CellPress
OPEN ACCESS

Trends in
Parasitology

Opinion

Defining schistosomiasis hotspots based on literature and shareholder interviews

Rivka M. Lim [1,*] Thomas M. Arme,[2] Amy B. Pedersen,[1] Joanne P. Webster,[3,4] and Poppy H.L. Lamberton[2,4]

The World Health Organization (WHO) recently proposed a new operational definition which designates communities with ≥10% prevalence of *Schistosoma* spp. infection as a persistent hotspot, when, after at least two rounds of high-coverage annual preventive chemotherapy, there is a lack of appropriate reduction. However, inconsistencies and challenges from both biological and operational perspectives remain, making the prescriptive use of this definition difficult. Here, we present a comprehensive analysis of the use of the term 'hotspot' across schistosomiasis research over time, including both literature searches and opinions from a range of stakeholders, to assess the utility and generalisability of the new WHO definition of a persistent hotspot. Importantly, we propose an updated definition based on our analyses.

Highlights

The World Health Organization (WHO) has recently published a draft definition of a persistent schistosomiasis hotspot, referring to, in brief, a location which satisfies specific prevalence and treatment intervention targets, but where transmission persists.

Inconsistencies between this draft WHO definition and those already used in published research and implementation manuals could, however, lead to confusion for program managers, with potential implications for who gets treated and how.

Using a comprehensive review of the literature, combined with interviews with stakeholders and an evaluation of each of the criteria in the draft WHO definition, we propose modifications to the definition of a persistent hotspot.

We suggest regional flexibility in some of the thresholds and highlight areas where more research is needed to enable a universal standardised definition.

'Schistosomiasis hotspot' is used to describe spatial heterogeneity in infection prevalence, intensity, and morbidity

Schistosomiasis is a debilitating water-borne **neglected tropical disease** (**NTD**) (see Glossary), which poses significant health and economic burdens in many countries, predominantly tropical and subtropical, across the world. Transmission is highly focalised and occurs through infection of definitive mammalian and intermediate freshwater snail hosts in a multihost life cycle. Heterogeneity in **prevalence**, **intensity**, and **morbidity** can be found at different geographic scales, with variance between countries, districts, villages, and even schools playing a key role in transmission dynamics [1–4]. This heterogeneity arises from a complex interplay between the definitive and intermediate hosts and their parasites [5], incorporating genetic, immunological, behavioural, socioeconomic, and environmental factors [4].

The current mainstay recommendation for schistosomiasis control is **mass drug administration** (**MDA**) of human populations in endemic countries, where treatment regimens are based on regional infection prevalence, and the anthelmintic drug **praziquantel** offered to at-risk members of the community regardless of infection status [6]. However, even with regular treatment campaigns and adequate coverage, the effectiveness and success of such interventions can vary significantly. Therefore, the concept of schistosomiasis hotspots has gained increasing attention in recent years [7,8]. The reason for these non/low-responding regions is often not clear, being most likely multifactorial, including transmission risk, for example, high baseline prevalence and/or intensity [9], high abundance of intermediate snail hosts [10,11], reservoir hosts [12,13], human behaviour [14–16], inadequate water, sanitation, and hygiene (WASH) infrastructures or access [17–19], as well as intrinsic drivers such as human [20] and parasite genetics [21,22].

In 2020, a new road map for NTDs and corresponding recommendations were released by the World Health Organization (WHO, which set ambitious targets to eliminate schistosomiasis as a

[1]Institute of Evolution and Ecology, School of Biological Sciences, Ashworth Laboratories, University of Edinburgh, Edinburgh, UK
[2]School of Biodiversity, One Health and Veterinary Medicine, Wellcome Centre for Integrative Parasitology, University of Glasgow, Glasgow, UK
[3]Department of Pathobiology and Population Sciences, Royal Veterinary College, University of London, Hatfield, Herts, UK
[4]These authors share joint senior authorship.

*Correspondence:
rivka.lim@ed.ac.uk (R.M. Lim).

public health problem [EPHP, defined as a reduction in prevalence of heavy intensity infections (≥400 eggs per gram of stool) to <1% [23]] by 2030 in all endemic countries, and interrupt transmission (IoT, defined as incidence of infection reduced to zero in humans [23]) in selected countries [24]. Persistent hotspots, which describe geographical regions where even with adequate treatment, an unacceptable level of infections persist after treatment, were recognised in the guidelines as a potential hurdle to gaining control of schistosomiasis. It was recommended that once a persistent hotspot was identified using WHO specific criteria (Box 1), MDA regimens should increase to treat the whole community twice a year [24]. However, the WHO proposed this preliminary definition while recognising the lack of scientific evidence surrounding the thresholds to defining a persistent hotspot. Without a standardised definition, there is often broad and sometimes ambiguous usage of the term hotspot, with little clarity around if it refers to schistosomiasis infection prevalence, intensity, morbidity, snail density, or even logistical and operational hotspots where **treatment coverage** is systematically low. These inconsistencies in describing persistent hotspots, and the draft nature of the WHO definition, means it is difficult to compare research and to identify drivers of hotspots, both of which are essential to enable development of effective control strategies which target these regions [7].

Therefore, the overarching goal of this perspective is to provide a comprehensive analysis of the use of the term *Schistosoma* 'hotspot' and to add clarity to the term's contextual usage in schistosomiasis research. If the WHO transmission, interruption, and elimination targets are to be met, persistent hotspots cannot be missed by potentially exclusionary thresholds of identification. Therefore, the prevalence and treatment targets in the WHO definition were compared with previous studies to determine the potential for these thresholds to exclude any persistent hotspots. Finally, using results from our analyses and interviews with stakeholders, we propose a definition guide to be used by the scientific community moving forward.

There is a lack of standardisation in the definition of a persistent hotspot

The Schistosomiasis Consortium for Operational Research and Evaluation (SCORE) was at the forefront of developing standardised definitions of a persistent hotspot in schistosomiasis. This conglomerate of researchers from around the world was established in 2008 with the goal of exploring strategic methods in the control and elimination of schistosomiasis. In an analysis which compared four distinct approaches to defining a persistent hotspot against a common dataset, they observed significant differences in the classification of the region as a hotspot [8]. These results suggested the choice of hotspot definition is critical in determining whether a region is identified as a hotspot or not. Members of the same consortium also conducted large-scale field studies in multiple countries across Africa to evaluate the impact of MDA strategies on disease transmission at the village level. However, within a proportion of villages (approximately 30%), in every country across the study, the prevalence and/or intensity of infection did not decline as anticipated after treatment [25–31]. The largest SCORE field study evaluated different intervention schedules to gain and sustain control of schistosomiasis [27,32], and these regions were used to assess potential predictors of a persistent hotspot and to evaluate definitions for persistent hotspots (Box 1).

Despite the proposal of persistent hotspot definitions by the WHO and SCORE (Box 1), discrepancies still, however, exist, thereby leading to difficulties in hotspot identification. Infection intensity was not included as a metric in the WHO definition, where instead their definition only included reduction thresholds for prevalence. The WHO guidelines for control and elimination of schistosomiasis do highlight that alternative definitions, which include changes in average intensity, could be considered [24], although a clear threshold has not been allocated for any intensity threshold change. Additionally, SCORE studies suggested an alternative definition when a region is nearing EPHP [33,34] (Box 1), something which is not yet addressed in the WHO definition. There are

Glossary

Cure rate: a measurement of the number of individuals in a population who are completely free of eggs in stool or urine after treatment.
Intensity: a quantitative measurement which infers the burden of disease at an individual level. Most often measured in *Schistosoma* spp. infection using a count of the eggs in the stool or urine.
Mass drug administration (MDA): distribution of medicines to all the community regardless of symptoms or infection status. Some predetermined exclusions may apply such as age, pregnancy etc.
Morbidity: evidence of detrimental impact on the health of an infected individual.
Neglected tropical diseases (NTDs): these diseases have limited resources to tackle them and are mostly ignored by global funding agencies.
Praziquantel: an antischistosomal drug which is most effective against the mature form of the worms.
Prevalence: a measurement based on whether parasitological analysis detects eggs or not from a host; it is used to give an estimate of how widespread the disease is.
Treatment coverage: the proportion of individuals in a population who took the treatment.

