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First bovine vaccine to prevent human schistosomiasis - a cluster randomised Phase 3 clinical trial

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A B S T R A C T

Objective: Schistosomiasis is a neglected tropical parasitic disease caused by blood flukes of the genus Schistosoma. Schistosoma japonicum is zoonotic in China, the Philippines, and Indonesia, with bovines acting as major reservoirs of human infection. The primary objective of the trial was to examine the impact of a combination of human mass chemotherapy, snail control through mollusciciding, and SJCTPI bovine vaccination on the rate of human infection.

Methods: A 5-year phase IIIa cluster randomized control trial was conducted among 18 schistosomiasis-endemic villages comprising 18,221 residents in Northern Samar, The Philippines.

Results: Overall, bovine vaccination resulted in a statistically significant decrease in human infection (relative risk [RR] = 0.75; 95% confidence interval [CI] = 0.69 to 0.82) across all trial follow-ups. The best outcome of the trial was when bovine vaccination was combined with snail mollusciciding. This combination resulted in a 31% reduction (RR = 0.69; 95% CI = 0.61 to 0.78) in human infection.

Conclusion: This is the first trial to demonstrate the effectiveness of a bovine vaccine for schistosomiasis in reducing human schistosome infection. The trial is registered with Australian New Zealand Clinical Trials Registry (ACTRN12619001048178).

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Introduction

Schistosomiasis is a neglected tropical parasitic disease caused by blood flukes of the genus Schistosoma. Globally, it ranks third among the most devastating tropical diseases and is a major cause of morbidity in Asia, Africa, South America, the Middle East, and the Caribbean [1,2]. Praziquantel (PZQ), a pyrazinoisoquino-line derivative, is the mainstay of treatment and a critical part of community-based schistosomiasis control programs [2–6]. There is currently no commercially available human vaccine against any of the human schistosomes.

Schistosomiasis japonica was first reported in the Philippines in 1906 [7]. Approximately 80% of the burden of disease now resides on the islands of Samar, Leyte, and Mindanao. An estimated 29 million people live in these three endemic zones [8–10]. Recent reports have found prevalence rates ranging from 0.7–47% for Western Samar, 5–46% for Northern Samar, and 25–60% for Leyte [8]. The current national control program comprises annual free mass drug administration with 40 mg/kg of PZQ in all schistosomiasis-endemic communities with a prevalence of > 10%.

In the study area of Laoang and Palapag in Northern Samar, an active schistosomiasis control program has been ongoing since...
1980 by the local Department of Health. From 1980 to 1990, the program consisted of active case finding and directly observed therapy (DOT) of all positive cases with 60 mg/kg of PZQ. Samples were obtained from approximately 10–20% of the target population aged 5-65 years. From 1990 to 2007, case finding was intensified to include approximately 30-50% of the entire schistosomiasis-endemic population. All stool-positive individuals again received DOT with 60 mg/kg of PZQ. There is presently intermittent mass drug administration (MDA) done by the National Department of Health in known highly endemic areas [7–10].

Schistosomiasis control in China and the Philippines is complicated by the zoonotic nature of the disease, with bovines (water buffaloes and cattle) acting as major reservoir hosts [8,11–14]. Alternative sustainable control strategies are required to combat schistosomiasis to overcome rapid reinfection, the potential threat of PZQ resistance, and problems of drug compliance currently only at levels of 25-40% in China and the Philippines [15–23]. A multifaceted integrated approach targeting transmission pathways for the disease could comprise complementing PZQ treatment with vaccination of bovines and snail control as the key to sustainable control and eventual elimination (defined as the reduction to zero in human incidence) [10–14]. In light of their importance as major reservoirs for S. japonicum, vaccination of bovines has been proposed as a tool to assist in long-term prevention, which is supported by mathematical modeling [10–14]. The intervention would be particularly applicable to areas where mechanized farming is unsuitable. Vaccination can reduce egg excretion from cattle and buffalo, thereby interrupting transmission from bovines to snails. We previously showed that a schistosome plasmid DNA vaccine (SjCTPI-Hsp70) induced very good efficacy against S. japonicum in Chinese water buffaloes when it was co-administered with an IL-12 expressing plasmid as adjuvant [24,25].

