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Stemming cholera tides in Zimbabwe through mass vaccination

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ABSTRACT

Background: In 2018, Zimbabwe declared another major cholera outbreak a decade after recording one of the worst cholera outbreaks in Africa.
Methods: A mathematical model for cholera was used to estimate the magnitude of the cholera outbreak and vaccination coverage using cholera cases reported data. A Markov chain Monte Carlo method based on a Bayesian framework was used to fit the model in order to estimate the basic reproductive number and required vaccination coverage for cholera control.
Results: The results showed that the outbreak had a basic reproductive number of 1.82 (95% credible interval [CrI] 1.53–2.11) and required vaccination coverage of at least 58% (95% CrI 45–68%) to be contained using an oral cholera vaccine of 78% efficacy. Sensitivity analysis demonstrated that a vaccine with at least 55% efficacy was sufficient to contain the outbreak but at higher coverage of 75% (95% CrI 58–88%). However, high-efficacy vaccines would greatly reduce the required coverage, with 100% efficacy vaccine reducing coverage to 45% (95% CrI 35–53%).
Conclusions: These findings reinforce the crucial need for oral cholera vaccines to control cholera in Zimbabwe, considering that the decay of water reticulation and sewerage infrastructure is unlikely to be effectively addressed in the coming years.

Introduction

For the second time within a decade, Zimbabwe declared a cholera outbreak on 11 September 2018 following the death of 20 people from the disease and >3500 reported cases since the beginning of September 2018 (Chipunza, 2018). Between 2008 and 2009, Zimbabwe recorded one of the worst cholera outbreaks in Africa, which resulted in 98,585 reported cases and 4287 deaths (Mukandavire et al., 2011). The timing of the 2018 outbreak was very similar to the 2008–2009 outbreak, which presented its first epidemic wave around August–October 2008 and a full epidemic wave started in November 2008 at the onset of the rainy season. The association between rainfall and cholera outbreaks is well documented (Camacho et al., 2018; Hashizume et al., 2010; Luque Fernandez et al., 2009; Goel and Jiang, 2011; Rinaldo et al., 2012; Eisenberg et al., 2013). The 2018 cholera outbreak had a distinct spatial pattern, with the emergence of the outbreak being located in Harare, where most of the reported cases were clustered, and started expanding to neighborhood districts and other parts of the country (Figure 1). Budiriro and Glen View suburbs in Harare were identified as the epicenter of the cholera outbreak (Figure 1).

Zimbabwe has gone through a debilitating political, social and economic crisis, which began in the last two decades. Due to declining funding over the years, the Zimbabwe National Water Authority has been unable to invest in maintaining critical infrastructure for water and sewerage reticulation, resulting in frequent bursts and collapse of the systems (MoHCC, 2018). The effects of the crisis have been felt in the healthcare system, as evidenced by a marked decline in health financing by the