Box 1. SCORE and WHO have definitions of a persistent hotspot

In 2021, the WHO released new guidelines on the control and elimination of schistosomiasis, in which they proposed a definition of a persistent hotspot. The reduction threshold outlined in this definition was considered preliminary, due to lack of scientific evidence supporting these thresholds [24].

'Communities with prevalence of *Schistosoma* spp. infection ≥ 10% that demonstrate lack of an appropriate response to two annual rounds of preventive chemotherapy, despite adequate treatment coverage (≥75%). The lack of an appropriate response should be (provisionally) defined as a reduction in prevalence of less than one third relative to the baseline prevalence survey and a repeat prevalence survey completed after two annual rounds of preventive chemotherapy. The intervening period should include a minimum of two rounds of mass drug administration to all at-risk groups at adequate treatment coverage (≥75%). The relative reduction in prevalence can be estimated as follows: [(prevalence at baseline – prevalence at year 3)/(prevalence at baseline)]. The science around this threshold is still evolving; this definition is marked provisional for that reason but is nevertheless provided to encourage standardization of reporting.' [24].

This novel definition includes four criteria (Table I) which a geographical region needs to fit to be designated as a persistent hotspot and be eligible for biannual treatment. The importance of correct allocation of these regions is critical to community quality of life and use of limited resources. Although these are the four main criteria within the proposed definition, the guidelines also recognised the need to account for epidemiological heterogeneity where different reduction metrics could be utilised such as calculation of absolute reduction in prevalence and intensity. However, prescriptive guidelines and thresholds for these were not stated in the manual, thus making it difficult to disseminate to local governments and program managers.

The Schistosomiasis Consortium for Operational Research and Evaluation (SCORE) conducted five randomised control studies in four countries, Cote d'Ivoire, Kenya, Mozambique, and Tanzania. The sustaining control studies focused on communities which had a baseline *S. mansoni* prevalence of 10–24%, these studies contained three arms with 25 villages in each. Each arm consisted of treatment by MDA in school children either annually for 4 years, annually for 2 years, then MDA holiday for 2 years, or MDA every other year [27]. The gaining control studies were carried out in villages with ≥25% prevalence of either *S. mansoni* or *S. haematobium.* These contained six arms, with the same MDA schedules as sustaining studies but with both school and community-based treatment regimens [32]. Both prevalence and intensity of infection were monitored each year of the studies.

The results of these studies found that in at least 30% of villages in all arms, the targets for a reduction in prevalence of at least 35% and or intensity of at least 50% were not met. These persistent hotspot villages were found in both the moderate (sustaining) and highly (gaining) endemic regions and some had above the target threshold for treatment coverage (>75%) [33].

Using data from the Zanzibar elimination study [34,60], the researchers were able to study hotspots in regions that had low infection prevalence. This randomised control study was conducted over 5 years and included 90 study areas (shehias) across three study arms. All arms used biannual MDA and one also included snail control and the other behavioural intervention. The authors of this study [34] and other SCORE researchers who were focussed on studying and defining persistent hotspots [33] both suggested a different approach in regions where prevalence was low and instead of measuring a relative change in prevalence from baseline, they opted for a set change from ≥10% prevalence at baseline to ≥5% after treatment being deemed a persisted hotspot.

Following these studies, the authors proposed several criteria for a persistent hotspot (Table II), considering the control stage of the region (control or elimination), the geographic region (rural, peri-urban, or urban), and local resources needed to identify potential risks, two of which relating to control are shown in Table II [33]. These definitions were developed with the goal of standardising the identification of persistent hotspots and assisting program managers in selecting appropriate control strategies for their respective regions [33].

Table I. Criteria set out by WHO to define a persistent hotpot

Criteria	Threshold
Baseline prevalence	≥10%
Previous preventive chemotherapy	2 rounds
Coverage at both rounds	≥75%
Reduction in prevalence	<1/3

Table II. Definitions of persistent hotspots proposed by SCORE field studies[a,b]

SCORE study	Definition of PHS	Study notes
Sustaining and gaining control studies [27,32]	Villages that failed to achieve at least a 35% decrease in prevalence relative to baseline and/or a 50% decrease in infection intensity relative to baseline after 4 years of MDA, either annually or twice in 4 years	Sustaining: Cote d'Ivoire and Kenya, starting prevalence 10–24%, three study arms, 25 villages. Gaining: Kenya, Mozambique, and Tanzania. Areas starting prevalence of ≥ 25%, six study arms, 25 villages.
Zanzibar elimination study [34,60,73]	Shehias with a prevalence ≥ 10% at baseline and ≥ 5% at the end of the study	90 shehias, three study arms.

[a]Abbreviations: PHS, persistent hotspots; SCORE, Schistosomiasis Consortium for Operational Research and Evaluation.
[b]Table adapted from [33].

also discrepancies between the reduction thresholds used in each of these studies and definitions, and although the WHO recognise the need for different metrics, they do not suggest what these thresholds might be. Therefore, to use this definition of a persistent hotspot as prescriptive to control strategies, clarity and potentially locally relevant flexibility in some of the thresholds is needed and will be addressed in this opinion piece.

Use of the term 'hotspot' in the schistosomiasis literature

To gain contextual knowledge of how the term 'hotspot' has been used in relation to schistosomiasis by the scientific community, we reviewed the published literature and conducted semi-formal interviews with stakeholders and program managers (Box 2).

In the literature, we identified 127 articles from 22 countries which have used the term 'hotspot' in relation to schistosomiasis and/or *Schistosoma* infection. We compiled a record of all the modifiers to the term 'hotspot' used in each article [7] . All articles could be described as (either overtly or by inference) using one (or more) of seven categories of hotspot: cluster, endemic, high risk, morbidity, persistent, prevalence and transmission. However, the metrics and thresholds used to define a hotspot varied considerably between authors (Table S1 in the supplemental information online), thus making consistent use of the term difficult.

The chronological analysis of the term 'hotspot' revealed a substantial increase in its frequency in published literature from 2016 to 2021, with a marked acceleration between 2020 and 2021, which accounted for 41% of all publications (Figure 1A). The increase in schistosomiasis hotspot associated research is likely due to the increased evaluation of MDAs after the WHO 2012 resolution proposing MDA in school age children for controlling morbidity in endemic settings [35]. This led to the widened realisation that some regions were not responding as well as expected [36,37] and therefore the concept of persistent hotspots was born. This term first emerged in two publications in 2016 [34,38] (Figure 1A, arrow) and continued in all the following years (Figure 1A). Persistent hotspots comprised the majority of all categories of hotspot definitions in 2019 (53%), 2020 (52%), and 2021 (70%). Notably, the number of publications in 2022 decreased from 2021, this could be attributed to the timing of the search, which was conducted before the year-end (4 November 2022), as well as potentially reduced field studies due to coronavirus disease 2019 (COVID-19) in 2020–2022, but it is possible that this trend is also truly diminishing.

High prevalence, high-risk, cluster, and transmission hotspots were used interchangeably across much of the published literature, and the endemic modifier was only found in only one publication. Hotspots which were outlined using the cluster modifier, were predominantly used to describe the

Box 2. Interviews with stakeholders

As not all opinions from the schistosomiasis community will be found in the published literature, we interviewed stakeholders to ask about their usage of the term hotspot, the importance they felt in defining it, and their views on the new WHO definition of a persistent hotspot.