We report here the results of a 5-year phase Ila cluster randomized control trial (RCT) using a multi-factorial design in Northern Samar, The Philippines. The trial aimed to determine the impact of a combination of human mass chemotherapy, snail control through mollusciciding, and the SjCTPI bovine vaccine, on the human incidence of S. japonicum.

Methods

Study design and randomization

Ethical consent for the trial was obtained from the human and animal ethical review boards of the National Department of Health in the Philippines (Institutional Review Board # 2012-13-0) and Griffith University (PBH/24/11/HREC0), Australia. The Research Institute for Tropical Medicine monitored the trial. Written informed consent was obtained from each individual, or, for those aged <15 years, from their parents/legal guardians before commencing the study. The phase Ila clustered RCT used a split-plot design with the main plots being the factor designating the non-vaccine intervention groups (i.e., control, human MDA, or mollusciciding) (Supplement 1). The 18 selected villages were arranged in pairs, within which villages were matched on baseline-assessed factors, which included human and bovine population numbers and prevalence, and factors affecting schistosomiasis transmission: numbers of snail colonies, type of snail habitat, water source, and distance to a health center. The nine sets of paired villages were then each randomly allocated to one of the three non-vaccine intervention groups, resulting in three pairs for each. Villages within each matched pair were allocated to one of two letter-codes for the vaccine/placebo intervention. The investigators, including the research team and study participants, were blind to the vaccine allocation to the letter code.

Participants

We commenced the phase Ila clustered RCT with a cross-sectional parasitological survey in July to October 2012 among 22 schistosomiasis-endemic barangays in the municipalities of Laoang and Palapag in Northern Samar, the Philippines (Figure 1) [26]. The baseline survey comprised 18,221 eligible residents (age range, 5-65 years). In brief, the baseline survey included (i) A medical questionnaire that comprised information on their demographic characteristics (name, age, sex, level of education, and occupation), schistosome exposure (place, frequency, and duration), treatment history (diagnosis, number of times treated, and participation in the MDA program in the past 5 years), and level of morbidity (fever, diarrhea, abdominal pain, malaise, hepatitis status, and alcohol intake); (ii) The head of each household completed a questionnaire that included information on home and land ownerships, number of animals owned and raising practices, animal waste disposal practices, pasturing of animals, sanitation, and housing characteristics (roof, wall, and floor materials); (iii) Collection of a human stool sample, which was tested for S. japonicum using the Kato Katz (KK) thick smear technique (three smears per stool) and to determine the infection intensity (Geometric Mean Eggs per Gram [GMEPG]) [26]; (iv) Collection of bovine stool samples, which were tested for S. japonicum using the formalin-ethyl acetate sedimentation-digestion (FEA-SD) [12] and to determine infection intensity; (v) Oncomelania snail surveys using the Chinese method of random quadrat sampling applied to marshland areas for each village [10]; and (vi) An ultrasonography study conducted on a subsample of patients who either reported symptoms of gastrointestinal illness or were believed to have clinical morbidity, based on physical examination [26].

Interventions

Following the baseline survey, the interventions were implemented in 18 villages from 2013 to 2017 (Supplement 2). All stool-positive residents (60 mg/kg split DOT dose) and bovines (30 mg/kg) were treated with PZQ in the 18 study villages. Interventions were then implemented in the allocated villages as described previously. Bovines received the priming SjCTPI DNA vaccine in 2012 and then the protein boost or placebo control in VacSIM 6 months later, in 2013, with subsequent booster vaccinations or placebo controls in VacSIM given in 2014, 2015, and 2016 (Supplement 2). Full details of the production and formulation of the SjCTPI vaccines (plasmids encoding SjCTPI-Hsp70 and UMVC3-mIL12 and recombinant SjCTPI), placebo control vaccine, the vaccination regimen, and the procedures for injecting bovines with the vaccine/placebo formulations have been provided [24]. VacSIM was previously described [25]. Briefly, buffalo were primed with GLP grade plasmid DNAs (SjCTPI and IL-12, 300µg of each) by intramuscular injection into the shoulder. Controls received naked plasmid DNA plus interleukin (IL)-12, 300µg of each. Approximately 6 months post-prime, bovines were boosted by intramuscular injection of 100µg of GLP grade recombinant SjCTPI in 1.0% VacSIM containing 100µgs Bovine CpGs (Bovine ODN 2007). Controls were given CpGs in saline in 1.0% VacSIM®. Human mass treatment with 40 mg/kg of PZQ was carried out annually in the treatment arms. Mollusciciding was conducted after the annual snail surveys. Targeted snail ‘hotspots’ (areas close to human habitations with maximum or daily access to both humans and bovines in an environment favored by snails) were sprayed with nicosamide (2 g/m²) annually [26]. One of the villages allocated to mollusciciding could not be treated for security reasons, so one of the other 18 villages, originally not selected to receive mollusciciding, was selected.
Outcomes

