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Within-host dynamics of SARS-CoV-2 infection: a systematic review and meta-analysis

Zhanwei Du[1,2+], Shuqi Wang[2+], Yuan Bai[1,2], Chao Gao[3], Eric H. Y. Lau[1,2], Benjamin J. Cowling[1,2*]

[1]WHO Collaborating Centre for Infectious Disease Epidemiology and Control, School of Public Health, LKS Faculty of Medicine, The University of Hong Kong, Hong Kong Special Administrative Region, China

[2]Laboratory of Data Discovery for Health Limited, Hong Kong Science Park, Hong Kong Special Administrative Region, China

[3] School of Artificial Intelligence, Optics, and Electronics (iOPEN), Northwestern Polytechnical University, Xian, China

* Correspondence: bcowling@hku.hk

[+]Zhanwei Du and Shuqi Wang contributed equally to this work.

Abstract

Within-host model specified by viral dynamic parameters is a mainstream tool to understand SARS-CoV-2 replication cycle in infected patients. The parameter uncertainty further affects the output of the model, such as the efficacy of potential antiviral drugs. However, gathering

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empirical data on these parameters is challenging. Here, we aim to conduct a systematic review of viral dynamic parameters used in within-host models by calibrating the model to the viral load data measured from upper respiratory specimens. We searched the PubMed, Embase and Web of Science databases (between December 1, 2019 and February 10, 2022) for within-host modelling studies. We identified seven independent within-host models from the above nine studies, including Type I interferon, innate response, humoral immune response, or cell-mediated immune response. From these models, we extracted and analyse seven widely used viral dynamic parameters including the viral load at the point of infection or symptom onset, the rate of viral particles infecting susceptible cells, the rate of infected cells releasing virus, the rate of virus particles cleared, the rate of infected cells cleared, and the rate of cells in the eclipse phase can become productively infected. We identified seven independent within-host models from nine eligible studies. The viral load at symptom onset is 4.78 (95% CI:2.93, 6.62) log(copies/mL), and the viral load at the point of infection is -1.00 (95% CI:-1.94, -0.05) log(copies/mL). The rate of viral particles infecting susceptible cells and the rate of infected cells cleared have the pooled estimates as -6.96 (95% CI:-7.66, -6.25) log([copies/mL]$^{-1}$ day^{-1}) and 0.92 (95% CI:-0.09, 1.93) day^{-1}, respectively. We found that the rate of infected cells cleared was associated with the reported model in the meta-analysis by including the model type as a categorical variable (p<0.01). Joint viral dynamic parameters estimates when parameterizing within-host models have been published for SARS-CoV-2. The reviewed viral dynamic parameters can be used in the same within-host model to understand SARS-CoV-2 replication cycle in infected patients and assess the impact of pharmaceutical interventions.

Keywords: COVID-19, SARS-CoV-2, Within-host model, Viral dynamic parameters, Review

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Main Text

Introduction

Cases of COVID-19 were first reported in Wuhan, China, in late December 2019 and rapidly emerged in cities throughout the world (The Washington Post, 2020). As of April 3, 2021, 491 million COVID-19 cases have been reported in over 200 countries or territories and 6.15 million deaths (WHO, 2020). Five variants of concern (VOC), together with eight variants of interest (VOI), have already been identified by WHO (WHO, 2022), with the potential to be more transmissible (Davies et al., 2020; Leung et al., 2021; Volz et al., 2021) and evade immunity acquired through prior infection or vaccination (Wang et al., 2021).

The health burden increases along with the virus continuing its global march outward. Mathematical models could deepen our understanding of the epidemiological impact of non-pharmaceutical interventions (such as wearing masks and social distancing) and the vaccine effectiveness (Vespignani et al., 2020) in the population level, and also the SARS-CoV-2 replication cycle of viruses at the within-host level (Challenger et al., 2022). However, it is challenging to estimate viral dynamic parameters, such as the rate of viral particles infecting susceptible cells and the rate of infected cells releasing virus, from empirical observations.