Semi-structured interviews were carried out with stakeholders who responded to invitations. The stakeholders were chosen as experts in a variety of schistosome research disciplines, and intervention programme managers. The aim was to obtain opinions from a diverse group from different countries and backgrounds who might be influential in how the terms of hotspots are interpreted and how that might affect control making decisions, with the final cohort consisting of; three program managers, three who worked for NGOs concerning NTD programme implementation and policy, two research scientists with a focus on epidemiology, and three clinical researchers. One limitation of this was the diversity of the stakeholders who were interviewed, out of the 25 invitations that were sent out, 11 responded and were interviewed, so we were limited by those who wished and had time to be involved. This means we do not have representative opinions from all endemic regions, for example, the Middle East, China, Southeast Asia, and the Caribbean. Unfortunately, there was not an equal representation of genders in this cohort, with 8 out of 11 interviewees being male, although this may reflect a current gender imbalance amongst key stakeholders.

Questions were formulated in conversation with all authors to capture the aims of the interview and to facilitate further conversation. Questions were sent via email to all participants before the meeting and interviews were conducted via Zoom (version 5.14.5), consent to record the conversation was obtained. Participants were shown this manuscript before submission for publication and asked to comment if they were not happy to continue. It was made clear that they could withdraw all comments at any time, and all would remain anonymous.

Table I is not an exhaustive list of all answers and conversations but is a clear and fair representation of the given opinions and thoughts of the stakeholders. While of interest and important in their own right, these interviews also helped form the new suggested definitions of hotspots.

Table I. Interview questions and answers with stakeholders

Questions	Summary	Quotes
Q1. How would you define hotspots in relation to schistosomiasis?	Most focussed-on regions which do not respond as expected to intervention. Programme managers were more likely to use examples of interventions, other than MDA. For this question we have included a one-line quote for each interviewee.	'Areas that are not responding to treatment as we would expect' 'Certain geographical area which is the source of reinfection to a larger area' 'Locations which retain high prevalence, that is refractory to mass drug administration' 'A region which fails to decrease meaningfully the prevalence and burden of schistosomiasis after multiple rounds of MDA' 'Residual transmission foci that remain after multiple years of intervention' 'Region in which the cure rate is not what is expected' 'A region where transmission is ongoing despite intervention (beyond MDA – education, WASH etc)' 'Areas which do not respond adequately following mass treatment. In terms of significant reduction in prevalence and intensity. With accepted level of coverage' 'A community (implementation unit) where burden of disease has remained high despite the interventions that have taken place' 'Specific regions where schistosomiasis prevention does fail despite multiple rounds of treatment. And this could reflect either high transmission or rapid reinfection and/or treatment failure' 'It depends on the setting and stage of control or elimination, an area where there is high potential for transmission. Ideally this area would have prevalence data collected over multiple years and ongoing interventions'
Q2.1 Is this how you have always defined it? Q2.2 Have you used the term in articles/research/work?	8/11 said this is how they have always defined it, while others commented on the changes due to implementation of MDAs. All had used the term in research, but only some commented that over the past few years this has become more difficult with authors/reviewers not agreeing on how the term is used.	'Pre MDA era I thought of hotspots as high prevalence locations. And the geographic scale of those locations is obviously very challenging. But broadly, above fifty percent prevalence, high, heavy intensity, and true clinical manifestations and organ damage. But now that we're at an era of MDA. I think that's changed a bit' 'We have always known that regions with high transmission exist, but it is only a recent phenomenon when it comes to disease control. Where we can have one standard definition for schistosomiasis's' 'I have always and still use the term persistent transmission hotspot'

Table I. (continued)

Questions	Summary	Quotes
Q3.1 Are you aware of the new WHO definition? Q3.2. What is your opinion on this?	Q3.1: This was split 4:7 (Yes: No), there was not a clear split between those working directly in control/policy and those not. Q3.2: The opinions were quite varied of this. These have been split into categories: thresholds and general comments.	Thresholds 'Just because the prevalence has reduced by 1/3 doesn't mean the burden has. Even if we have a reduction in prevalence and intensity, we might not see a reduction in morbidity. ' 'When you want to give a definition of something maybe you should be careful not be going into detail, because the more detail the more impractical this could be from an operational point of view' 'The definition should also include behaviour of communities' 'I think it is important to take into account the issue of infection intensity because we are defining this in terms of disease control. If e.g., you are intervening and intensity not reducing significantly this means morbidity is not reducing and therefore you are not succeeding in your control program. I think the reason it is not in the WHO definition is because they assumed if there is a reduction in prevalence then there will also be a reduction in intensity. In most cases it works like that, but in some cases it doesn't.' 'I think maybe the 33% reduction is not enough to only capture hotspots and not just endemic regions, especially if you are going back after 4–5 years of MDA. Needs to be bit more stringent, fifty percent reduction or sixty percent reduction.' 'I don't think we need to have an MDA to define a hotspot. This could be determined by the environmental component and the behaviour of people and women activities and so on. Therefore, we could define a potential transmission hotspot and give that particular focus on those setting to reduce the cost of the interventions.' 'WHO recommend surveying after 5–6 years, and if we go back to places we suspect to be hotspots after 2 years we are biasing our sample. And that this plan is not very clear - when do we survey? How often? etc.' 'There are a lot of quantities, these cut offs might mean you miss hotspots, I would refrain from having such strict values to the definition of a hotspot, not ambiguous but something that means we have enough flexibility when we get to the field, making sure that in context specific situations can actually fit into them' 'this needs to be different in elimination settings, we especially need an intensity measurement' 'what about regions which have persistent infections but have a baseline prevalence of under 10%?' General comments 'I think it's fine, I don't think it is particularly evidence based. But I don't think that is too important. I think we need to have something to start the conversation, maybe it doesn't end up here but it's a good place to start.' 'I do not think it is straightforward to understand.' 'This is defining a persistent hotspot in respect to MDA performance, so it makes sense. But if thinking about the epidemiology of hotspots broadly, the definition could be quite different depending on what your question or goal is.' 'I think that when this is coming out of the WHO, it has to be programmatic. It has to be something that is meaningful to a program manager, and that it's measurable, and that it has implications for how the program is going to actually run in the field'

(continued on next page)

Table I. (continued)

Questions	Summary	Quotes
		'The issue is that we have a finite amount of drugs' 'I am worried about drug resistance with increasing to biannual. I think we need different drugs with different targets'
Q4. Do you think it is important to have well defined definitions of hotspots, if you do, please tell me why?	All agreed this was needed, some commenting that this is particularly important in the MDA era and for communicating results.	'The importance isn't how you define it but having a framework of understanding. But I think it important for the WHO to put something out there, even if it is imperfect as you can then adapt with evidence from the field.' 'When talking about control yes' 'At least to prevent miscommunication between different research groups and writing protocols' 'I think the word hotspot should definitely be defined when being used, that seems straightforward so that everyone can communicate effectively. I think similarly for scientific purposes, having a consensus definition, would be helpful in terms of understanding mechanisms and providing studies have a consistent definition to make sure the results are interpreted more easily. If we cannot reach a consensus definition, it should at least be encouraged for people to define their own definition when using it in publications' 'Yes but I wouldn't be too rigid, I would try to create ones that are as inclusive as possible. So, programme managers can act in a more adaptable manner. Not something that is predefined. Should not be a predefined, rigid concept. A goal we want to work towards.'
Q5. Do you think coverage of MDA is required in the definition of a hotspot?	Most thought that we usually get the measurement wrong, so it is not very informative. Some pointed out that adequate coverage is needed to be able to define a region as persistent post treatment.	Issues with measuring coverage 'We often don't know how many people are in the population – denomination issues. Uptake, recall bias etc.' 'There is likely a gap between reported coverage of the delivered drug and the actual uptake.' 'If individuals are not observed when taking the drug, we do not actually know if they took it' Issues with compliance 'Non-compliance on an individual level, it makes a difference if this is always the same individual or if it is random' 'And the elephant in the room with *Schistosoma* is that people don't like praziquantel. It's a rough drug and I think that there is a section of community who evade treatment or hide the fact they are not consuming it. Praziquantel is known to cause gastro-intestinal upset so if people know or have been told if can cause illness and they do not feel ill with schistosomiasis, they may choose not to take it.' 'You see coverage reduce over the years and this is because communities don't want to take it. And the main cause of that is the reluctance of communities, because schistosomiasis is a subtitle morbidity disease. And when you are going every year and giving treatment to the people, when they are not sick.' 'If people are going to be drinking alcohol they do not take it' Coverage needed to be called persistent 'A hotspot definition operationally changes a mass drug administration strategy. It increases the frequency. It seems like logical that if you were to say that mass drug administration is not working annually, it needs to be biannually that you would need a sufficient coverage. And also when you think about the relative cost effectiveness,