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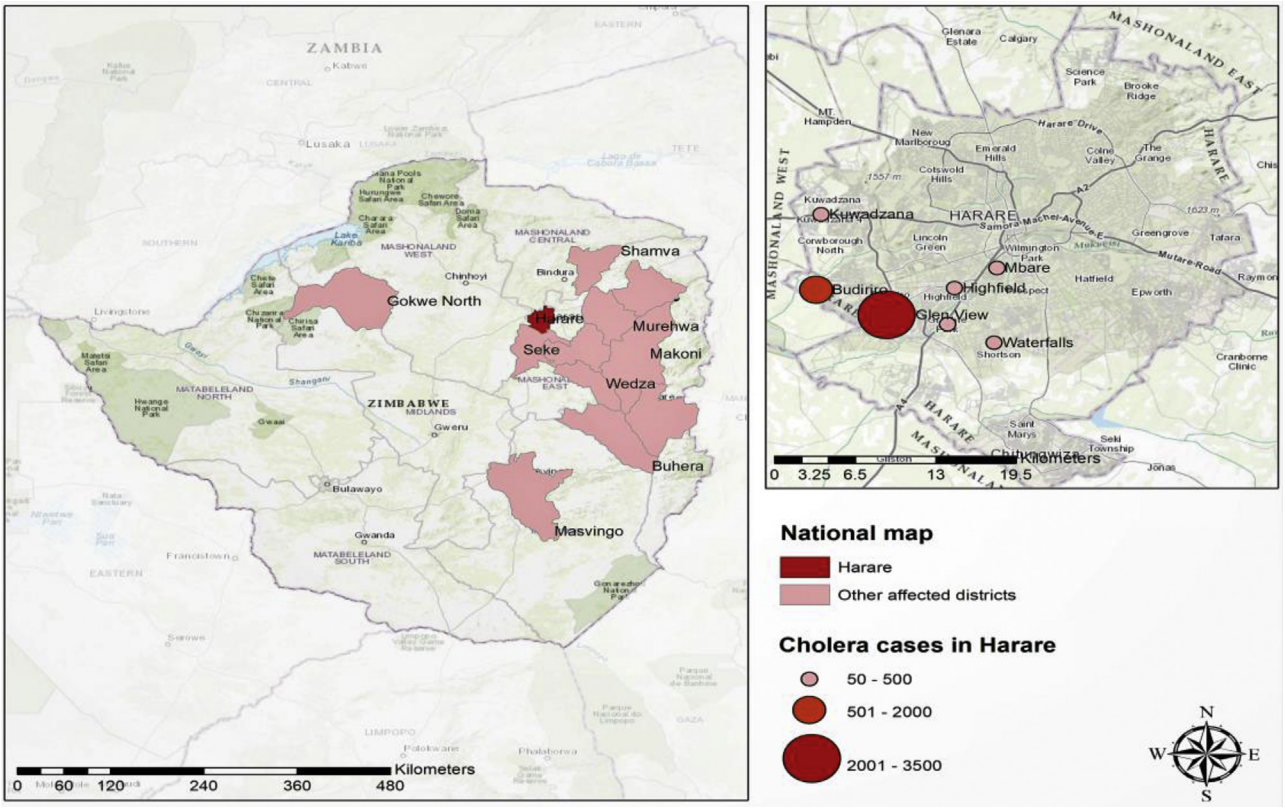

Figure 1. Map showing Budiriro and Glen View (the epicenter of the outbreak) and other regions reporting cholera by 18 September 2018 (MoHCC, 2018a). Maps were created using ArcGIS® by ESRI version 10.5 (http://www.esri.com) (ESRI, 2004).

government, inadequate or non-availability of essential medicines and consumables, high attrition rates, and poorly motivated human resources for health (Cuneo et al., 2017). The availability of portable water and adoption of proper hygiene practices are essential for long-term cholera prevention, control and eradication. Unfortunately, in the timescale of cholera epidemics, improving infrastructure for clean water and adequate sanitation is impossible, particularly in a country recovering from economic crisis. Antibiotics for treating cholera are recommended for use in severe cases and their use for mass administration against cholera infection is strongly discouraged by the World Health Organization (WHO), as they could contribute to antimicrobial resistance (WHO, 2018a). Recent findings of significant resistance to first-line commonly available antibiotics by the National Microbiology Reference Laboratory has raised concerns, particularly given the well-documented resistance to the typhoid outbreak in Harare that started in 2016 (MoHCC, 2018).

The current-generation oral cholera vaccine (OCV) have renewed interests in using vaccination for cholera prevention and control (Shin et al., 2011), with overwhelming evidence supporting their effectiveness in cholera endemic settings (Lucas et al., 2005; Sur et al., 2009; Thiem et al., 2006; Clemens et al., 1990; Clemens et al., 1988Lucas et al., 2005; Sur et al., 2009; Thiem et al., 2006; Clemens et al., 1990; Clemens et al., 1988Lucas et al., 2005; Sur et al., 2009; Thiem et al., 2006; Clemens et al., 1990; Clemens et al., 1988Lucas et al., 2005; Sur et al., 2009; Thiem et al., 2006; Clemens et al., 1990; Clemens et al., 1988). In recent years, the WHO has recommended the use of cholera vaccines in endemic settings and pre-emptively during epidemic and outbreak settings, and established a global stockpile of oral cholera vaccine (Martin et al., 2012; WHO, 2010). Some OCVs such as Vaxchora have been reported to reduce the chance of severe diarrhea in humans by 90% at 10 days after vaccination and by 80% at 3 months after vaccination (PVOCVA, 2018). Currently, WHO requalified safe and effective OCVs are available on the market at a modest cost ($1.30–1.85 per dose) (PVOCVA, 2018; Kirpich et al., 2017; Ivers, 2017). Moreover, some of the OCVs available on the market remain stable at 37 °C for 30 days, avoiding waste and a stringent cold chain (Kirpich et al., 2017). The WHO has put in place the Global Task Force on Cholera Control (GTFCC) (WHO, 2018b) to support countries to implement effective cholera control programs. Zimbabwe's Ministry of Health and Child Care (MoHCC) endorses the new global strategy by the GTFCC 'Ending Cholera—A Global Roadmap to 2030' (Ending cholera, 2018). This operationalizes the new global strategy for cholera control at a country level and provides a concrete path towards a cholera-free world. The GTFCC processes requests from Ministries of Health to use OCV in highly endemic cholera settings (hotspots) with the goal of providing equitable access for the populations most exposed to the risk of cholera.