Motivated by the availability of virus load within the host measured from upper respiratory specimens after symptom onset, viral dynamic parameters can be estimated by calibrating the within-host model to the viral load data. We conduct a systematic review of viral dynamic parameters estimated in the fitted within-host models which characterise the dynamic of target cells infected by SARS-CoV-2 and the dynamic of SARS-CoV-2 replication.

Materials and Methods

Data source and searches

We performed a systematic review of peer-reviewed studies on within-host models of SARS-CoV-2 in PubMed, Embase, and Web of Science on February 10, 2022. We searched studies in the above three databases with a combination of the following search terms, with no restriction on publication language: (“SARS-CoV-2”, “COVID-19”, “COVID 2019”,

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"coronavirus 2019", or "novel coronavirus") and ("within-host", "in-host", "withinhost", or "inhost"). The searched studies were set to be published between December 1, 2019, and February 10, 2022.

Study selection

We (Z.W D., and S.Q.W.) assessed eligible studies, extracted relevant data, and conducted cross-checked. Conflicts over the study selection were resolved by another researcher (Y.B.). We excluded studies based on screening titles and abstracts if they were 1) duplicate publications; 2) reviews; 3) non-modelling studies; 4) not conducted in humans. Then we further excluded studies based on screening full texts if: 1) the within-host models are not the main topic; 2) the primary outcome is not the viral load measured from upper respiratory specimens; 3) all virus dynamic parameters are based on simple assumptions for numerical simulations. We reported studies following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.

Data extraction and analysis

Information was extracted on the viral dynamic parameters coupled with the corresponding 95% confidence interval (CI). We use the I^2 index to assess heterogeneity between studies into the following 3 categories: I^2<25% (low heterogeneity), I^2=25-75% (average heterogeneity), and I^2 >75% (high heterogeneity). Because of the high I^2 value that was calculated in our results, as well as the significance of the Cochran Q test, a random-effects model was further used to perform a meta-analysis in this study. Analyses were conducted in R version 4.1.1.

Results

We identified 1106 studies through the electronic search of the databases between December 1, 2019 and February 10, 2022 (386, PubMed; 358 Embase; and 362, Web of Science). 459 studies left after excluding duplicates. After 391 studies were excluded based on titles and abstracts screening, we retrieved 68 studies eligible for the full-text screening. Next, after we excluded 59 studies based on full-text screening, nine studies met the inclusion criteria and were included in the systematic review (**Fig. 1, Table 1)**.

We identified seven independent within-host models from the above nine studies (**Fig. S1**).