Table I. (continued)

Questions	Summary	Quotes
		trade-offs of increasing coverage versus biannual treatment.' 'It is really important to have sufficient treatment coverage, if it is low you are not able to say for sure that what you are dealing with is a hotspot. Transmission may have not reduced significantly simply because coverage was low. But if it is high enough, then you can say for sure that I could dealing with is a hotspot because treatment reached almost everybody.' Other comments 'We have good coverage and there are still hotspots' 'I think there is an issue with the 75% threshold. What about the 25% not treated. If they do not change their behaviour and maybe practice open defecation, transmission will continue.'

use of a spatial/temporal analysis for understanding the drivers of schistosomiasis transmission. This could relate to clusters of infected snails, humans, animal reservoirs, suitable habitats, or more. Interestingly, four categories (prevalence, high-risk, cluster, and transmission) were used more commonly in the studies from outside of Africa, and conversely all but two articles which used the persistent category were from studies inside Africa (Table S1), thus suggesting that the perception of persistence post-treatment may be mostly associated to Africa not elsewhere. Reasons for this are unclear and whether this is an indication of simply an increased use of the term in African studies or whether there is actually greater persistence post-treatment in Africa is difficult to disentangle. It could be that persistence is due to the increased poor sanitation found in some rural regions of Africa. During one of our stakeholder interviews, they commented that persistent hotspots post-treatment were not a problem in Brazil, in part because of widespread possession of septic tanks or flushing toilets, and if rarely infection intensity is not reducing as expected, this is because of noncompliance to treatment by particular individuals rather than a biological factor (Box 2).

To understand the increase in the use of the term 'hotspot' and to determine if any articles or study groups were driving this trend in research, we carried out a network analysis [39]. This designates a cited article as a parent and articles containing the citation an offspring. Amongst the 127 articles reviewed here, 54 contained at least one citation to the term 'hotspot'. Network analysis revealed that the top four most cited articles with reference to hotspot were produced by researchers in SCORE [8,28,33,40] (Figure 1B) and were all from the persistent hotspot category. This shows that the SCORE group's work has been highly influential to the use of the term, especially focusing on persistent hotspots.

In our search of the literature, we also notably found a lack of consensus on the delineation of graphical scales when defining a schistosomiasis hotspot, whether it was on a localised scale such as a village [41,42], or a school [16,43] or a broader scale encompassing clusters of villages along a coastline [40]. There is also a lack of clarity within the WHO definition which uses the ambiguous terms of 'community' or 'area' or 'setting' [24]. There is evidence that persistent hotspots tend to exhibit spatial clustering [28,40,44], likely in part attributed to environmental factors including distance to infected water bodies [9,17,19,34]. Therefore, we propose that the precise delineation of this scale should be guided by locally informed definitions of community, reflecting the scale of treatment, and potentially other intervention strategies (see Outstanding questions). The exact scale should remain adaptable, subject to definition by control programs and may differ across countries and regions. This approach aligns

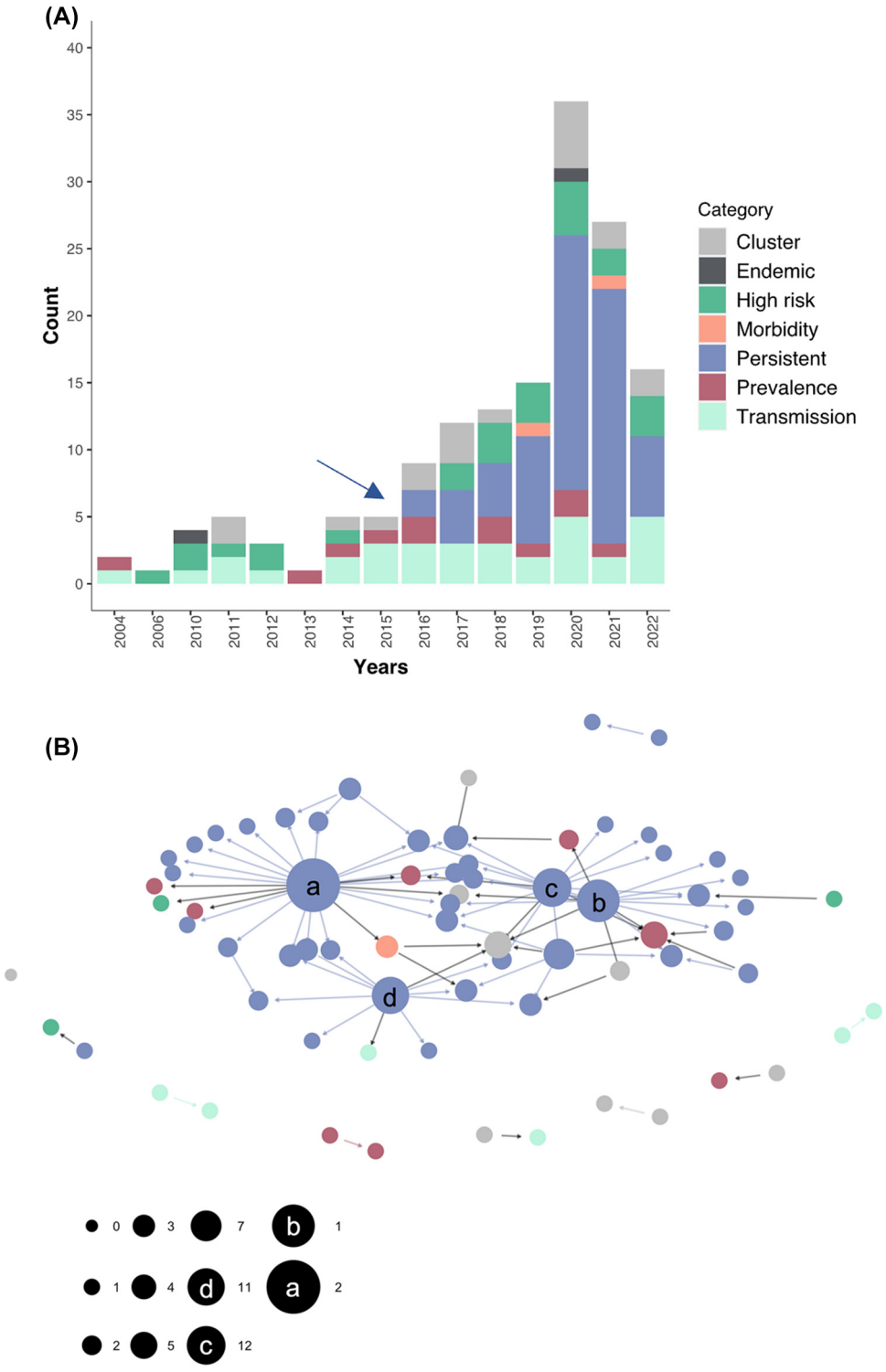

Figure 1. Evolution and influence of the term hotspot in relation to schistosomiasis. (A) All publications from a published literature search which use the term hotspot in relation to schistosomiasis from 2004 to 2022. These are

(Figure legend continued at the bottom of the next page.)

with the focal point of disease transmission and adds flexibility within control efforts across diverse geographical regions.

