



Setting priorities for patient-centered surveillance of drug-resistant infections



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ABSTRACT

Methods: A priority-setting process (PSP) was launched to define priorities for patient-centered antimicrobial resistance (AMR) surveillance and research in low- and middle-income countries (LMICs). A list of uncertainties related to AMR surveillance in human health was generated using an online survey of stakeholders in LMICs, which asked for unanswered questions about diagnosis, treatment, or prevention of antibiotic resistance.

Results: A total of 445 respondents generated 1076 questions that were mapped to a final shortlist of 107 questions. The most common theme was the treatment of drug-resistant infections, followed by diagnosis, then prevention, and requests for local AMR data. The most asked question was a request for local AMR data, revealing the lack of basic information in many LMICs to guide actions to tackle AMR. The steering group recommended three research areas to be prioritized for funding in the next five years: infection prevention and control in LMICs, improved electronic patient records, starting with laboratory information management systems, and sustainable behavior change among doctors and other health care professionals with a focus on diagnostic stewardship.

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1. Background & Rationale

Low- and middle-income countries (LMICs) are predicted to be hit hardest by drug-resistant infections (DRI) (O'Neill, 2016). The burden of infectious diseases is higher, laboratory infrastructure is weaker, antibiotic use and quality are less regulated, and the healthcare workforce is smaller per population and less sub-specialized than in higher-income settings. There is evidence that healthcare-associated infections, which are more likely to be drug-

resistant, occur more frequently in LMICs (Allegranzi et al., 2011). Currently, high-income countries approaches to tackling antimicrobial resistance (AMR) are being adapted in LMICs, but there is a lack of evidence for how these should be prioritized, taking into account differences in the DRI burden, the fact that human and financial resources are much more limited, and that there may be different competing health-priorities.

The Surveillance and Epidemiology of Drug-resistant Infections Consortium (SEDRIC) is a global think-tank that brings together a range of international experts to take action to tackle the gaps in drug-resistant infection surveillance and epidemiology. Its mission is to strengthen the availability of information needed to monitor and track risks and to support the translation of surveillance data into interventions, changes in policy, and application of more

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effective practices. The work described here was an activity of the first SEDRIC working group. A priority-setting process (PSP) was launched to define priorities for AMR surveillance and research to benefit human health in LMICs. Priority-setting exercises are used increasingly in health research (Sibbald et al., 2009). The rationale for using this method was that in order to rank the multiple competing priorities for tackling DRIs, stakeholders from LMICs should first be consulted to generate a list of uncertainties, rather than relying on expert opinion. The PSP described here was adapted from The James Lind Alliance (2018) and the Child Health and Nutrition Research Initiative (CHNRI) priority-setting partnership methods (Rudan et al., 2008). Guiding principles were to have a transparent process driven by stakeholders working in LMICs.

The aim of this priority-setting process was to identify priorities for DRI surveillance or research in LMICs with the goal of reducing DRIs spread, transmission, and associated morbidity and mortality. The scope was restricted to human health, with the beneficiaries from the research intended to be patients affected by AMR in LMICs. Resistance to anti-tuberculous or antimalarial or antiretroviral drugs was not considered. The time-frame of interest in which to see improvements when selecting priorities was set as the next three to five years. The SEDRIC working group acted as the steering group for the process. Members were selected based on their knowledge and expertise of AMR, understanding of the patient and clinician populations, their experience of working in LMICs, and access to networks who could participate in the PSP.

2. Methods

The PSP was conducted in four steps (Box 1):

- 1) Survey. An online survey was piloted and then launched to generate a list of uncertainties related to AMR surveillance in human health in low-and middle-income countries. This was designed using SurveyMonkey® and translated from English into French and Spanish (Supplementary Material). The main survey question was, “Please write down questions about diagnosis, treatment, or prevention of antibiotic resistance that, if fully answered, could make a difference to your practice and to the health and well-being of your patients.” Respondents could enter up to three questions, and they were asked to be specific and focus on questions they considered to be of high priority.

The target stakeholders were clinicians, pathologists, or researchers involved in patient care in LMICs. Respondents’ anonymity was protected, but some demographic information was collected: gender, age range, country working in, occupation, and grade. We disseminated the survey via professional networks of the steering group using flyers, email, and Twitter. Our target was to keep the survey open for two months or until we had reached 500 respondents (whichever occurred first).