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Uninfected cells enter an eclipse state or an infected state after infection. A portion of infected cells reproduce viruses that are contagious or not, which may be blocked by Type I interferon, innate response, humoral immune response, and cell-mediated immune response. The studies were published during the COVID-19 pandemic and the empirical virus load data were collected from five countries, including Germany, Singapore, China, Korea and America. We summarise seven widely used viral dynamic parameters from these studies and estimate the mean, 95% CI (**Fig. 2 and Table S1**). Specifically, the viral load at symptom onset, $V(0)^{\$}$, is 4.78 (95% CI:2.93, 6.62) log(copies/mL) in three models from four studies (Iwanami et al., 2021; Jenner A.L. et al., 2021; Jeong et al., 2021; Kim K.S. et al., 2021), and the viral load at the point of infection, $V(0)^{\&}$, is -1.00 (95% CI:-0.94, -0.05) log(copies/mL) in three models from three studies (Hernandez-Vargas and Velasco-Hernandez, 2020; Czuppon P. et al., 2021; Fatehi et al., 2021) (**Fig. 2A**). The rate of viral particles infecting susceptible cells (virus infection rate, β) is -4.97 (95% CI:-9.77, -0.16) log([copies/mL]$^{-1}$ day^{-1}) in six models from eight studies (Hernandez-Vargas and Velasco-Hernandez, 2020; Fatehi et al., 2021; Iwanami et al., 2021; Jenner A.L. et al., 2021; Jeong et al., 2021; Ke et al., 2021; Kim K.S. et al., 2021; Sadria M. and Layton A.T., 2021) (**Fig. 2B**), with pooled estimates of -6.96 (95% CI:-7.66, -6.25) log([copies/mL]$^{-1}$ day^{-1}) (**Table S1**). The rate of infected cells releasing virus (virus replication rate, p) is 0.77 (95% CI:-5.39, 6.94) log((copies/mL day^{-1}cell^{-1}) in three models from three studies (Hernandez-Vargas and Velasco-Hernandez, 2020; Czuppon P. et al., 2021; Fatehi et al., 2021) (**Fig. 2C**). The rate of virus particles cleared (virus clearance rate, c) is 5.19 (95% CI:-3.42, 13.81) day^{-1} in four models from five studies (Hernandez-Vargas and Velasco-Hernandez, 2020; Czuppon P. et al., 2021; Fatehi et al., 2021; Jenner A.L. et al., 2021; Ke et al., 2021) (**Fig. 2D**). The rate of infected cells cleared (infected cell clearance rate, δ) is 0.88 (95% CI:-0.25, 2.02) day^{-1} in seven models from nine studies (Hernandez-Vargas and Velasco-Hernandez, 2020; Czuppon P. et al., 2021; Fatehi et al., 2021; Iwanami et al., 2021; Jenner A.L. et al., 2021; Jeong et al., 2021; Ke et al., 2021; Kim K.S. et al., 2021; Sadria M. and Layton A.T., 2021) (**Fig. 2E**), with pooled estimates of 0.92 (95% CI: -0.09, 1.93) day^{-1}. The rate of cells in the eclipse phase can become productively infected (transition rate from the eclipse phase to the productively infected, k) is 3.75 (95% CI:-0.04, 7.54) day^{-1} in five models from five studies (Czuppon P. et al., 2021; Fatehi et al., 2021; Jenner A.L. et al., 2021; Jeong et al., 2021; Ke et al., 2021) (**Fig. 2F**). Using the random-effects model, we estimated the rate of viral particles

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infecting susceptible cells (virus infection rate, β) and the rate of virus particles cleared (virus clearance rate, c) have the pooled estimates as -6.96 (95% CI: -7.66, -6.25) log([copies/mL]$^{-1}$ day^{-1}) and 0.92 (95% CI: -0.09, 1.93) day^{-1}, respectively (**Fig. S2 and S3, Table S1**).

High heterogeneity of the rate of infected cells cleared (infected cell clearance rate, δ) were reported among the included studies with respect to models studied (I^2=92%, p<0.01) (**Fig. S4**). To explore the potential association between the within-host models and the rate of infected cells cleared (infected cell clearance rate, δ), we conducted the meta-regression analysis for this parameter. We found that the value of this parameter summarised in seven models from nine studies (Hernandez-Vargas and Velasco-Hernandez, 2020; Czuppon P. et al., 2021; Fatehi et al., 2021; Iwanami et al., 2021; Jenner A.L. et al., 2021; Jeong et al., 2021; Ke et al., 2021; Kim K.S. et al., 2021; Sadria M. and Layton A.T., 2021) was associated with the reported model in the meta-analysis by including the model type as a categorical variable (p<0.01) (**Fig. S4**). This may be because of the model-specific differences in characterising the viral replication and clearance.

Discussion

The future of the pandemic is uncertain given the continuing emergence of new variants (Wang et al., 2021). Within-host modelling could help to characterise the transmission dynamics within a host. We performed a systematic review and meta-analysis of the published estimates of viral dynamic parameters in the within-host models.

