Availability, scope and quality of monkeypox clinical management guidelines globally: a systematic review

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ABSTRACT
Background Monkeypox (MPX) is an important human Orthopoxvirus infection. There has been an increase in MPX cases and outbreaks in endemic and non-endemic regions in recent decades. We appraised the availability, scope, quality and inclusivity of clinical management guidelines for MPX globally.

Methods For this systematic review, we searched six databases from inception until 14 October 2021, augmented by a grey literature search until 17 May 2022. MPX guidelines providing treatment and supportive care recommendations were included, with no exclusions for language. Two reviewers assessed the guidelines. Quality was assessed using the Appraisal of Guidelines for Research and Evaluation II tool.

Results Of 2062 records screened, 14 guidelines were included. Overall, most guidelines were of low-quality with a median score of 2 out of 7 (range: 1–7), lacked detail and covered a narrow range of topics. Most guidelines focused on adults, five (36%) provided some advice for children, three (21%) for pregnant women and three (21%) for people living with HIV. Treatment guidance was mostly limited to advice on antivirals; seven guidelines advised cidofovir (four specified for severe MPX only); 29% (4/14) tecovirimat, and seven guidelines advised cidofovir (four specified for severe MPX only); 29% (4/14) tecovirimat, and three (21%) for people living with HIV. Treatment advice for children, three (21%) for pregnant women and people living with HIV or on immunosuppression. Only one guideline produced by Nigeria Centre for Disease Control provided more detailed guidance on the management of acute MPX and secondary complications, such as bacterial infection, bronchopneumonia, encephalitis, keratitis and psychological complications.

Conclusion Our results highlight a lack of evidence-based clinical management guidelines for MPX globally. There is a clear and urgent need for research into treatment and prophylaxis including for different risk populations. The current outbreak provides an opportunity to accelerate this research through coordinated high-quality studies. New evidence should be incorporated into globally accessible guidelines, to benefit patient and epidemic outcomes. A ‘living guideline’ framework is recommended.

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WHAT IS ALREADY KNOWN ON THIS TOPIC
⇒ Monkeypox (MPX) virus is endemic in parts of Central and West Africa, with an increase in cases and outbreaks in traditionally endemic and new regions in the past decades. For most people MPX causes a mild disease. According to limited data, the case fatality rate depends on the clade, with estimates from earlier outbreaks in Africa ranging from 1.0% to 10.6%, with the highest risk observed in younger children. Antivirals and vaccines against smallpox/MPX are available, but their efficacy and their optimal use is unclear, and they are not widely available globally.

WHAT THIS STUDY ADDS
⇒ We identified a lack of evidence-based clinical management guidelines to guide clinical decision-making for patients diagnosed with MPX. Most identified guidelines were of poor methodological quality, lacked detail and covered a narrow range of topics. Recommendations on use of antivirals and vaccines varied, and there were limited recommendations for different risk groups, such as children, pregnant women and people living with HIV or on immunosuppression. Only one guideline produced by Nigeria Centre for Disease Control provided more detailed guidance on the management of acute MPX and secondary complications, such as bacterial infection, bronchopneumonia, encephalitis, keratitis and psychological complications.

INTRODUCTION
Monkeypox (MPX) is a zoonotic disease caused by an Orthopoxvirus belonging to the same genus as smallpox. The MPX virus was discovered in 1958,1,2 with the first human infection identified in 1970 in the Democratic Republic of Congo (DRC).3 Since then human MPX has mostly been reported in Central and Western African countries. Two
Febrile illness, headache, tonsillitis, cough, myalgia and fatigue. A vesicular–pustular illness, which may be preceded by psychological symptoms. Younger children and pregnant women are at higher risk of severe disease. The incubation period is up to 21 days. Interactions with infected animals and individuals is associated with risk of infection. Human-to-human transmission occurs through direct contact (body fluids, skin lesions, mucosal surfaces, respiratory droplets), indirectly (contaminated objects) and vertically from mother-to-fetus through the placenta.

**METHODS**

This is a systematic review of the availability, inclusivity, scope and quality of clinical management guidelines for MPX. We included guidelines that provided advice on treatment or supportive care for MPX. This study is nested within an extensive systematic review of supportive care and clinical management guidelines for high consequence infectious diseases. The study is registered with the prospective international register of systematic reviews (PROSPERO) and follows the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines on the conduct of systematic reviews.