Are the WHO criteria for defining a persistent hotspot inclusive enough?

With the WHO definition marked as preliminary, we set out to gain a greater understanding of how this persistent hotspot definition, and each of the individual threshold metrics, relate to studies which report a persistent hotspot. To achieve this, we analysed the 17 articles which had: (i) identified a persistent hotspot within their study based on quantitative data; (ii) the study data came from human participants; and (iii) included a definition of a persistent hotspot, which may have been derived from previous research or from the authors themselves.

Each of the four criteria outlined in the WHO definition of a persistent hotspot (Box 1) were examined to infer their influence on the designation of a persistent hotspot. Each study was given a score from zero to four, depending on how many of the four criteria they met. Each criterion was treated individually that is, if baseline prevalence was under 10%, this was still compared with study prevalence to calculate reduction metric. If the article contained results from a larger study and baseline prevalence, or other information was available publicly elsewhere, we included it in the analysis. Unfortunately, some information was not available in the published articles (denoted by '[a]' in Table 1).

Out of a possible total maximum score of four, 8 of 17 studies (~47%) received the highest score, fully matching the WHO definition of a persistent hotspot. Seven studies received a score of 3 (~41%), with two failing to meet the required ≥75% treatment coverage, one not reporting treatment coverage, one not reporting specific baseline prevalence, and three failing to show a reduction in prevalence of at least 1/3. Two studies received a score of 2 (12%), with one failing to report treatment coverage and having a baseline prevalence of >10%, and the other failing to report specific baseline prevalence and therefore not allowing for the calculation of reduction.

We found that the most restrictive criteria for matching the WHO definition (and achieving a full score of 4) was the need for ≥75% treatment coverage and a reduction in prevalence of at least 1/3, with both criteria either missing data or not passing the threshold five times in the published literature. These results highlight the need for more data to determine if these metrics could hinder identification of persistent hotspots requiring additional treatment.

Establishing hotspot definitions in the schistosomiasis community: a resource for standardising reporting practices

It is critical to establish a standardised, easy to follow definition of a persistent hotspot which can be disseminated to the local program managers. To facilitate progress in this area, we used results from our analysis of the WHO definition of a persistent hotspot, along with extensive research already carried out by SCORE [33], and discussions with stakeholders (Box 2), to suggest modifications and practical usage to the WHO definition of a persistent hotspot [24] (Table 2).

The main points that we propose here are as follows: (i) prescriptive usage of the term hotspot should be either biological (relating to the treatment not being successful enough to reduce transmission) or

stratified by hotspot category term used. The blue arrow indicates the first time the term 'persistent hotspot' was used in relation to schistosomiasis in published literature. Skewness of full dataset = 1.325, indicating right-skew. (B) Network analysis of all articles cited when using the term 'hotspot' in schistosomiasis publications. Each node is an article, parent nodes are articles which have been cited, offspring nodes are articles which have cited the parent articles. The parent nodes are weighted by how many times they have been cited. The colour of the nodes represents the hotspot category in the article (not all categories are represented as they may not have been referenced). The thin arrows are coloured if a parent and offspring article are the same category and are black if they link articles using different categories of hotspot. The letters indicate the four most cited articles a, [8]; b, [28]; c, [40]; d, [33].

Table 1. Studies included in the evaluation of the WHO definition of a persistent hotspot, and their score against the four criteria

Human studies, with persistent hotspot	Country	Community	Baseline prevalence ≥10%	Undergone at least two rounds of MDA	≥75% treatment coverage	Reduced by less than 1/3 (33.3%)	Total score
[74]	Zanzibar	Shehia	Yes	Yes	Yes	Yes	4
[8]	Tanzania	Village	Yes	Yes	Yes	Yes	4
[41]	Madagascar	Village	Yes	Yes	Yes	Yes	4
[34]	Zanzibar	Shehia	Yes	Yes	Yes	Yes	4
[17]	Cote d'Ivoire	School	Yes	Yes	Yes	Yes	4
[75]	Kenya and Tanzania	Arm	Yes	Yes	Yes	Yes	4
[76]	Cote d'Ivoire	Arm	Yes	Yes	Yes	Yes	4
[28]	Côte d'Ivoire, Kenya, Mozambique, and Tanzania	Arm	Yes	Yes	Yes	Yes	4
[77]	Uganda	Arm	Yes	Yes	No	Yes	3
[16]	Ethiopia	Schools	Yes	Yes	No	Yes	3
[40]	Kenya	Village	Yes	Yes	Yes	No	3
[31]	Kenya	Arm	Yes	Yes	Yes	No	3
[78]	Cote d'Ivoire	Arm	Yes	Yes	Yes	No	3
[43]	Sudan	School	Yes	Yes	No[a]	Yes	3
[42]	Kenya	Village	Yes	Yes	Yes	No[a]	3
[19]	Kenya	Villages	Yes	Yes	No[a]	No[a]	2
[44]	Zanzibar	Shehia	No	Yes	No[a]	Yes	2

[a]Data not available in published article.

operational (not reaching intervention and/or surveillance targets). There should be a clear distinction between these two types of hotspots. (ii) Intensity and morbidity surveillance should be encouraged alongside prevalence (wherever logistically feasible). (iii) The reduction thresholds ought to be determined by regional governments and health boards, considering stage of control. (iv) Other interventions should be used in conjunction with MDA wherever EPHP or IoT is targeted.

Biological and operational hotspots

Recognising the distinction between a biological and operational hotspot is vital to effectively address factors which drive high transmission and prevalence, as well as to correctly allocate resources for control initiatives. This is due to each type of hotspot requiring distinct strategies for mitigation. For instance, in an operational hotspot where treatment targets are not met, increasing to biannual treatment will not address this underlying issue causing persistent infections post treatment. By including the ≥75% coverage threshold in the definition of a persistent hotspot, regions can be identified that require supplementary investigation and support to

Table 2. Modifications to WHO definition of persistent hotspot

WHO criteria	WHO threshold	Modification
Baseline prevalence	≥10%	Included
Previous preventive chemotherapy	Two rounds	Included
Coverage at both rounds	≥75%	Included but a clearer distinction between biological and operational hotspots suggested
Reduction in prevalence	Regionally set	Intensity and morbidity added, and threshold removed, suggested to be set by local governments

address this treatment shortfall. Crucially, the inclusion of operational hotspot designation in our definition framework (Figure 2), simultaneously works to highlight both biological and operational hotspots.