The primary outcome was human *S. japonicum* infection status at two follow-ups in 2014/2015 and 2016/2017, with a positive infection defined as the presence of at least one egg on a KK slide. The secondary outcome was a human geometric mean intensity of infection in positives, as determined by the KK method.

Statistical analysis

All data management and analyses used SAS (r) Proprietary Software 9.4 (TS1M2) (2002–2012, SAS Institute Inc., Cary, North Carolina, USA, Licensed to University of Queensland - EAS, Site 10005036). Data were double-entered into a specially designed Microsoft Access-based database we developed; electronic copies of all entered data were saved offline, and backup paper duplicates were stored in a secure location [23,26]. Questionnaire survey data and results of the stool examinations were collected during the baseline survey from 2012 to 2013 and at follow-ups from 2014 to 2017 (Figure 2). Baseline and follow-up data for each village were cleaned and combined for the analyses in this paper. Based on intervention efficacy estimations (bovine vaccine efficacy 50%, human chemotherapy efficacy 85%, and targeted mollusciciding predicted efficacy 75%), an average infection rate of 10% in non-intervention villages, and a design effect (relating to paired differences) of 1.5, the study was proposed to have at least 90% power to detect the intervention effects [19,23]. A SAS program was written to carry out the randomization of each intervention group [19–23].

Analyses of human infection were restricted to those who satisfied the initial inclusion criteria (e.g., age, current residency, expected residency during the trial) and had baseline questionnaire and stool results and at least one follow-up stool result. Interventions were analyzed as intention-to-treat; i.e., the two villages not treated according to their original allocation to mollusciciding were assigned their original allocation for the purpose of analysis. Baseline infection prevalence and intensity were compared across intervention groups using logistic regression and normal regression (log-transformed EPG in those infected), respectively, with account taken of cluster effects within villages.

For intervention assessment, the primary outcome was human *S. japonicum* infection status at two follow-ups in 2014/2015 and 2016/2017, with a positive infection defined as the presence of at least one egg on a KK slide [26]. The intervention analysis used a random effects model with village pairs as a random factor. The main plot factor (control, human treatment, mollusciciding) and the vaccine allocation were treated as separate 3-level and 2-level factors, respectively. A Poisson/log link model was used with robust variances specified, as described by Zou and Donner [27], thus yielding relative risks with appropriate standard errors as effect estimates. Using Proc GLIMMIX in SAS 9.4, a full factorial model was first fitted, including a factor for time (baseline, follow-ups one and two), with baseline infection status, sex, and age group as covariates. The GLIMMIX specification incorporated three RANDOM statements, one specifying the use of an over-dispersion factor to obtain robust estimates of variance, one specifying the split-plot design with village pair as a random factor, and one specifying the repeated measures within individuals over time. The complete factorial model involves a third-order interaction (main plot x vaccine x time), which was clearly non-significant ($P = 0.99$) and was removed from the model. The second-order interaction between the main plot factor and the vaccine was retained.
Results

Baseline findings

A total of 18,221 individuals completed an individual medical questionnaire, and 18,163 completed the head-of-household questionnaire. A total of 10,435 eligible individuals aged 5-65 years provided stool specimens for fecal examination. Ultrasonography was conducted on 736 individuals who either reported symptoms of gastrointestinal illness or were believed to have clinical morbidity based on physical examination. Ultrasonography revealed high levels of schistosomiasis-induced morbidity in the schistosomiasis-endemic communities. Left lobe liver enlargement (≥70 mm) was evident in 89.3% of subjects. A total of 25% of the study population had grade II/III liver parenchyma fibrosis, and 13.3% had splenomegaly (≥100 mm). Despite an active schistosomiasis control program in Northern Samar for over 30 years, which included an MDA campaign in the last 5 years, the mean prevalence of schistosomiasis among 10,435 evaluated subjects was 27.1%, and the geometric mean intensity of infection among 2,832 egg-positive subjects was 17.2 EPG of feces.