It is important to understand the utility of OCV for this outbreak, for which Zimbabwe made the first attempt to implement reactive mass vaccination in some areas (MoHCC, 2018b). Mathematical models provide a valuable tool for this purpose and there is an increasing appreciation of mathematical models in informing public health policy in the emergency situation of an initial cholera epidemic (Mukandavire et al., 2013; Mukandavire and Morris, 2015). OCV mass vaccination campaigns in Zimbabwe were conducted in four high-density suburbs in Harare (Budiriro, Glen Norah, Glen View, and Mbare) and then moved to other areas (MoHCC, 2018b). This study used a previously developed Zimbabwe cholera model to estimate the basic reproductive number of the epicenter of the outbreak

(Budiriro and Glen View) and make public health recommendations on the usefulness of OCV in controlling the outbreak.

Methods

This study used a model that was developed for the 2008–2009 cholera outbreak in Zimbabwe (Mukandavire et al., 2011; Mukandavire and Morris, 2015). The cholera compartmental model divides the human population of density N into susceptibles S, infected I and recovered R. The concentration of *Vibrios* in contaminated water is denoted by B. In the model, the susceptible individuals acquire cholera infection either by ingesting environmental *Vibrios* from contaminated aquatic reservoirs (a 'slow' transmission route requiring a higher infectious dose) or through close contact with infected humans associated with ingestion of 'hyperinfectious' *Vibrios* (Nelson et al., 2009; Merrell et al., 2002) (a 'fast' transmission route related to the observed decrease in infectious dose seen among *Vibrio cholerae* (*V. cholerae*) within a matter of hours of passage in diarrheal stool) at daily per-capita rates

$$\lambda_e = \frac{\beta_e B}{\kappa + B} \quad \text{and} \quad \lambda_h = \beta_h I$$

respectively, with the subscripts e and h denoting environment-to-human and human-to-human transmission routes. The constant κ is a shape parameter that determines the human infectious dose: when B equals κ the probability of ingestion resulting in human disease is 0.5. Parameters β_e and β_h are rates of exposure to *Vibrios* from the contaminated environment and through human-to-human interaction, respectively. Infected individuals recover from infection at a rate γ. Cholera infected individuals contribute to *V. cholerae* in the aquatic environment at a daily rate χ and *Vibrios* have a net death rate δ in the environment. Readers interested in the mathematical properties of the model should refer to (Mukandavire et al., 2011). The resulting model as a system of differential equations is as follows:

$$\begin{aligned}
\frac{dS}{dt} &= \mu N - \beta_e S \frac{B}{\kappa + B} - \beta_h S I - \mu S, \\
\frac{dI}{dt} &= \beta_e S \frac{B}{\kappa + B} + \beta_h S I - (\gamma + \mu) I, \\
\frac{dR}{dt} &= \gamma I - \mu R, \\
\frac{dB}{dt} &= \chi I - \delta B.
\end{aligned} \tag{1}$$