Antivirals for SARS-CoV-2 were initially developed by repurposing approved therapies for other diseases that did not require extra clinical trials. Eight SARS-CoV-2 treatments have been licensed by the Food and Drug Administration (FDA) for use in the United States as of March 25, 2022 (Zimmer et al., 2020). Remdesivir was originally developed to treat Ebola and Hepatitis C (Zimmer et al., 2020; Gottlieb et al., 2022), which was the first repurposed and approved drug by FDA in October 2020 and had treated over nine million patients around the world by December 2021 (Gilead Sciences, Inc., n.d.). Another antiviral against SARS-CoV-2 infections, Molnupiravir, got FDA emergency use authorization on December 23, 2021 (Merck & Co., Inc., 2021), which could reduce the risk of hospitalisation by 30% (Food and Drug Administration, 2021). Paxlovid (combination of nirmatrelvir and ritonavir)

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received the FDA emergency authorization on December 22, 2021, with the reduction of hospitalisation risks by 88% (Hammond et al., 2022).

Within-host modelling provides a framework to study the impacts of antiviral therapy on the transmission dynamics of SARS-CoV-2. COVID-19 can be treated mainly in one of two ways (Fatehi et al., 2021): that inhibits virus production (e.g., Remdesivir (Beigel et al., 2020), Molnupiravir (Bai et al., 2022)), and convalescent plasma therapy (Duan et al., 2020). The emergence of COVID-19 variants, on the other hand, makes rigorous evaluation of effective treatment procedures challenging in clinical trials, highlighting the value of mathematical within-host models. The seven study models in this review could be used to evaluate the efficacy of antivirals against SARS-CoV-2 virus, for example, the target cell limited model with eclipse phase was used to evaluate the impact of antiviral treatment timing on reducing SARS-CoV-2 viral load for Remdesivir (Gonçalves et al., 2020), and the standard target cell limited model was used to evaluate the effect of Molnupiravir for oral treatment of COVID-19 (Bai et al., 2022). Regarding the CP therapy, its impact on viral dynamics could be modelled by other models with immune response (Fatehi et al., 2021), which is considered to be effective against COVID-19 with limited side effects in clinical trials (Duan et al., 2020). To model viral transmission, the infectiousness of an individual is mainly linked to the viral load into three types of viral load-infectiousness coupling functions: logarithmic, sigmoid and linear (Handel and Rohani, 2015; Néant et al., 2021). The seven within-host models could all provide insights into the efficacy of different treatment starts to combat the COVID-19 pandemic by evaluating the viral load dynamics over time. The parameter uncertainty analysis on the impacts of antiviral therapy could provide more information before using the results to make a decision.

We provide an overview of the limitations of our study. First, those studies only study the wide-type SARS-CoV-2 virus, with no VOC variant included. Second, most of the eligible studies do not account for the difference between different age groups and risk groups, and the waning vaccine-derived immunity and re-infection, which may introduce a bias if directly used for variants. Third, the pooled parameter values would be preferable to target wide-type viruses without vaccination and natural infection.

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Conclusion

In conclusion, joint viral dynamic parameters estimates when parameterizing within-host models have been published for SARS-CoV-2, with models associated with the reported estimates of the rate of infected cells cleared. The reviewed viral dynamic parameters can be used in the same within-host model to understand SARS-CoV-2 replication cycle in infected patients and assess the impact of pharmaceutical interventions.

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Author Contributions

ZD, SW, YB, BJC: conceived the study, designed statistical methods, conducted analyses, interpreted results, wrote and revised the manuscript. CG and EHYL: data analysis and revised the manuscript.

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Conflict of Interest

BJC consults for AstraZeneca, GlaxoSmithKline, Moderna, Pfizer, Roche and Sanofi Pasteur. BJC is supported by the AIR@innoHK program of the Innovation and Technology Commission of the Hong Kong SAR Government. Other authors declare no competing interests. The authors report no other potential conflicts of interest.

Ethics approval

No ethical approval was required for this study since this is a review of published studies.