Trial descriptors

The recruitment and follow-up by intervention are illustrated in Figure 2. A total of 14,441 eligible residents met the selection criterion for entry into the trial among the 18 endemic study villages. A total of 10,866 (75%) individuals were randomly allocated into nine matched pairs comprising three groups of three villages. A total of 75% of the study population had baseline and at least one follow-up stool result. A total of 48% of the study population was male (Table 1). There was no statistically significant difference in the sex ratio among the three trial arms. The majority (74%) were under 40 years of age, with a primary level (73%) of education. Most were farmers (19%), students (24%), or housewives (46%) by occupation. A large number (66%) of study participants reported less than weekly contact with potentially schistosome-contaminated waters (Table 1). At baseline, stool samples were obtained from 497 bovines. The overall prevalence of infection was 42.5%, and intensity was 4.84 EPG. Village prevalence ranged from 6.9% to 64.7%, and intensities from 3.36 to 11.65 EPG. Within the 331 Carabaos, the prevalence was 33.5% and intensity 4.20 EPG. Within the 166 cattle, THE prevalence was 61.4%, and the intensity was 5.66 EPG. The bovine vaccine coverage rate was 53% across all follow-ups. Greater overall bovine health, including growth and weight gain, was observed among the vaccinated animals.

Incidence and intensity of human infection

Table 2 depicts human infection (%) by intervention group at baseline and at two subsequent trial follow-up points. For ‘Human Controls,’ both bovine-vaccinated villages, and bovine unvaccinated (placebo) villages had significant decreases in human infection at follow-up one (i.e., approximately two years after baseline human treatment), but infection increased slightly at the second follow-up. It is noteworthy that the human infection rate at follow-up two was still lower than the baseline human prevalence. For the ‘Human Treatment,’ group the villages that received bovine vaccination had the best outcomes. After baseline human treatment, human infection decreased at both follow-ups. In the villages that received ‘Mollusciding,’ again the best outcomes were seen in the villages where the bovines were vaccinated. Human infection declined significantly in subsequent follow-ups (P = 22.4; 95% confidence interval [CI] 14.8, 33.9). The results of human infection by village are shown in Figure 3. It is evident that the bovine-vaccinated villages overall had the greatest reductions in human infection following baseline treatment. Vaccination worked additively with either human mass treatment or mollusciding. Table 3 displays human infection intensity (EPG) by intervention group and follow-up (2). The outcomes are consistent with those seen for human reinfecion (%).
In Table 1, the description of intervention and vaccine groups at baseline, N (%), is shown. The table includes data on sex, age, education, occupation, water contact, and whether the individual had follow-ups. The table also includes data on the control group, placebo vaccine, and Mollusciciding vaccine.

Table 2 presents the human infection (%) by intervention group, vaccine, and year. The table includes data on the baseline, follow-up 1, and follow-up 2 for each group, including the number tested, prevalence, and 95% CI.

Table 3 shows the human infection intensity (geometric eggs per gram) by intervention group and year. The table includes data on the baseline, follow-up 1, and follow-up 2 for each group, including the number positive, EPG (95% CI), and number positive EPG (95% CI).

Intention-to-treat analysis

Table 4 describes the intention-to-treat analysis. Overall, bovine vaccination resulted in statistically significant decreases in human infection (relative risk [RR] = 0.75; 95% CI = 0.69 to 0.82) across all trial follow-ups. Snail mollusciciding on its own resulted in a statistically significant increase (RR = 1.52; 95% CI = 1.06 to 2.19) in human infection at follow-up one. Human treatment on its own had no statistically significant difference (RR = 1.13; 95% CI = 0.72 to 1.75) impact on human infection across all follow-ups. However, when bovine vaccination was combined with human mass treatment, there was a significant decrease (RR = 0.84; 95% CI = 0.73 to 0.97) in the human infection across all follow-ups. Combining bovine vaccination was combined with snail mollusciciding resulting in the greatest reduction (RR = 0.69; 95% CI = 0.61 to 0.78) in human infection.