**Search strategy**

We searched Ovid MEDLINE, Ovid Embase, Ovid Global Health, Scopus, Web of Science Core Collection and WHO Global Index Medicus from inception until 14 October 2021, using predefined Medical Subject Headings words (online supplemental file 1). Search strategies applied the Canadian Agency for Drugs and Technologies in Health database guideline search filter. No limits were applied to the search results. We augmented this with an extensive grey literature search in Arabic, English, French, German, Mandarin, Russian and Spanish using Google and Google Scholar, until 17 May 2022. The full....
search strategy is shown in the online supplemental material.

**Eligibility criteria**
Guidelines that included advice on treatment and supportive care for MPX were included. Guidelines that purely focused on public health or diagnostics were excluded if they did not provide any treatment advice. Local hospital standard operation protocols were excluded as per our systematic review protocol, we made no exclusions on languages.

**Screening and data extraction**
Two reviewers independently screened the guidelines for inclusion and extracted data using Rayyan systematic review software. Data were extracted using a standardised form, previously piloted for related reviews. For each guideline data on source, target population and clinical topics (treatment and supportive care) were extracted (online supplemental file 2). Disagreements were resolved via consensus or by a third reviewer. For non-English guidelines, team members with good to excellent knowledge of the language assessed the guidelines.

**Quality appraisal**
Two reviewers independently appraised the quality using the Appraisal of Guidelines for Research and Evaluation II (AGREE II) Instrument. The AGREE II tool provides an objective framework which assesses the guideline quality based on the development process, it does not assess the validity of recommendations. The tool consists of six domains and two global ratings. The six domains are: scope and purpose, stakeholder involvement, rigour of development, clarity of presentation, applicability and editorial independence. The score was completed by two independent assessors. There are several subcriteria within each domain which are scored based on whether the criteria are met using a 7-point Likert scale, from 1 (strongly disagree) to 7 (strongly agree). A score of 1 is given when there is no information relevant to the AGREE II item provided. Guidelines were assessed as of high quality if they scored more than 60% in at least three domains including domain three (rigour of development), as this is considered a high-quality indicator. They were assessed as of moderate quality if they scored more than 60% in at least three domains, but not in domain three and low if they did not reach any of these criteria. Graphics were produced using R V.4.0.2.

**Patient and public involvement**
There was no public or patient involvement in the course of this project due to the pandemic constraints.

**RESULTS**
Of the 2026 records screened, 14 guidelines met the eligibility criteria for inclusion (figure 1). Forty-three per cent (6/14) were aimed for global use, 21% (3/14) for Asia, 21% (3/14) for Europe, 7% (1/14) for Africa and 7% (1/14) for North America (table 1). Most were produced by organisations in high-income or upper-middle-income countries. Eighty-six per cent (12/14) were in English, 14% (2/14) in Mandarin. There was a lack of comprehensive clinical management guidelines identified, only one guideline, which was produced by the Nigerian Centre for Disease Control (NCDC) provided more detailed guidance including detailed recommendations on supportive care and treatment of complications. The guidelines made limited provision for different risk groups such as children, pregnant women and people living with HIV or immunocompromised patients.

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**Figure 1** Preferred Reporting Items for Systematic Reviews and Meta-Analyses flowchart. Abbreviations: CMG: Clinical Management Guidelines
Quality assessment

Overall quality was low (figure 2). The median overall quality was 2 out of 7 points (range: 1–7). Only one guideline was assessed as of high quality. The domain that scored the highest across the guidelines was clarity of presentation (median (IQR): 61% (50–64%)). Domains in which all of the guidelines scored poorly in were rigour of development (median (IQR): 16% (8–20%)), applicability (median (IQR): 15% (12–21%)), scope and purpose (median (IQR): 19% (19–42%)), stakeholder involvement (median (IQR): 22% (19–44%)) and editorial independence 0% (0–33%). The low score for certain domains, such as editorial independence, may be partly due to a lack of information provided. We observed a lack of documentation of the methodology used to develop the guidance, few guidelines used systematic reviews and clear links to evidence were lacking. Often clinical guidance was embedded within a document that primarily focused on infection control. Only two guidelines stated that the guidelines would be updated as new evidence became available.