Biological hotspots are the focus of the WHO and SCORE definitions of a persistent hotspot and are used to describe a region which even with adequate treatment, an unacceptable level of infections persist post treatment [24,33]. In this instance, the term 'biological' refers to persistent infections resulting from inherent natural factors. An example of a biological driver of a persistent hotspot is the abundance of cercariae produced by snail populations in the water body of that region [45,46]. Though parasite–host compatibility varies greatly between snail species, a single suitable *Biomphalaria* or *Bulinus* snail can shed up to 1000 cercariae a day [47,48] and continue shedding for months [48], thus increasing the chance of rapid reinfection [43,49,50]. Another example is the evolutionary capacity of parasite populations, which could be suspectable to contrasting treatment pressures [22]. High parasite fecundity could potentially drive elevated

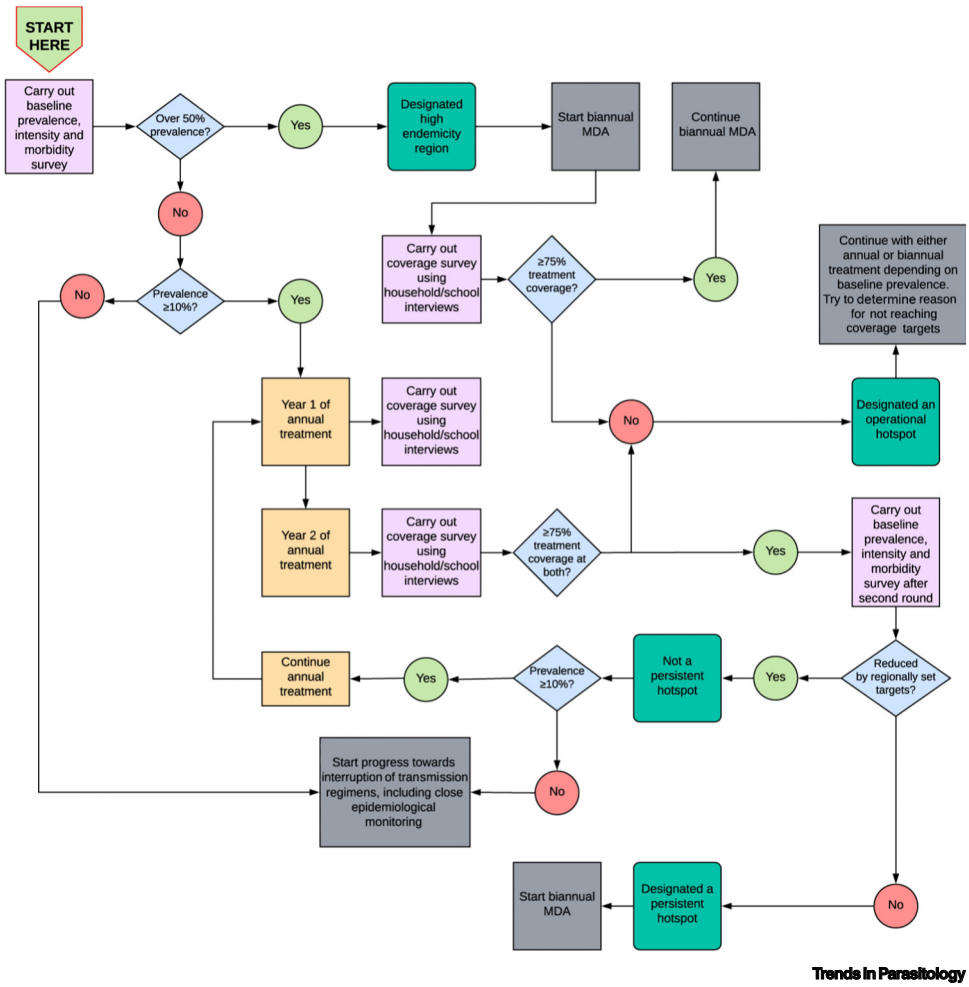

Figure 2. Hotspot designation framework and decision tree. A decision tree should be followed when determining whether a geographical location is a persistent hotspot which requires biannual mass drug administration (MDA). This includes our four modified criteria from the WHO definition of a persistent hotspot (blue triangles), suggested surveys (pink boxes), and definition designation (green boxes). Along with treatment timings (yellow and grey boxes).

transmission in hotspots [22] as could the emergence of drug resistant *Schistosomes* [38]. Additionally, the implications of viable hybrids produced by coinfection of both human and animal parasites on treatment efficacy and effective control measures within persistent hotspots warrants further investigation [51,52].

By contrast, operational hotspots emerge from specific activities, processes, or their absence. A notable example of operational impacts on endemic diseases transpired during the COVID-19 pandemic. In April 2020 in response to the ongoing crisis, the WHO recommended the suspension of MDAs and discontinuation of routine surveillance and population surveys for NTDs [53]. This caused delays in treatment, delivery of medication, and loss of personnel in target countries [54]. Although these recommendations were revised in July the same year, and control programmes gradually restarted, there were missed rounds of annual MDA and disruptions to scheduled vector control [55]. Using mathematical modelling to analyse the repercussions of suspending MDAs on the target of EPHP, predictions suggest a potential delay of up to 2 years in reaching the targets [56,57]. Although this produces the same outcome as a biological hotspot (persistent prevalence, intensity, and morbidity), the drivers and changes needed to address the operational hotspot are fundamentally different.

The WHO have set a target for schistosomiasis treatment coverage of at least 75% when carrying out MDAs [24]. However, something that is recognised in many NTD control initiatives is the difficulty in regularly reaching high treatment coverage. This can be due to the unavailability of funds, political events, or programmatic difficulties, including poor understanding of the village boundaries [58,59], inaccurate calculations of the target population size [59–61], difficulty reaching some members of the community [61], community acceptance [60,62], or lack of supervision when taking the medication [59,61,63]. According to the WHO data portal, only 11 countries out of 47 requiring preventive chemotherapy for schistosomiasis in 2019 achieved ≥75% treatment coverage and when looking at a more focal level, 14 countries had 100% of implementation units reach the ≥75% coverage goal in school-age children[i]. Furthermore, our evaluation of the preliminary WHO thresholds for persistent hotspots indicates that the requirement to reach ≥75% treatment coverage could be exclusionary to hotspot designation.

Community-wide education into the need for interventions has been noted in the literature [16,60,64], and discussed in several interviews with stakeholders. Issues relating to uptake of praziquantel and the acceptance of treatment within the community was also considered, particularly concerns around people's perception and understanding of needing to take the treatment when not ill [60,62] (Box 2). The WHO guidelines recognise that with the increase to biannual treatment, communities and drug distributors may require additional programs to incentivise them [24].

Monitoring of effectiveness of treatment campaigns is recognised as a crucial part of control programs [24], this is reliant on volunteers from the community, so in regions where treatment is increasing to biannual there will be a greater need for these unpaid workers, again requiring more community-wide education and incentives for volunteers and teachers. Additionally, it is crucial that we find individuals or families who continually miss treatment. Research by Adriko *et al*. [63] in Mayuge District, Uganda, found that 35% of residents had never taken praziquantel despite annual MDA for over 15 years. The most common reason that community members had never taken the treatment was due to not being offered it (49%), rather than noncompliance [63]. Thus, these individuals are both at risk of chronic morbidity and being reservoirs of infection to the community. These are just some of the issues facing communities who do not reach treatment target goals and should be classed an operational hotspot. Therefore, future research is needed to understand pressures, and hurdles that hinder these goals being met, this research should be

prescriptive and process-driven to tackle these issues effectively (see Outstanding questions), we hope that highlighting these regions in our prescriptive definition framework (Figure 2) will encourage future research and discussion in this area.

Individual intensity and morbidity surveillance should be encouraged alongside estimation of community prevalence

Relating evidence from well designed, randomised control field studies in multiple countries, with varying stages of control [27], researchers from SCORE suggested flexibility in the definition of persistent hotspots, particularly when dealing with locations who have achieved or are nearing EPHP, where a simple percent change in prevalence will not be feasible [8] (Box 1). Several studies have found significant associations between **cure rate** and infection intensity [65,66], highlighting the importance of intensity in monitoring praziquantel efficacy. Furthermore, it is not uncommon for infection intensity to reduce while prevalence does not. For example, *Schistosoma mansoni* infection intensity significantly reduced post treatment in a study in Mali despite maintained prevalence [67]. Therefore, to comprehensively evaluate MDA impact, it is important to incorporate both intensity and prevalence and we have suggested the inclusion of intensity calculations at all community surveys (Figure 2).