- 2) Categorization. Survey responses were collated by organizing them into themes and mapping to a shortlist of questions. Initial collation and classification of the questions into themes were performed independently by two members of the Steering Committee. Responses that fell out of the scope of the survey were excluded. Theme headings were generated by the first reviewer (EA). Where differences in theme allocation between the two reviewers occurred, a third member of the steering committee made the final decision on thematic categorization. Once questions had been organized into themes, similar or duplicate questions were combined and mapped to a shorter list of questions by one member of the steering committee (EA). For each theme, the long and short lists of questions were reviewed by a second member of the steering group with questions added or edited if the meaning of the original questions on the long list was determined to have not been adequately captured.
- 3) Interim prioritization. The members of the Steering Group then each ranked their top ten questions. These were combined to come up with a ranking score, which took into account the number of times a question was ranked by different steering group members (top-ranked preference given 20 points; tenth preference, 11 points).
- 4) Final prioritization. The final step was to identify three questions to be recommended as priorities for further research to the SEDRIC board according to the following defined criteria; this was reached by consensus. Criteria for final prioritization included: a) questions were within the scope of the PSP, b) they identified a clear gap in knowledge regarding AMR surveillance in LMICs, c) they had the potential to be answerable by research within three to five years, d) they were amenable to a funding call, e) there was minimal overlap with other initiatives.

Fig. 1

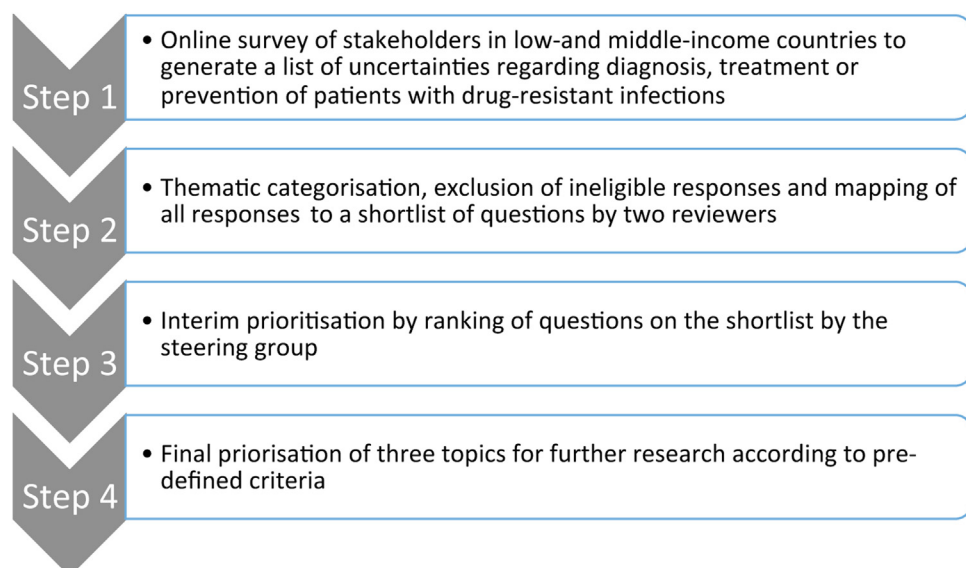


Fig. 1. Steps in the priority-setting process.

3. Results

The survey was launched on 6th December 2018 during the 59th Colloquium of the Institute of Tropical Medicine, Antwerp, held in Phnom Penh, Cambodia. Wider dissemination by the Steering Group started on 3rd January 2019 using a standard invitation sent out by email or Twitter, and the survey closed two months later on 4th March 2019. 445 respondents generated 1076 questions. Because the survey was disseminated via social media and informal networks, we could not estimate the response rate. While our sampling strategy could not ensure population representativeness, the survey respondents' characteristics confirm that the majority of them (80%) were from low- and middle-income countries and were practicing clinicians or microbiologists involved in patient care. The locations of the respondents are shown in Fig. 2. The largest number of respondents came from Myanmar (n = 44), followed by South Africa (31), UK (27), India (22), and Ghana (16). Most respondents submitted their questions in English (386/445 or 87%), followed by Spanish (n = 32) and French (n = 27). Most were senior grade physicians or pathologists with < 5% from surgical specialties. Respondent characteristics are shown in Table 1.

