using the estimated parameters for each patient. The data
833 underlying this Figure is given in S1 Data.
834

835 **Figure 2. Predicted outcomes under anti-SARS-CoV-2 monotherapies.** (**A-C**)
836 Expected viral load and uninfected target cell proportion trajectories with and without
837 treatment for the three different treatments. The black curves are without treatment.
838 The blue curves are with treatment (efficacy is 95%) initiated at 4 days since symptom
839 onset. Both red, green and orange curves are with treatment initiated at 1 day since
840 symptom onset, but with different efficacy (95%, 90% and 50%, respectively). The
841 dotted vertical lines correspond to the timing of treatment initiation. (**D-F**) The heatmap
842 shows the reduction in the viral load AUC with treatment compared to without
843 treatment. The timing of treatment initiation and treatment efficacy was varied. Darker
844 colors indicate a larger reduction in the viral load AUC. The parameter setting used for
845 the simulation in Panels (**A-C**) is indicated by the same colored squares in Panels (**D-**
846 **F**). The data underlying this Figure is given in S2 Data.
847

848 **Figure 3. Predicted outcomes under anti-SARS-CoV-2 combination therapies.**
849 (**A-C**) Expected viral load and uninfected target cell proportion trajectories with and
850 without treatment for the three combination therapies. We assumed the same
851 efficacies and timing of treatment initiation for the two combined treatments. The black

curves are without treatment. The blue curves are with treatment (efficacy is 95%) initiated at 4 days after symptom onset. Both red and green curves are with treatment initiated at 1 day after symptom onset, but with different efficacy (95% and 90%, respectively). The dotted vertical lines correspond to the time of treatment initiation. (**D-F**) The heatmap shows the reduction in the viral load AUC with treatment compared to without treatment. The time of treatment initiation and the treatment efficacy was varied. Darker colors indicate a larger reduction in the viral load AUC. The parameter setting used for the simulation in Panels (**A-C**) is indicated by the same colored squares in Panels (**D-F**). The data underlying this Figure is given in S3 Data.

Table 1. Estimated parameters (fixed effect) for SARS-CoV-2, MERS-CoV, and SARS-CoV infection

Parameter Name	Symbol (Unit)	SARS-CoV-2	MERS-CoV	SARS-CoV
Parameters in the model				
Maximum rate constant for viral replication	γ (day^{-1})	4	$1.46^{\#}$	4.13
Rate constant for virus infection	β ((copies/ml)$^{-1}$ day^{-1})	5.2×10^{-6}	$1.4 \times 10^{-8\#}$	$4.9 \times 10^{-8\#}$
Death rate of infected cells	δ (day^{-1})$^{\&}$	0.93	0.93	0.93
Viral load at symptom onset	$V(0)$ (copies/ml)	6.5×10^{3}	6.6×10^{4}	$3.3 \times 10^{-2\#}$
Quantities derived from the parameters				
Mean duration of virus production	L (days)	1.08	1.08	1.08
Within-host reproduction number at symptom onset	R_{S0}	4.30	$1.57^{\#}$	4.44
Critical inhibition level	C^{*}	0.77	$0.38^{\#}$	0.75
Time from symptom onset to viral load peak	T_p (days)$^{\$}$	2.0	12.2	$7.2^{\$}$

$^{\#}$ Statistically different from SARS-CoV-2 (the Wald test). $^{\$}$ T_p was computed from simulation, and the difference from SARS-CoV-2 was tested by the Jack-knife test. $^{\&}$ the death rate of infected cells was assumed to be the same between the viruses in the process of model selection.