A Markov chain Monte Carlo (MCMC) based on a Bayesian framework (in R FME package (Soetaert and Petzoldt, 2010)) was used to fit the Zimbabwe cholera model to aggregated reported cholera cases for Budiriro and Glen View (the epicenter of the outbreak) to estimate the basic reproductive number and the vaccination coverage required to contain the epidemic. We used data on reported cholera cases published by the City of Harare, which covered the period from 1 September to 10 September 2018 (CHHD, 2018). Similar to Haiti, these data may well be underestimates because of the weak health system in Zimbabwe. However, despite data quality, this study presents the best estimate of the magnitude of the outbreak and potential vaccine coverages needed to contain the outbreak. In the fitting, β_e and β_h were estimated to match the reported cholera cases and the initial infected population was also varied with other fixed parameters, as given in Supplementary Table 1. A Gaussian likelihood was used to draw model parameter posteriors assuming uniform non-informative priors, while the variances were regarded as nuisance parameters. The MCMC chain was generated with at least 100,000 runs for the final fitting excluding the burn-in period. Chain convergence was examined visually and using the Coda R package. Extended runs were carried out in cases in which convergence was not evident. Uncertainty of each estimated parameter was evaluated by analyzing the MCMC chains and calculating the 2.5% and 97.5% quantiles to give the 95% credible interval (CrI).

The basic reproductive number ($\mathcal{R}_0$) is defined as a measure of the average number of secondary cases generated by a primary case. Understanding its magnitude and variation can help to identify cholera 'hot spots' and design targeted surveillance programs. The two transmission routes of cholera are quantitatively described by partial reproductive numbers, $\mathcal{R}_h$ and $\mathcal{R}_e$ that describe new cases that arise from either the fast human-to-human or the slower environment-to-human transmission routes, respectively. The mathematical expressions of $\mathcal{R}_0$, $\mathcal{R}_h$ and $\mathcal{R}_e$ are given in Supplementary material. The corresponding minimum vaccination coverage (c) for a cholera vaccine with 78% efficacy for the Budiriro and Glen View outbreak was based on a formula in (Dietz, 1993) (and was applied elsewhere (Mukandavire et al., 2011)),

$$c \geq \frac{1 - \mathcal{R}_0^{-1}}{1 - (1 - r)(1 - s)} \tag{2}$$

where r is the fraction of the vaccinated population who are completely immunized and s is the proportional reduction of the susceptibility for those partially immunized.

Results

Figure 2 shows fitted aggregated cholera cases for Budiriro and Glen View. Table 1 provides estimates of the basic reproductive

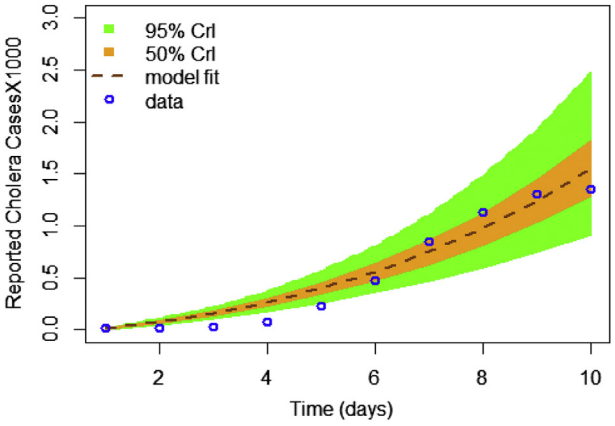

Figure 2. Cholera model fitting for the cumulative cholera cases where the orange and green regions are the 50% and 95% CrIs, the dashed brown line is the median model projection, and the blue circle marks are the reported data for the cumulative number of cholera cases in Budiriro and Glen View.

Table 1
Estimates of $\mathcal{R}_e$, $\mathcal{R}_h$, $\mathcal{R}_0$ and minimum vaccination coverages with 95% CrIs, assuming a 78% vaccine efficacy.

Parameter description	Estimated values (95% CrIs)
Partial reproductive numbers due to 'slow' transmission through the environment, $\mathcal{R}_e$	0.15 (0.122–0.19)
Partial reproductive numbers due to 'fast' human-to-human transmission, $\mathcal{R}_h$	1.67 (1.41–1.92)
Basic reproductive number, $\mathcal{R}_0$	1.82 (1.53–2.11)
Vaccination coverage resulting in disease control	58% (45–68%)

number ($\mathcal{R}_0$) and partial reproductive numbers due to 'fast' human-to-human transmission ($\mathcal{R}_h$) and 'slow' transmission through the environment ($\mathcal{R}_e$), and corresponding minimum OCV coverage that would be required to control the disease in Budiriro and Glen View when using vaccine with 78% efficacy (Lucas et al., 2005).