Table 2

3.1. Categorization into themes-

After excluding 417 questions that fell outside the scope of the survey (including blank or incomprehensible responses), the remaining 659 questions were categorized into themes (including one miscellaneous category). The most common theme was the treatment of drug-resistant infections, followed by diagnosis, then prevention, and then requests for local AMR data. All of the themes are shown in Fig. 3. The 659 questions were mapped to a shortlist of 107 questions as described in the methods. The top ten most asked questions are shown in Fig. 4.

3.2. Results of interim prioritization-

Each member of the Steering Committee ranked their top ten questions from the shortlist of 107 questions. These were combined to come up with a top ten list of surveillance priorities (Table 3).

Table 1

Characteristics of 445 survey respondents

Characteristic	n/N (%)
Gender	
Female	186/433 (43%)
Male	242/433 (56%)
Rather not say	5/433 (1.2%)
Age	
21–30 years	40/433 (9.2%)
31–40 years	150/433 (35%)
41–50 years	138/433 (32%)
51–60 years	63/433 (15%)
61 or older	36/433 (8.3%)
Rather not say	6/433 (1.4%)
Income group	
High income	83/428 (19%)
Upper middle income	91/428 (21%)
Lower middle income	180/428 (42%)
Low income	74/428 (17%)
WHO Region	
African (AFRO)	142/428 (33%)
South-East Asia (SEARO)	115/428 (27%)
European (EURO)	65/428 (15%)
Pan-America (PAHO)	48/428 (11%)
Western Pacific (WPRO)	47/428 (11%)
Eastern Mediterranean (EMRO)	11/428 (2.6%)
Language	
English	386/445 (87%)
Spanish	32/445 (7.2%)
French	27/445 (6.1%)
Specialty: Medical (except Pediatrics)	113/433 (26%)
Specialty: Pathology (includes Microbiology)	85/433 (20%)
Specialty: Pediatrics	59/433 (14%)
Specialty: General practice	38/433 (8.8%)
Specialty: Surgical	14/433 (3.2%)
Grade	
Consultant/Attending	218/433 (50%)
General Practitioner	57/433 (13%)
Trainee/Resident	40/433 (9.2%)
Other (please specify)	118/433 (27%)
Institution has prescribing guidelines	
Yes	259/433 (60%)
No	128/433 (30%)
Don't know	46/433 (11%)
Institution has laboratory	
Yes	359/433 (83%)
No	59/433 (14%)
Don't know	15/433 (3.5%)

n/N (%) are presented. Note: 12 survey respondents provided no personal information but still submitted questions.

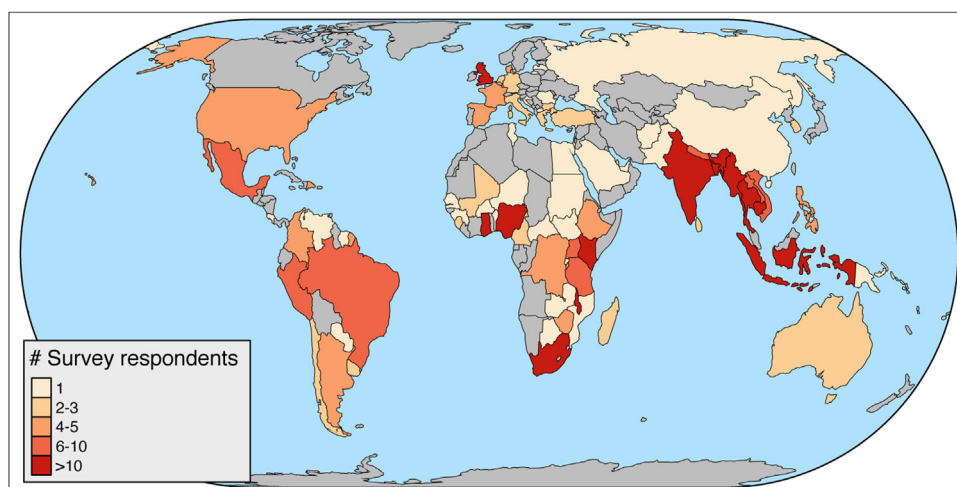


Fig. 2. Number of survey respondents from each country. 428/445 survey respondents provided this information.