The concept of morbidity hotspots was discussed in the review by Mawa and colleagues [4] and although the exact relationship between morbidity, prevalence, and intensity is not fully elucidated, it can be broadly described as a geographic region which has high or persistent morbidity caused by a *Schistosoma* spp. infection. Morbidity hotspots represent a significant challenge to control and are not easy to identify. This is especially pertinent as some evidence suggest regions with similar infection prevalence can exhibit markedly different morbidity profiles. For example, in two geographically adjacent villages on Lake Victoria in Uganda with comparable *S. mansoni* prevalence of 92.5% and 87.9%, researchers found significantly different community morbidity prevalence (31.5% and 6.1% respectively) of periportal fibrosis which is an indication of intestinal *Schistosoma* pathology [68]. During interviews, one stakeholder mentioned a reduction in prevalence and even intensity post intervention, but specifically noted a much smaller reduction in morbidity, although the time frame for this result was not described. Therefore, we would like to propose, wherever logistically feasible, that morbidity markers are also included in surveillance and planning (Figure 2). However, we do appreciate that the use of ultrasound at every survey is often not feasible, and the limited association between egg count and morbidity, especially with *S. mansoni* [69,70], will make accurate predictions difficult until new methods for identifying morbidity are developed. Therefore, we have highlighted the need for more research and funding in this area (see Outstanding questions).

Reduction thresholds should be determined by regional governments and health boards, considering stage of control

The assignment of relative reduction metric has thus far been evidenced mostly via modelling studies and field evidence is lacking, therefore the WHO suggest that the alternative calculation of absolute reduction could also be favoured depending on baseline prevalence and the epidemiology of the setting [24]. There is a need for more research into the correct allocation of this reduction metric to make it clear when disseminating to regional organisations (see Outstanding questions). It is imperative that each government can implement successful control strategies [71,72], therefore we suggest that it is clear there can be some region-specific flexibility in describing a persistent hotspot. This indicates the importance of local surveillance and local decisions on how to act and use the WHO guidelines as a starting point to launch these.

An issue highlighted by stakeholders was the need to have a baseline prevalence of ≥10% to be deemed a persistent hotspot by the WHO (Box 2). The concern here being the potential oversight of regions which have low prevalence and persistent post-treatment infections. Although biannual MDA may not be required in these regions, it is critical to maintain vigilant surveillance once prevalence drops below 10% as per recommendation two in the WHO guidelines [24]. This was illustrated in surveys of shehias and schools in Zanzibar where, after five years of biannual MDA, coupled with snail control and behaviour change interventions, prevalence dropped to below 10% in all areas. However, after a treatment gap of 16 months, a strong rebound of *Schistosoma haematobium* infections was noted in selected areas, with a significant increase among boys 8–16 years of age. The overall prevalence shift after the treatment gap was from 2.8% to 9.1% (+225%) [44]. Therefore, to achieve the aim of IoT in areas which have successfully reached EPHP, the implementation of surveillance alongside targeted test and treat should be enacted [24]. For regions experiencing recrudescence, as seen in Zanzibar [44], swift and intensified interventions are critical to success.

Including other interventions in conjunction with MDA

A growing consensus, well documented in the literature and highlighted across the stakeholder interviews (Box 2), is the requirement to use alternate interventions alongside MDA if schistosomiasis is to be successfully eliminated. Recommendation five in the WHO guidelines underscore the need for supplementary interventions, such as improvement in WASH practices and infrastructure, snail control, and education on behavioural change. Furthermore, recommendation six addresses the need to test non-human mammals and snail hosts to tackle the potential for reservoirs of infection in the community [24]. This is particularly important in persistent hotspots that have achieved high treatment coverage, where intensified snail control is advised along with MDA.

Using our proposed definition framework allows for identification of regions which have persistent infections post treatment attributed to either biological or operational dynamics, while concurrently measuring the magnitude of prevalence, intensity, and morbidity. This will equip programme managers with the information to create more nuanced and effective disease control strategies, tailoring interventions to the precise stage of disease control and underlying drivers of persistence.

Concluding remarks

With the inclusion of persistent hotspots as a prescriptive measure for the type of treatment regimen initiated in a region [24], accurate, consistent, and inclusive identification of these areas is more important now than ever before. A common understanding of operational terminology among the scientific community and program managers is vital [7], as it will facilitate progression toward the WHO targets of EPHP and IoT of schistosomiasis, and the ultimate aim of affecting the morbidity and quality of life burden caused by the disease.

Using knowledge from stakeholders, our own analysis of the WHO definition and published research, we have suggested some changes to the definition of a persistent hotspot. As progress towards EPHP produces heterogeneous responses to MDA, it is clear some flexibility in the definition is required; therefore, we suggest that the reduction thresholds to define a persistent hotspot be set on a regional basis, which will require support to governments and local health division's [71,72]. Furthermore, we have suggested that all surveillance campaigns use both prevalence and intensity as a reduction measure and, when the diagnostics become more feasible, include community morbidity surveillance. As high treatment coverage is essential before designation of a biological persistent hotspot, we propose that the ≥75% coverage be maintained in the

Outstanding questions

What is the correct reduction threshold to use when assessing a persistent hotspot? This remains unclear for both prevalence and intensity, likely varying across diverse settings and stages of control. Furthermore, baseline prevalence and intensity levels will influence this calculation.

What methods can be employed to accurately, efficiently, and cost-effectively measure schistosomiasis-related morbidity in a community?

How will communities accept biannual treatment and additional measures? This will require campaigns to encourage community acceptance and additional workers to implement both education and molluscicide treatment.

What are the key obstacles which hinder communities reaching target treatment coverage?

How can we effectively tackle low-prevalence persistent hotspots?

At what geographical scale should a hotspot delineation occur? Is using human community boundaries sufficient?

definition, however, we encourage a clear distinction between a biological or an operational hotspot. For these suggestions to be integrated effectively, further research is required on how to calculate meaningful reduction thresholds, cost-effective morbidity markers must be developed, and the issues that result in a community not reaching treatment targets need to be determined (see Outstanding questions). A key challenge in the designation of a new persistent hotspot for schistosomiasis will be community acceptance, additional interventions accompanied by an increase to biannual treatment of the entire population, mean community involvement and acceptance will be fundamental to the success of these strategies.

Acknowledgments

We would like to express a huge thank you to the stakeholders and program managers who took the time to meet with us to be interviewed. We had such interesting and thought-provoking conversations with you all and it really helped to formulate the definition framework produced here. We are grateful to our funders, R.M.L. supported by the Wellcome Trust program (218492/Z/19/Z; under the supervision of A.B.P., J.P.W., and P.H.L.L.), and European Research Council starting grant (PHLL: SCHISTO_PERSIST_680088).

Declaration of interests

J.P.W. is a member of the *Trends in Parasitology* advisory board and is or has been on the following WHO advisory boards/expert advisory groups/guideline development groups: TAGG Working sub-Group to produce 'Manual on the control of zoonotic schistosomiases' (2022-current); TAGG Working sub-Group to produce 'Manuals of validation of soil-transmitted helminthiasis and schistosomiasis as Eliminated as a Public Health Problem (EPHP)' (2022-current); WHO Global Working Group on Monitoring of Drug Efficacy (WG MDE) (2010 -current); WHO Schistosomiasis Guideline Development Group (GDG) (2018-2022). The remaining authors have no interests to declare.

Resources

[i]https://apps.who.int/neglected_diseases/ntddata/sch/sch.html

Supplemental information

Supplemental information associated with this article can be found online at https://doi.org/10.1016/j.pt.2023.09.006.