Using estimates of $\mathcal{R}_0$, sensitivity analysis of cholera vaccine efficacy was carried out to explore possible scenarios that may arise from using different types of vaccines by considering an efficacy range of 50–100%. The results suggest that a cholera vaccine with 55% efficacy (see Figure 3) is sufficient to contain the cholera outbreak but requires higher vaccination coverage 75% (95% Crl 58–88%). The required vaccination coverage for epidemic control decreases with increase in efficacy, with a vaccine of 100% efficacy requiring 45% (95% Crl 35–53%) coverage. However, most of the new-generation OCVs have shown efficacy of >65% (Lucas et al., 2005; Sur et al., 2009; Thiem et al., 2006; Clemens et al., 1990 Lucas et al., 2005; Sur et al., 2009; Thiem et al., 2006; Clemens et al., 1990Lucas et al., 2005; Sur et al., 2009; Thiem et al., 2006; Clemens et al., 1990Lucas et al., 2005; Sur et al., 2009; Thiem et al., 2006; Clemens et al., 1990) for periods sufficient to control outbreaks.

Discussion

The cholera outbreak, which started in the capital, Harare, and rapidly spread to other districts (MoHCC, 2018b) (see Figure 1) presented a short window in which to consider targeted cholera vaccination in Zimbabwe. This quantity of $\mathcal{R}_0 > 1$ clearly showed that this outbreak had the potential to spread and spill over to other areas. The current results suggest that a cholera vaccine of 55% would have been sufficient to contain the Budiriro and Glen View outbreak, although at a higher vaccination coverage (see Figure 3). However, it is noted that vaccination coverage significantly decreases for higher vaccine efficacy, suggesting that a vaccine with higher efficacy would be preferable when considering vaccination in Zimbabwe. Thus, the Euvichol Plus OCV, which was administered a few weeks after the outbreak (MoHCC, 2018b) with sustained protection of >60% for at least 3 years after two doses (WHO, 2017), could have contained the outbreak if it had been timeously implemented and the desired coverage had been achieved. Unfortunately, data were unavailable to assess the impact of OVC in vaccinated areas using mathematical models.

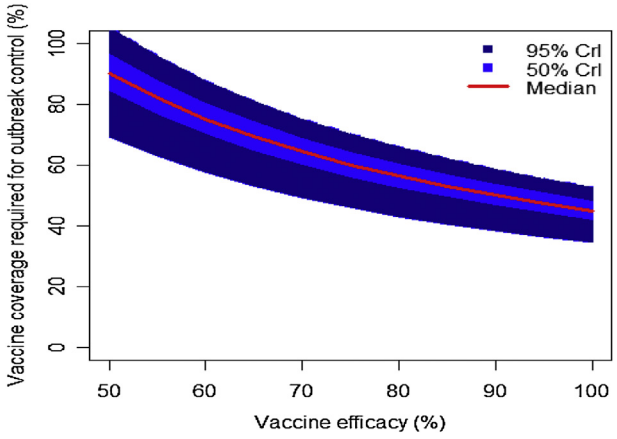

Figure 3. Sensitivity analysis plot showing different vaccination coverages for different OCV efficacy. The blue and dark blue regions are the 50% and 95% CrIs and the red line is the median.

A previous study for the 2008–2009 cholera outbreak in Zimbabwe estimated the required OCV coverages to contain the epidemic to be in the range of 13–82% in 10 provinces (Mukandavire et al., 2011; Mukandavire and Morris, 2015) (assuming vaccine efficacy of 78%). Similar to this study (see Figure 3), analysis of the 2008–2009 cholera in Zimbabwe at provincial level showed that a vaccine of at least 65% efficacy would be able to control the epidemic in the entire country (see Supplementary Table 2). Similar results were also reported for the Haiti outbreak, with OCV coverages ranging from 7–80% in all 10 departments (Mukandavire et al., 2013) and 65% vaccine efficacy was sufficient for disease control. Estimated $\mathcal{R}_0$ values for Haiti were very similar to those for Zimbabwe. A similar modeling study on cholera in the Ouest Department of Haiti demonstrated that a vaccine of at least 60% can successfully eliminate cholera within a few years (PVOCVA, 2018). However, in this study and previous studies (Mukandavire et al., 2011; Mukandavire et al., 2013) vaccination coverage estimates were based on direct vaccine protection and would potentially reduce if herd protection of cholera vaccines was taken into account (Ali et al., 2005). In the context of the Budiriro and Glen View cholera outbreak, the required vaccination coverage needed to achieve outbreak control could be further reduced with population immunity (Nelson et al., 2009) from recent sporadic cholera outbreaks (McAteer et al., 2018).