Table 2

Interim prioritization of top 10 questions

	Ranking score ^a	N respondents asking this Q	N steering group members who ranked this Q in their top 5
1 Which IPC interventions should be prioritized in LMICs taking into account the context (overcrowding, no isolation facilities, poor infrastructure, low availability of PPE, water and sanitation issues) and limited financial resources	94	37	6
2 How can we bring about sustainable behavior change among doctors and other health care professionals with regard to managing infections and prescribing antibiotics?	65	14	4
3 Can diagnosis of infections be improved and made more rapid, ideally available at the point of care?	59	24	3
4 What is the prevalence of AMR/ What are the antimicrobial susceptibility patterns of infections encountered in my institution/country/region? Includes distinguishing community from hospital acquired	51	64	3
5 What is the role of improved information patient management systems including electronic prescribing, to tackle AMR?	51	2	3
6 What is the most appropriate methodology to assess the mortality/burden of AMR?	49	1	3
7 What is the role of combination antibiotic therapy to treat or prevent drug-resistant infections?	43	11	3
8 What is the potential impact of vaccines to reduce AMR?	42	5	3
9 Can more rapid methods be developed, e.g., an affordable POCT that can diagnose drug resistant infections	38	53	2
10 Will improved diagnosis lead to appropriate antimicrobial use and a reduction in AMR?	36	7	2

^a The ranking score was derived by combining the rankings of the individual steering group members (first preference is given 20 points; tenth preference 11 points).

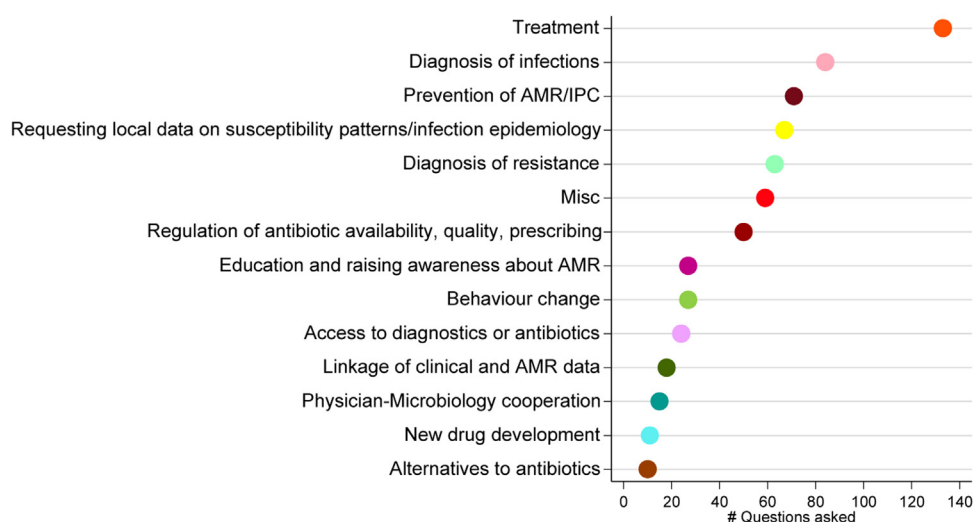


Fig. 3. Number of questions asked by theme. 659/1076 questions could be classified into a theme. 417 questions were excluded.