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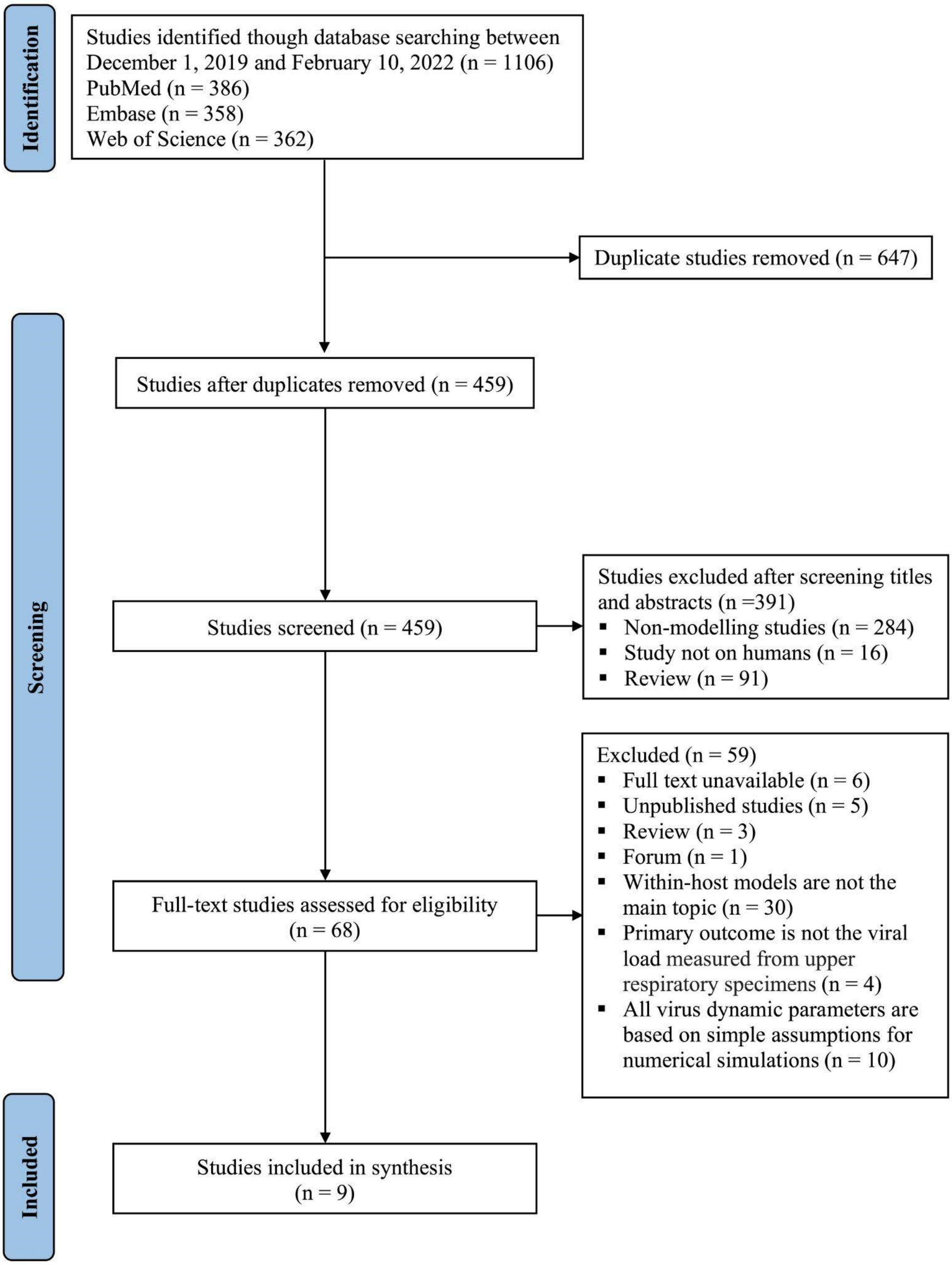

Fig. 1 PRISMA flow diagram for searching and selecting studies in the systematic review