Treatment recommendations

Generally, the clinical recommendations provided by the guidelines were non-specific and covered a narrow range of topics (table 2). Guidance varied, such as in recommendations on the type of antiviral drugs to consider, and type of vaccine for prophylaxis. Seven guidelines advised cidofovir, with four noting that it should only be considered in people presenting with severe illness (table 3). One guideline advised the use of brincidofovir as an alternative, citing an improved safety profile over cidofovir. Three guidelines advised tecovirimat or cidofovir whereas a more recent guideline produced by the WHO only advised tecovirimat as part of a clinical research study. None of the guidelines provided further details to guide optimal timing of treatment, dosage and duration. Two guidelines advised that vaccina immune globulin (VIG) may be considered in severe cases. Two guidelines recommended the use of antibiotics for the treatment of secondary complications (table 4).
The guideline produced by the NCDC was the only one providing recommendations on supportive care and treatment of complications, such as secondary infections and sepsis, bronchopneumonia, encephalitis, ophthalmology and psychological complications, including advice on treatments and referrals for further specialist assessments when indicated. Empirical oral or parenteral cephalosporins or beta-lactam antibiotics were recommended for the treatment of secondary bacterial infections (eg, boils, abscesses, skin dermatitis). Empirical broad-spectrum

| Table 2 | Overview of the recommendations provided in the guidelines |
|---|---|---|---|---|---|
| Guideline | Country | Year | Symptom management | Antivirals | Antibiotics | Prophylaxis |
| China (MoH) | China | 2003 | R | NS | R* | R |
| Dermatology Advisor | Global | 2017 | NS | C | NS | R |
| DermNet | Global | 2014 | NS | C | NS | R |
| ECDC | Europe | 2019 | NS | NS | NS | R |
| eMedicine | Global | 2020 | NS | C | NS | R |
| Ireland HPSC | Ireland | 2021 | NS | C | NS | R |
| Medscape | Global | 2019 | R | NS | NS | R |
| NCDC | Nigeria | 2019 | R | NS | R* | R |
| PHE/UKHSA | England | 2019 | NS | C | NS | R |
| Singapore FETP | Singapore | 2020 | NS | NS | NS | R |
| Taiwan CDC | Taiwan | 2009 | NS | NS | NS | R |
| UpToDate | Global | 2021 | R | C | NS | R |
| US CDC | USA | 2018 | NS | C | NS | R |
| WHO | Global | 2019 | NS | C | NS | R |

*If secondary complications; C, considered; NS, not specified; R, recommended.

CDC, Centers for Disease Control; ECDC, European Centre for Disease Control and Prevention; FETP, Singapore Field Epidemiology Training Programme; HPSC, Health Protection Surveillance Centre; MoH, Ministry of Health; NCDC, Nigeria Centre for Disease Control; PHE, Public Health England; UKHSA, UK Health Security Agency.

| Table 3 | Recommendations on use of antivirals |
|---|---|---|---|---|
| Guideline | Country | Year | Antivirals | Indications |
| China (MoH) | China | 2003 | NS | NA |
| Dermatology Advisor | Global | 2017 | Cidofovir | For severe cases only, due to risk of nephrotoxicity |
| DermNet | Global | 2014 | Cidofovir | Severe cases |
| ECDC | Europe | 2019 | NS | NS |
| eMedicine | Global | 2020 | Cidofovir | Severe life threatening cases |
| Ireland HPSC | Ireland | 2021 | NS | NS |
| Medscape | Global | 2019 | Cidofovir | NS |
| NCDC | Nigeria | 2019 | NS | NA |
| PHE/UKHSA | England | 2019 | Cidofovir, tecovirimat | NS |
| Singapore FETP | Singapore | 2020 | NS | NS |
| Taiwan CDC | Taiwan | 2009 | NS | NS |
| UpToDate | Global | 2021 | Cidofovir, tecovirimat | Cidofovir: risk of nephrotoxicity |
| US CDC | USA | 2018 | Cidofovir, brincidofovir, tecovirimat | Consider cidofovir and brincidofovir in severe cases |
| WHO | Global | 2019 | Tecovirimat | Only as part of clinical research |

An overview of the antiviral treatments recommended to consider in monkeypox. None of the guidelines provided further indications to guide optimal timing, dose or duration of treatment.