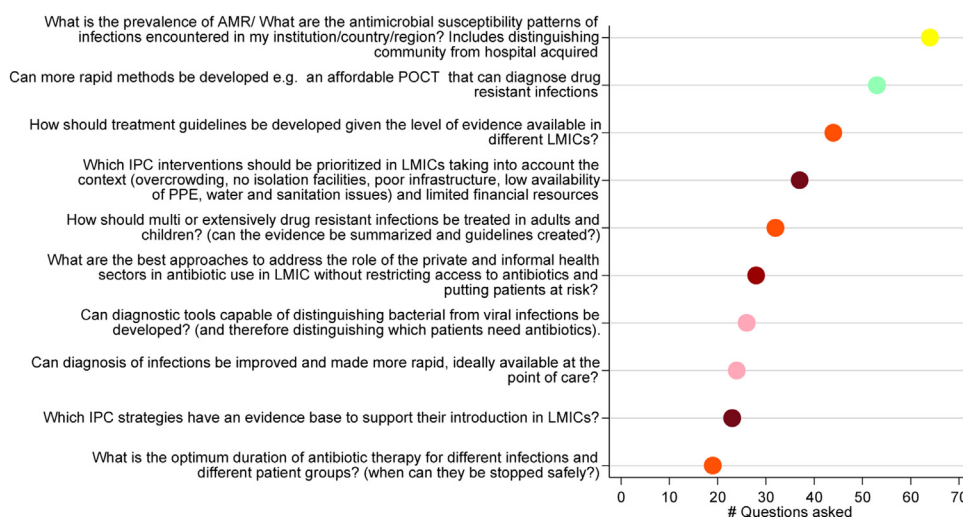


Fig. 4. Top 10 number of mapped questions asked by survey respondents. Marker color reflects theme (see Fig. 3).

3.3. Results of final prioritization-

To make the final prioritization, the Steering Group reviewed the top 10 questions according to the predefined criteria. The final prioritization of three questions for further research and prioritization for funding were:

1. **Which IPC interventions should be prioritized in LMICs, taking into account the context (overcrowding, no isolation facilities, poor infrastructure, low availability of PPE, water, and sanitation issues) and limited financial resources?** This was considered a high priority because there are significant knowledge gaps, and it is an area where most approaches implemented in high-income settings are not feasible in lower-income settings. Case-definitions of HCAs used in high-income countries are difficult to operationalize in LMICs because they frequently require more investigations such as radiology and blood testing that add to healthcare costs. Adapted definitions and surveillance methods may be needed. Some IPC interventions can be introduced without laboratory surveillance.
2. **What is the role of improved information patient management systems, including electronic prescribing, to tackle AMR?** The highest priority in LMICs was considered to be laboratory information systems in the next 3–5 years with electronic patient records showing potential as tools for AMR and antimicrobial use (AMU) surveillance in the longer term.
3. **How can we bring about sustainable behavior change among doctors and other health care professionals concerning managing infections and prescribing antibiotics?** The steering group identified this as another high priority area, however, the focus should be aligned with the objective of improving AMR surveillance and data. Targeting diagnostic stewardship, specifically changing clinician behavior when requesting blood cultures, was recommended.

Development of diagnostics was not prioritized by the group because several other stakeholders (commercial interests, non-profit organizations, e.g., FIND, and academic organizations) are working on diagnostic development, including improvements to existing methods, novel markers, transcriptomic signatures, and leapfrog technologies. Making a significant breakthrough within three to five years was also judged to be unlikely.

Generating local data and network strengthening was also not prioritized because providing guidance on AMR surveillance is one of the normative functions of the WHO. Strengthening laboratory AMR surveillance in LMICs is the primary goal of the UK aid program, the Fleming Fund, and several countries have received grants to build and strengthen their surveillance capacity.

4. Discussion

The results of our survey revealed that many clinicians in LMICs lack AMR data from their local area with the top question ($n=64$) being a request for basic surveillance data at the local or country level. Most responses were about the treatment of drug-resistant infections ($n=133$). This included questions about antibiotic stewardship, but typically respondents were asking for guidance on optimal treatment of drug-resistant infections in their patients. There are global treatment guidelines for malaria, tuberculosis, and HIV and for some specific syndromes requiring antibiotics, published by the WHO, but as yet there are no comprehensive treatment guidelines for drug-resistant bacterial or fungal infections. Given the differing epidemiology of AMR between institutions, regions, and nations, issuing a comprehensive global treatment guideline would be challenging. However, authoritative evidence reviews of the treatment of drug-resistant infections

would be useful, and guidelines could also be used by countries to facilitate access to second-line antimicrobial treatments.