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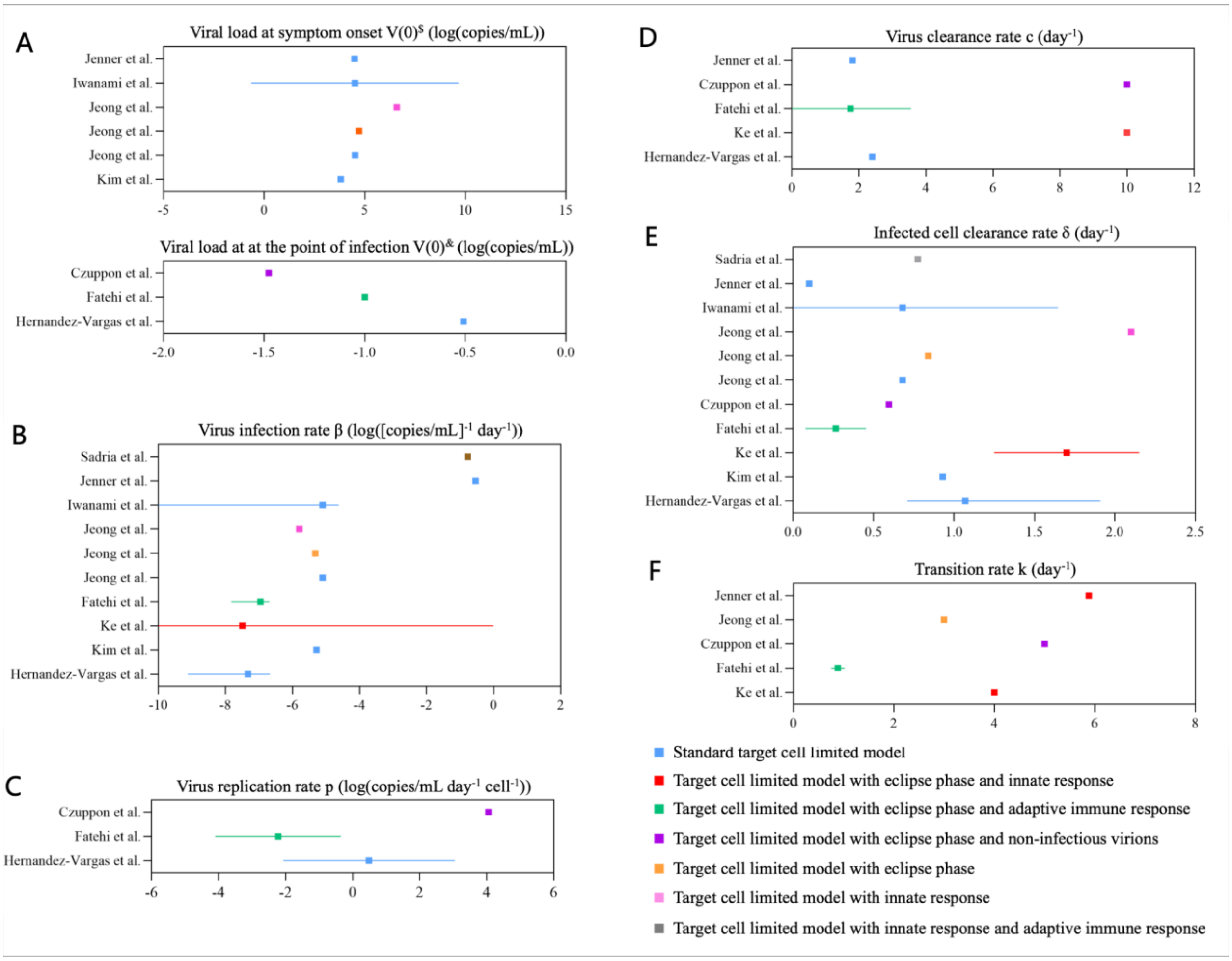