Studies on cholera vaccination strategies suggest that ring vaccination deployed in the most affected geographical areas targeting individuals at highest risk of infection could reduce the number of doses needed to control the disease (Ali et al., 2016; Deen and von Seidlein, 2018; Azman et al., 2018). Recent studies have also shown that reactive vaccination campaigns using a single dose of OCV may be more cost-effective than a standard two-dose campaign when vaccine supplies are limited, and it reduces logistical challenges associated with vaccination campaigns in resource-constrained settings (Ciglenecki et al., 2018). Using spatially targeted ring vaccination and a single-dose vaccination approach could have been an important vaccination strategy in Zimbabwe, considering limited OCV supply (500,000 doses (MoHCC, 2018b; Muvishi, 2018)) and timing (the rainy season was approaching). Nevertheless, if data were available, actual outcomes of the mass vaccination could have been used to assess the value of future vaccination campaigns and strategies using mathematical models.

Ciprofloxacin, tetracycline and Rocephin (ceftriaxone) resistance was confirmed in the 2018 cholera outbreak in Zimbabwe (Mavhunga, 2018). There was a significant challenge as to which drug to give to patients, considering that azithromycin was unavailable in health facilities (Mavhunga, 2018). The WHO called for the review of the vaccine used in Zimbabwe due to multidrug resistance (RCV, 2018). Additionally, the substantial structural and operational challenges facing water and sewerage systems in Budiriro and Glen View could not be addressed and resulted in communities spending many hours without drinking water and long delays in repair of sewer blockages. This makes targeted cholera vaccination a very viable option for controlling cholera outbreaks in Zimbabwe.

This study had some limitations. The estimate of $\mathcal{R}_0$ was based on available data and this estimate could have possibly changed depending on the quality of the data from the start of the epidemic and the resolution of the modeling. It is noted that there was no separate data on reported cases for Budiriro and Glen View, as this would have been important in modeling the dynamics of the cholera outbreaks of the two suburbs individually. However, estimates of $\mathcal{R}_0$ and the required vaccination coverage to contain the outbreak in the two suburbs are important in understanding the magnitude of the cholera outbreaks in Zimbabwe. As Zimbabwe has now embraced cholera vaccination (MoHCC,

2018b), these numbers may guide public health officials on expected vaccination coverages to contain future outbreaks.

Currently in Zimbabwe, as in Haiti initially, there is a lack of understanding on the role of cholera vaccines in outbreak control because of limited experience in using OCVs in outbreak settings (Kirpich et al., 2017). In light of the current lack of extensive public health resources and the absence of a robust long-term cholera control strategy, this work highlights the key role that cholera vaccines will play in the short-term relief and stemming cholera tides. However, the potential public health benefits of widespread or targeted vaccination programs in a humanitarian emergency need to be carefully balanced against the potential ethical issues that may arise (Moodley et al., 2013; Stop Cholera, 2018). Nonetheless, to achieve optimal protection of the population at risk, OCVs should be integrated with water, sanitation and hygiene activities to permanently decrease the risk of transmission from environmental sources.

Author contributions

ZM was responsible for construction of the model and initial manuscript preparation. ZM, conducted the model analysis. PM, FN, DFC, GM, and JGM assisted with conceptualization of the project and preparation of the manuscript. All authors were involved in writing the manuscript.

Conflict of interest

The authors declare that they have no conflict of interest.

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Ethical approval

Ethics approval was not required for this study.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at https://doi.org/10.1016/j.ijid.2020.03.077.

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