Discussion

In the Philippines, the current schistosomiasis drug coverage is estimated to be <40%, and drug compliance is less than 50% [28-31]. Over the past 30 years, MDA has been highly sporadic.
Figure 3. Comparison of percentage of human infected at each time point, for vaccinated vs placebo, within each pair of villages for Control, MDA, and Mollusciciding interventions.

Note: BL = Baseline (July-September 2012), FU1 = Follow-up 1 (October-December 2014), FU2 = Follow-up 2 (October-June 2017), Control = No MDA or Mollusciciding allocated, MDA = Allocated to mass drug administration in humans, Mollusciciding = Allocated to mechanized tractors within villages.

Table 4

<table>
<thead>
<tr>
<th>Follow-up 1</th>
<th>Follow-up 2</th>
<th>All Follow-ups</th>
</tr>
</thead>
<tbody>
<tr>
<td>RR (95% CI)</td>
<td>P</td>
<td>RR (95% CI)</td>
</tr>
<tr>
<td>Overall effects</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bovine Vaccine</td>
<td>0.75 (0.67, 0.83)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Human treatment</td>
<td>1.21 (0.84, 1.74)</td>
<td>0.31</td>
</tr>
<tr>
<td>Mollusciciding</td>
<td>1.52 (1.06, 2.19)</td>
<td>0.023</td>
</tr>
<tr>
<td>Vaccine effect within:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Control Group</td>
<td>0.73 (0.62, 0.87)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Human treatment</td>
<td>0.83 (0.71, 0.97)</td>
<td>0.022</td>
</tr>
<tr>
<td>Mollusciciding</td>
<td>0.68 (0.60, 0.79)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Human treatment within placebo vaccine</td>
<td>1.14 (0.78, 1.66)</td>
<td>0.51</td>
</tr>
<tr>
<td>Active vaccine</td>
<td>1.28 (0.88, 1.89)</td>
<td>0.20</td>
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<tr>
<td>Mollusciciding within placebo vaccine</td>
<td>1.58 (1.08, 2.30)</td>
<td>0.018</td>
</tr>
<tr>
<td>Active Vaccine</td>
<td>1.47 (1.01, 2.14)</td>
<td>0.045</td>
</tr>
</tbody>
</table>

CI, confidence interval; RR, relative risk.

and highly dependent on donor support [7,8,28–31]. The zoonotic nature of schistosomiasis in the Philippines and in China further complicates control efforts. Bovines have been shown to be responsible for over 80% of the transmission to people, and over 80% of the bovines in the Philippines are heavily infected with the parasite [11–14]. Unlike China, disease transmission in the Philippines is year-round (5 months in China), and it is unlikely that bovines will be replaced by mechanized tractors in the foreseeable future due to poverty [1,9,10]. Therefore, we and others have proposed that a bovine vaccine may be a critical component for a future national control strategy leading to disease elimination [1,9–14].
This is the first trial to provide evidence that bovine vaccination is effective in preventing human schistosomiasis, and we suggest it warrants consideration as part of a future national integrated control strategy to eliminate the disease in the Philippines. The situation in China is less clear. We conducted a similar study in China, but the results were inconclusive, mainly due to the removal or treatment of trial bovines by the government [23]. Most of the animals have now been replaced by mechanized tractors in most endemic zones in a further attempt to eliminate the disease from the country [23]. Thus, it is hoped this strategy will be the final element required to eliminate the disease [1,23]. Given the economic successes in China over the past decade, this was a viable alternative for the national integrated control strategy, but in the Philippines, this is simply not possible given the current economic constraints [23].