Fig. 2. Estimates of parameters of SARS-CoV-2 within-host model. The dots and error bars demonstrate the estimated mean and 95% confidence interval, respectively, from seven independent within-host models from nine studies (**Fig. S1, Table 1**). **A** The viral load at symptom onset or at the point of infection (V(0)$^{\$}$ or V(0)$^{\&}$). **B** The rate of viral particles infecting susceptible cells (virus infection rate, β). **C** The rate of infected cells releasing virus (virus replication rate, p). **D** The rate of virus particles cleared (virus clearance rate, c). **E** The rate of infected cells cleared (infected cell clearance rate, δ). **F** The rate of cells in the eclipse phase can become productively infected (transition rate from the eclipse phase to the productively infected, k).

Table 1. Description of studies on parameters included in the systematic review and meta-analysis. We include nine studies following the inclusion criteria (**Fig. 1**), in which

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there are seven independent within-host models (**Fig. S1**).

Study	**Viral load V(0) (copies/mL)**	**Virus infection rate β ([copies/mL]$^{-1}$ day^{-1})**	**Virus replication rate p (copies/mL day^{-1}cell^{-1})**	**Virus clearance rate c (day^{-1})**	**Infected cell clearance rate δ (day^{-1})**	**Transition rate from the eclipse phase to the productively infected infectious k (day^{-1})**	**Region of empirical dat collection / Sampling sit**
Hernandez-Vargas et al.(Hernandez-Vargas and Velasco-Hernandez, 2020)	$0.31^{\&}$	$4.71*10^{-8}$	3.07*	2.40	1.070	--	Munich, Germa pharynx
Kim et al.(Kim K.S. et al., 2021)	$6.5*10^{3\ \$}$	$5.20*10^{-6}$	--	--	0.930	--	Singapore / nasopharynx Zhuhai, China nose; Korea / nasopharynx a oropharynx; Munich, Germa pharynx
Ke et al.(Ke et al., 2021)	$0^{\&}$	$3.20*10^{-8}$	--	10.00	1.700	4.000	Bavaria, Germany/nasop ynx and oropharynx; Orlando, America/nasoph nx and orophar
Fatehi et al.(Fatehi et al., 2021)	$0.1^{\&}$	$1.11*10^{-7}$	$5.98*10^{-3}$	1.75	0.265	0.884	Singapore / nasopharynx
Czuppon et al.(Czuppon P. et al., 2021)	$0.03^{\&}$	--	$1.12*10^{4}$	10.00	0.595	5.000	Singapore / nasopharynx
Jeong et al.(Jeong et al., 2021)	$3.30*10^{4\ \$}$	$7.90*10^{-6}$	--	--	0.680	--	Singapore / nasopharynx Zhuhai, China nose; Korea / nasopharynx a oropharynx;

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							Munich, Germa pharynx
Jeong et al.(Jeong et al., 2021)	$5.20*10^{4\ \$}$	$4.80*10^{-6}$	--	--	0.840	3.000	Singapore / nasopharynx Zhuhai, China nose; Korea / nasopharynx a oropharynx; Munich, Germa pharynx
Jeong et al.(Jeong et al., 2021)	$3.93*10^{6\ \$}$	$1.60*10^{-6}$	--	--	2.100	--	Singapore / nasopharynx Zhuhai, China nose; Korea / nasopharynx a oropharynx; Munich, Germa pharynx
Iwanami et al.(Iwanami et al., 2021)	$3.27*10^{4\ \$}$	$7.95*10^{-6}$	--	--	0.680	--	Singapore / nasopharynx Zhuhai, China nose; Korea / nasopharynx a oropharynx; Munich, Germa pharynx
Jenner et al.(Jenner A.L. et al., 2021)	$3.16*10^{4\ \$}$	0.29	--	1.81	0.1	5.8824	Singapore / nasopharynx Munich, Germa pharynx
Sadria et al.(Sadria M. and Layton A.T., 2021)	--	0.17	--	--	0.775	--	Munich, Germa pharynx; China / orophar

[&] Viral load at the point of infection

[$] Viral load at symptom onset

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