CDC, Centers for Disease Control; ECDC, European Centre for Disease Control and Prevention; EMA, the European Medicines Agency; FETP, Singapore Field Epidemiology Training Programme; HPSC, Health Protection Surveillance Centre; MoH, Ministry of Health; NCDC, Nigeria Centre for Disease Control; NS, not stated; PHE, Public Health England; UKHSA, UK Health Security Agency.
antibiotics were advised for bronchopneumonia and encephalitis. In patients with encephalitis, they further advised close monitoring of nutrition/hydration and consideration of nasogastric feeding for unconscious patients and anticonvulsants for seizure control. Supportive care recommendations covered the management of rashes, pruritus and ulcers (antiseptic cleaning, saline baths, antihistamines); antipyretics (paracetamol, NSAID) to manage fever and pain, and metoclopramide (intravenous) for adults and chlorphenamine syrup for children for nausea and vomiting. For dehydration, they advised using oral rehydration salts, particularly in children and intravenous fluids (0.9% saline or dextrose) as indicated. The guideline also recommends screening of patients’ psychological health status on and during the admission, and to refer to a specialist if indicated. Further, recommendations to include a licenced mental health practitioner in the treatment team.

Table 4  Recommendations on use of antibiotics and immunoglobulins

| Guideline | Country | Year | Antibiotics | Indications | Immunoglobulins | Indications |
|-----------|---------|------|-------------|-------------|----------------|-------------|
| China (MoH)54 | China | 2003 | R | Secondary bacterial infections. | NS | – |
| Dermatology Advisor47 | Global | 2017 | NS | – | VIG | Consider in severe infection. |
| DermNet48 | Global | 2014 | NS | – | NS | – |
| ECDC56 | Europe | 2019 | NS | – | NS | – |
| eMedicine49 | Global | 2020 | NS | – | NS | Notes that VIG has not shown efficacy for treatment. |
| Ireland HPSC53 | Ireland | 2021 | NS | – | NS | – |
| Medscape51 | Global | 2019 | NS | – | NS | Notes that VIG has not shown efficacy in treatment. |
| NCDC44 | Nigeria | 2019 | R | Secondary bacterial infections cefuroxime 500 mg two times, 5 days (oral/parenteral) or ceftiraxone intravenous 1 g, 5 days or B-lactam antibiotics (amoxyl/clavulanic acid, 625 mg x2/day, ≥5 days. | NS | – |
| PHE/UKHSA52 | England | 2019 | NS | – | NS | – |
| Singapore FETP46 | Singapore | 2020 | NS | – | NS | – |
| Taiwan CDC55 | Taiwan | 2009 | NS | – | NS | – |
| UpToDate50 | Global | 2021 | NS | – | NS | – |
| US CDC55 | USA | 2018 | NS | – | VIG | Can be considered in severe cases. |
| WHO18 | Global | 2019 | NS | – | NS | – |

CDC, Centers for Disease Control; ECDC, European Centre for Disease Control and Prevention; FETP, Singapore Field Epidemiology Training Programme; HPSC, Health Protection Surveillance Centre; MoH, Ministry of Health; NA, not applicable; NCDC, Nigeria Centre for Disease Control; PHE, Public Health England; UKHSA, UK Health Security Agency; VIG, vaccinia immune globulin.

Recommendations on pre-exposure and post-exposure prophylaxis

The older generation smallpox vaccines is no longer part of routine immunisation programmes. There have been several developments of modified smallpox vaccines in recent years, including second generation vaccines such as ACAM2000 which was recommended for post-exposure prophylaxis (PEP) in three guidelines (table 5). A third-generation vaccine, commonly...
## Table 5: Recommendations on pre-exposure and post-exposure prophylaxis