To eliminate the disease in the Philippines, the government must first recognize that schistosomiasis is a serious public health problem among the poorest segment of their society [7,8]. With political will, there must come significant financial investment for an integrated control strategy that will comprise annual DOT MDA of endemic communities (with >10% human prevalence) with 60 mg/kg of PZQ (split DOT dose), annual mollusciciding (niclosamide 2 g/m²) of the snail intermediate host in identified ‘hotspots’ of transmission, annual treatment (30 mg/kg of PZQ) and vaccination (SJCTPI DNA vaccine and protein boost in VectSIM) of bovines with at least 50% coverage [1,10,16,18–21,24–26,32–36]. The total cost of the prime/boost regime is $1.65/buffalo using ‘pilot trial’ costs. However, we expect these costs to be reduced by 5–10-fold with large-scale production. The benefit of adding bovine vaccination to the current control strategies is the overall reduction in the incidence of schistosomiasis in both humans and bovines. Moreover, greater overall bovine health, including growth and weight gain, was observed among the vaccinated animals.

There were several limitations to this trial. As mentioned, the overall bovine vaccination rate was 53% across all follow-ups. Carabaos are highly prized domestic animals and vital for rice farming in the rural Philippines. Thus, many farmers were reluctant to vaccinate their animals with an experimental vaccine. We anticipate that if the vaccine is formally approved by the government that vaccination rates will improve. Another issue was related to the KK Thick Smear Stool Examination. When the trial was undertaken, the KK technique was (and still is) the World Health Organization’s (WHO) gold standard for the detection of human infection of schistosomiasis, although there are issues related to its sensitivity. In a recent meta-analysis by Vaillant et al [36] the authors indicated that conventional diagnostic tools for humans deploying the KK and cathodic circulating antigen methods for S. mansoni and urine microscopy for S. haematobium have reasonable sensitivity and excellent specificity. Moreover, conventional diagnostic tools are well-accepted, low-cost, and feasible, given their widespread implementation [36]. Newer diagnostic tools, such as molecular-based and immunologic diagnostics, lack sufficient data on sensitivity and specificity, and their utility is further limited by challenges with feasibility and resource implications [36]. The results of this review were used in the recently published (2022) WHO guidelines on the control and elimination of schistosomiasis [37]. In sum, we anticipate that the use of these procedures for all treatment arms would not impact the overall conclusions.

We believe bovine vaccination is the missing component of an integrated control package required for the elimination of schistosomiasis from Asia. Annual bovine vaccination will be required, given their intense exposure and infectivity. The final step for the Philippines will be to improve the bovine vaccination rate and to replicate this trial in several endemic locations. If successful, it may contribute to a new national schistosomiasis control strategy.

Declaration of competing interest

The authors have no competing interests to declare.

Funding

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Ethical approval

Ethical consent for the trial was obtained from the human and animal ethical review boards of the National Department of Health in the Philippines (Institutional Review Board # 2012-13-0) and Griffith University (PBH/24/11/HREC0), Australia. The Research Institute for Tropical Medicine monitored the trial. Written informed consent was obtained from each individual or, for those aged <15 years, from their parents/legal guardians before the commencement of the study. All questionnaires were translated into the local dialect, and responses were back-translated into English. Individuals found to be positive for schistosomiasis, apart from pregnant women, were treated (with DOT) with 60 mg/kg of PZQ (split dose), following the Department of Health National Guideline. Annual human mass treatment with 40 mg/kg of PZQ (single dose) followed both World Health Organization and Department of Health National Guidelines. The trial is registered with Australian New Zealand Clinical Trials Registry (ACTRN12619001048178).

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We also like to thank the numerous local staff and study participants living in the municipalities of Laonag and Palapag for their tremendous contributions to conducting the field trial. In memory of Dr Remigio Olveda, MD, and Mr Julius Chy, who contributed greatly to the coordination of the field studies. Gone but not forgotten old friends!

Author contributions

Concept and design: AR, DH, DG, GW, and DM. Acquisition, analysis, or interpretation of data: all authors. Drafting of the manuscript: AR, DH, GW, and DM. Critical revision of the manuscript for important intellectual content: AR, GW, DM, and DG. Obtained funding: AR, RO, YL, DH, and DG. Administration, technical or material support: AR, DH, GW, RO, AI, DC, JC, JG, and LS. Supervision: AR, RO, DH, YL, DC, and JC. The authors declare no conflict of interest, and all authors read and approved the manuscript.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.ijid.2023.01.037.

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