Another common theme was a call for improved diagnostics. The most common questions expressed a need for more rapid diagnostic tests, ideally at the point of care, both to distinguish bacterial from viral infections and to diagnose drug-resistant infections more quickly. Laboratory diagnoses of infections in most LMICs, where it exists, rely on conventional bacteriology and an array of immunochromatographic tests that frequently lack sensitivity or are not well-validated. There have been major advances in the development of close to point-of-care molecular diagnostics direct from patient samples in recent years, including a small number of tests for drug resistance such as the Cepheid GeneXpert® testing platform (MRSA from superficial swabs, *N. gonorrhoeae* and *C. trachomatis* from vaginal or urethral swabs, respiratory virus PCRs from nose or throat swabs and carbapenemase genes from cultured isolates) and the BioFire® FilmArray® panels (meningitis/encephalitis, gastrointestinal infections, respiratory infections, blood culture identification including AMR genes). However, these are not accessible to most patients in LMICs because of high unit cost (15–200USD/patient depending on the number of targets). Furthermore, molecular diagnostic methods do not always lead to a definitive diagnosis. Clinical presentations with respiratory illness are one of the main drivers of antibiotic prescription, but reliable etiological diagnosis of bacterial pneumonia by nasopharyngeal sampling is still very challenging, as demonstrated in the Pneumonia Etiology Research for Child Health (PERCH) study. ([Pneumonia Etiology Research for Child Health Study, 2019](#))

Infection prevention and control remain relatively neglected in LMICs. The most high profile global initiative is the “Save Lives: Clean your Hands” campaign of the WHO. Uptake of good hand hygiene practices varies in all countries but is very low in many LMICs where there is poor access to soap and water or alcohol gel in many areas. Other interventions practiced in high-income countries, e.g., terminal cleaning of patient bed areas on discharge from hospital, cleaning mattresses and curtains, patient isolation, use of personal protective equipment, screening for carriage of antimicrobial-resistant bacteria, HCAI surveillance, outbreak investigation, policy development, hand hygiene, and other IPC audits require a level of resources that is not available in most LMICs. Survey respondents asked for guidance on which IPC interventions should be prioritized in the LMIC context. The steering committee considered this to be a high priority area for research given the lack of evidence, the potential impact for reducing AMR, and the fact that HCAI surveillance can be performed without a laboratory. None of the questions mentioned surveillance or prevention of healthcare-associated infections, which suggests that awareness of these is still too low, especially given the burden in LMICs ([Allegranzi et al., 2011](#)). Good case-definitions adapted to LMIC contexts are needed.

Development of actions to promote behavior change to tackle AMR falls under objective 1 of the global action plan on AMR (Improve awareness and understanding of antimicrobial resistance through effective communication, education, and training). Many behavior-change initiatives targeting healthcare professionals focus on antimicrobial prescribing/stewardship and hand hygiene. Behavior change that could be prioritized to lead to improved surveillance data is in the area of diagnostic stewardship, for example, finding ways to achieve appropriate requesting of blood cultures in patients, and avoiding selection bias.

Improving data management was mentioned by a low number of survey respondents but was considered a high priority by the steering group. In general, the survey respondents focused on having access to data rather than the mechanisms needed to acquire it. Linkage of laboratory and clinical data is an aspiration in

most LMICs at present and unlikely to be achieved in the short term, with most hospitals still using paper-based systems. The development of open access laboratory information management systems is more likely to be achievable ahead of the widespread implementation of electronic patient records.

Strengths of this PSP include canvassing opinion from stakeholders based in LMICs- i.e., the clinicians and pathologists involved in patient care, using open-ended questioning, and translating the questionnaire into French and Spanish. Limitations include the lack of respondents from surgical specialties, poor uptake by non-Anglophone respondents, and the fact that the survey was only available in three languages. A number of responses fell outside the survey's scope and did not follow the instructions, suggesting it was not well understood by all participants despite pilot testing.

AMR is a complex and multidimensional topic. Increased awareness and funding for AMR research mean there is now a lot of activity on this subject, but there have been many different approaches to the problem. Here we have given an example of one approach to setting human health priorities in LMICs when tackling AMR. We propose three high priorities for research: infection prevention and control, improved information management, and behavior change among healthcare providers.

Conflict of interest statement

None declared

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Ethical approval

The survey was discussed with the Oxford Tropical Ethics Committee (OxTREC), who reviewed the content and advised it was exempt from the ethics committee review.

Data sharing statement

Survey data are available as supplementary material

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Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at <https://doi.org/10.1016/j.ijid.2020.05.121>.

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