| Guideline                | Country     | Year  | Vaccination               | Indications                                                                                           | Immunoglobulins | Indications                                                                 |
|--------------------------|-------------|-------|---------------------------|-------------------------------------------------------------------------------------------------------|-----------------|-----------------------------------------------------------------------------|
| China (MoH)              | China       | 2003  | A smallpox vaccine        | Individuals after contact with suspected animal or human case.                                        | NS              | –                                                                           |
| Dermatology Advisor      | Global      | 2017  | A smallpox vaccine        | Individuals at risk of infection prior to exposure. Contraindication: immunocompromised individuals, that is, T-cell deficiency, HIV with CD4 <200, or by medication. | VIG             | In immunocompromised patients. Notes that VIG should only be used in severe disease. |
| DermNet                  | Global      | 2014  | A smallpox vaccine        | All healthcare workers and all close contacts with infected cases.                                      | NS              | –                                                                           |
| ECDC                     | Europe      | 2019  | MVA-BN/Imvanex            | NS.                                                                                                   | NS              | –                                                                           |
| eMedicine                | Global      | 2020  | ACAM2000 and Jynneos      | ≤2 weeks, ideally ≤4 days. Exposed healthcare workers, household contacts of confirmed cases. Note: for ACAM2000 avoid risk of spread from inoculation site to other sites and individuals. | NS              | Notes that VIG has not shown efficacy as prophylaxis.                      |
| Ireland HPSC             | Ireland     | 2021  | Vaccinia, Imvanex (third generation) | Imvanex for healthcare workers, close contacts including in outbreak settings and first responders. Can be used for individuals for whom previous smallpox vaccinations were contraindicated. | NS              | –                                                                           |
| Medscape                 | Global      | 2019  | Jynneos, ACAM2000        | Exposed healthcare workers and household contacts of confirmed cases. Note: care to avoid spread from inoculation site (ACAM 2000). | NS              | Notes that VIG has not shown efficacy as prophylaxis.                      |
| NCDC                     | Nigeria     | 2019  | ACAM2000, Imvamune (third generation) | NS.                                                                                                   | NS              | –                                                                           |
| PHE/UKHSA                | England     | 2019  | A smallpox vaccine        | NS.                                                                                                   | NS              | –                                                                           |
| Singapore FETP           | Singapore   | 2020  | A smallpox vaccine        | Post-exposure prophylaxis within 4 days, up to 14 days.                                               | NS              | –                                                                           |
| Taiwan CDC               | Taiwan      | 2009  | Vaccinia                  | People who care for sick patients, or animals, study the virus or MPX epidemics who have not been vaccinated, should be vaccinated. | NS              | –                                                                           |
| UpToDate                 | Global      | 2021  | MVA, Imvamune and Jynneos| Contacts (expect immunocompromised patients).                                                          | VIG             | If immunocompromised                                                        |
| US CDC                   | USA         | 2018  | Jynneos (Imvamune, Imvanex) | For contacts of cases.                                                                                  | VIG             | If severe immunodeficiency, T-cell dysfunction if smallpox vaccination is contraindicated. |

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Known as Imvamune/Imvanex or Jynneos was recom-
mended for PEP by seven guidelines. Only two guide-
lines provided advice on the optimal timing of PEP.46 49
The guidance on PEP for different at risk populations
were limited and at times conflicting. Two guidelines
provided advised on PEP in children and pregnant
women,50 one stating that although smallpox vaccination
may be contraindicated in pregnancy, age and a history
of eczema in the pre-
event context, they can be used with
care in the event of exposure.47 Another guideline
advised against vaccination of infants (<1 years old) and
pregnant women.45 Two guidelines specifically recom-
mended against the use of the vaccinia smallpox vaccine
in people with immunosuppression (ie, in people with
HIV and a CD4 counts <200, or on chemotherapy).45 47

The guidance on the use of VIG was contradictory. Three
guidelines advised considering VIG in individuals with
compromised immune function47 50 55 whereas two guide-
lines did not provide any recommendations on its use,
but advised that data on its effectiveness for treatment
and PEP is lacking.6 Six guidelines recommended
immunisation of people at risk of MPX exposure such as
healthcare workers.48 49 51 53–55

Table 5 Continued

| Guideline | Country | Year | Vaccination | Indications | Immunoglobulins | Indications |
|-----------|---------|------|-------------|-------------|-----------------|-------------|
| WHO18     | Global  | 2019 | A smallpox vaccine | NS.         | NS              | –           |

MVA- BN, Modified Vaccinia Ankara - Bavarian Nordic; CDC, Centers for Disease Control; ECDC, European Centre for Disease Control and Prevention; FETP, Singapore Field Epidemiology Training Programme; HPSC, Health Protection Surveillance Centre; MoH, Ministry of Health; MPX, monkeypox; NCDC, Nigeria Centre for Disease Control; NS, not stated; PHE, Public Health England; UKHSA, UK Health Security Agency; VIG, vaccinia immune globulin.
the WHO guideline advised to consider tecovirimat. Similar variations in guidance were observed for PEP, with more recently updated guidelines advising use of the newer generation smallpox/MPX vaccines.44 49–51 53 55 56 This highlights a fundamental issue in the development of guidelines for the management of neglected infectious diseases, which was also observed in other reviews.42 57 We observe a tendency of guidelines being developed rapidly in response to outbreaks, never to be revisited again, and still being available in public domains. Failure to recall out-of-date guidelines as new evidence emerges, pose a risk to patient care. Few guidelines report mechanisms for updates or monitoring.

Our review also identified a concerning lack of guidance on the treatment and PEP, and at times contradictory advice, for different population groups such as children, pregnant women and people living with immunosuppression, which could exacerbate their vulnerability in outbreaks.

Variations in the recommendations may reflect that some guidelines were produced before newer treatments and vaccines were authorised in various regions. Most are only authorised in a limited number of countries. This may also partly explain some of the variations in recommendations identified between guidelines, and raises important questions on equity in access to best available care worldwide. Considering MPX is a mild disease in most, there was a surprising lack of advice on the management based on the severity of illness. Only one guideline identified, produced by NCDC, gave detailed supportive care recommendations, including on the management of symptoms and secondary complications, such as bacterial infections, encephalitis, ophthalmological and psychological conditions.41 Many guidelines were positioned within public health guidance, which may partly explain the limited details provided to guide treatment and patient management. There is an argument for combining clinical management and hospital infection control advise to protect healthcare workers and reduce risk of nosocomial transmission. This requires that the guidance is supported by evidence, as the implementation of control measures may have wide direct and indirect impact on healthcare systems, especially in resource constraint settings and context.

Even with a limited evidence base, clinical management guidelines are important tools for guiding decision-making and to reduce risk of inappropriate treatments. The variation seen, and the lack of recommendations for high-risk populations underline the importance of a gold standard framework for guideline development. The lack of clarity between guidelines creates uncertainty for clinicians treating patients with MPX which may impact patient care. This review is not without its limitations. First, most guidelines were published as grey literature, and although we made an extensive search in different languages, we may have missed additional guidelines available. Second, even though guidelines that required translations were assessed by a reviewer with good knowledge of the language, there is a risk that finer nuances may have been lost in translation. Third, the AGREE II tool was primarily designed for guidelines produced in non-emergent settings, and although we are confident of its applicability to a variety of settings, it may contribute to the lower average quality scores. Finally, the quality assessment focuses on the development process, but does not assess the validity of the recommendations. Nevertheless, we identified limited availability of comprehensive clinical management guidelines for people affected by MPX, which may have impact on patient care.

Our study highlights a need for a rigorous framework for producing guidelines ahead of epidemics and a recognised platform for rapidly reviewing and updating guidance during outbreaks, as new evidence emerges. Human MPX is providing a challenge even in high-resource settings with well-resourced healthcare systems. The lack of guidelines may especially impact clinics with limited previous experience in managing patients with MPX. Given the recent global publicity surrounding MPX, this is an opportune moment for harnessing interest and investment for research into the efficacy of therapeutics and vaccines, to inform optimal treatment and prophylaxis strategies for the whole population.

Developing guidelines is resource intensive. The most comprehensive guideline identified was developed by a national public health organisation (NCDC) based in an endemic country.44 This emphasises the need for wide stakeholder involvement in guideline development, including experienced topic experts and affected communities. Guidelines developed by global organisations in collaboration with clinicians with experience in managing patients in different settings may be the optimal solution to improve quality, standardisation of recommendations and applicability. Ensuring that organisations that clinicians may turn to for guidance during outbreaks, such as the WHO, has the resources to provide the best possible guidelines and for these to be updated is important. A ‘living guideline’ framework for infectious disease is recommended to improve availability of up-to-date clinical management guidelines, developed using robust methodologies and inclusive of different at-risk populations. Urgent investments into research to identify optimal treatment and prophylaxis strategies are needed for the whole population, in any setting, to benefit patient care and outcomes.

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