References

1. Tiruneh, A. *et al.* (2020) Identification of transmission foci of *Schistosoma mansoni*: narrowing the intervention target from district to transmission focus in Ethiopia. *BMC Public Health* 20, 769
2. Meurs, L. *et al.* (2013) Micro-geographical heterogeneity in *Schistosoma mansoni* and *S. haematobium* infection and morbidity in a co-endemic community in Northern Senegal. *PLoS Negl. Trop. Dis.* 7, e2608
3. Manyangadze, T. *et al.* (2016) Risk factors and micro-geographical heterogeneity of *Schistosoma haematobium* in Ndumo area, uMkhanyakude district, KwaZulu-Natal, South Africa. *Acta Trop.* 159, 176–184
4. Mawa, P.A. *et al.* (2021) Schistosomiasis morbidity hotspots: roles of the human host, the parasite and their interface in the development of severe morbidity. *Front. Immunol.* 12 Published online March 12, 2021. https://doi.org/10.3389/fimmu.2021.635869
5. McManus, D.P. *et al.* (2018) Schistosomiasis. *Nat. Rev. Dis. Primer* 4, 14
6. Montresor, A. *et al.* (1998) *Guidelines for the Evaluation of Soil-Transmitted Helminthiasis and Schistosomiasis at Community Level: A Guide for Managers of Control Programmes*, World Health Organization
7. Lessler, J. *et al.* (2017) What is a hotspot anyway? *Am. J. Trop. Med. Hyg.* 96, 1270–1273
8. Kittur, N. *et al.* (2017) Defining persistent hotspots: areas that fail to decrease meaningfully in prevalence after multiple years of mass drug administration with praziquantel for control of schistosomiasis. *Am. J. Trop. Med. Hyg.* 97, 1810–1817
9. Walker, J.W. *et al.* (2020) Environmental predictors of schistosomiasis persistent hotspots following mass treatment with praziquantel. *Am. J. Trop. Med. Hyg.* 102, 328–338
10. Mutuku, M.W. *et al.* (2019) A search for snail-related answers to explain differences in response of *Schistosoma mansoni* to praziquantel treatment among responding and persistent hotspot villages along the Kenyan shore of Lake Victoria. *Am. J. Trop. Med. Hyg.* 101, 65–77
11. Wood, C.L. *et al.* (2019) Precision mapping of snail habitat provides a powerful indicator of human schistosomiasis transmission. *Proc. Natl. Acad. Sci.* 116, 23182–23191
12. Gower, C.M. *et al.* (2017) Should we be treating animal schistosomiasis in Africa? The need for a One Health economic evaluation of schistosomiasis control in people and their livestock. *Trans. R. Soc. Trop. Med. Hyg.* 111, 244–247
13. Léger, E. *et al.* (2020) Prevalence and distribution of schistosomiasis in human, livestock, and snail populations in northern Senegal: a One Health epidemiological study of a multi-host system. *Lancet Planet. Health* 4, e330–e342
14. Angora, E.K. *et al.* (2019) Prevalence and risk factors for schistosomiasis among schoolchildren in two settings of Côte d'Ivoire. *Trop. Med. Infect. Dis.* 4, 110
15. Arinaitwe, M. *et al.* (2021) Residence time, water contact, and age-driven *Schistosoma mansoni* infection in hotspot communities in Uganda. *Am. J. Trop. Med. Hyg.* 105, 1772–1781
16. Gal, L.B. *et al.* (2022) Sustainable elimination of schistosomiasis in Ethiopia – a five-year follow-up study. *Trop. Med. Infect. Dis.* 7, 218
17. Assare, R.K. *et al.* (2020) Characteristics of persistent hotspots of *Schistosoma mansoni* in western Cote d'Ivoire. *Parasit. Vectors* 13, 337
18. Donohue, R.E. *et al.* (2017) Biosocial determinants of persistent schistosomiasis among schoolchildren in Tanzania despite repeated treatment. *Trop. Med. Infect. Dis.* 2, 61

19. Musuva, R.M. *et al.* (2021) Unprotected water sources and low latrine coverage are contributing factors to persistent hotspots for schistosomiasis in western Kenya. *PLoS One* 16, e0253115
20. Huyse, T. *et al.* (2018) Evolutionary epidemiology of schistosomiasis: linking parasite genetics with disease phenotype in humans. *Int. J. Parasitol.* 48, 107–115
21. Vianney, T.J. *et al.* (2022) Genome-wide analysis of *Schistosoma mansoni* reveals limited population structure and possible praziquantel drug selection pressure within Ugandan hot-spot communities. *PLoS Negl. Trop. Dis.* 16, e0010188
22. Webster, J.P. *et al.* (2020) Parasite population genetic contributions to the Schistosomiasis Consortium for Operational Research and Evaluation within sub-Saharan Africa. *Am. J. Trop. Med. Hyg.* 103, 80–91
23. World Health Organization (2020) *Ending the Neglect to Attain the Sustainable Development Goals: a rationale for continued investment in tackling neglected tropical diseases 2021–2030*, WHO Published online January 28, 2022. https://iris.who.int/bitstream/handle/10665/351193/9789240042414-eng.pdf?sequence=1
24. World Health Organization (2022) *WHO Guideline on Control and Elimination of Human schistosomiasis*, WHO Published online February 14, 2022. https://iris.who.int/bitstream/handle/10665/351856/9789240041608-eng.pdf?sequence=1
25. Campbell, C.H. *et al.* (2020) SCORE operational research on moving toward interruption of schistosomiasis transmission. *Am. J. Trop. Med. Hyg.* 103, 58–65
26. Colley, D.G. *et al.* (2020) Contributions of the Schistosomiasis Consortium for Operational Research and Evaluation (SCORE) to schistosomiasis control and elimination: key findings and messages for future goals, thresholds, and operational research. *Am. J. Trop. Med. Hyg.* 103, 125–134
27. King, C.H. *et al.* (2020) Impact of different mass drug administration strategies for gaining and sustaining control of *Schistosoma mansoni* and *Schistosoma haematobium* infection in Africa. *Am. J. Trop. Med. Hyg.* 103, 14–23
28. Kittur, N. *et al.* (2019) Persistent hotspots in Schistosomiasis Consortium for Operational Research and Evaluation Studies for Gaining and Sustaining Control of Schistosomiasis after Four Years of Mass Drug Administration of Praziquantel. *Am. J. Trop. Med. Hyg.* 101, 617–627
29. Olsen, A. *et al.* (2018) Comparison of the impact of different mass drug administration strategies on infection with *Schistosoma mansoni* in Mwanza Region, Tanzania – a cluster-randomized controlled trial. *Am. J. Trop. Med. Hyg.* 99, 1573–1579
30. Phillips, A.E. *et al.* (2017) Assessing the benefits of five years of different approaches to treatment of urogenital schistosomiasis: a SCORE project in Northern Mozambique. *PLoS Negl. Trop. Dis.* 11, e0006061
31. Secor, W.E. *et al.* (2019) Comparison of school-based and community-wide mass drug administration for schistosomiasis control in an area of Western Kenya with high initial *Schistosoma mansoni* infection prevalence: a cluster randomized trial. *Am. J. Trop. Med. Hyg.* 102, 318–327
32. Ezeamama, A.E. *et al.* (2016) Gaining and sustaining schistosomiasis control: study protocol and baseline data prior to different treatment strategies in five African countries. *BMC Infect. Dis.* 16, 229
33. Kittur, N. *et al.* (2020) Discovering, defining, and summarizing persistent hotspots in SCORE studies. *Am. J. Trop. Med. Hyg.* 103, 24–29
34. Pennance, T. *et al.* (2016) Urogenital schistosomiasis transmission on Unguja Island, Zanzibar: characterisation of persistent hot-spots. *Parasit. Vectors* 9, 646
35. World Health Organization (2012) *Accelerating Work to Overcome the Global Impact of Neglected Tropical Diseases: A Roadmap for Implementation*, WHO Published online. https://iris.who.int/handle/10665/70809
36. Deol, A.K. *et al.* (2019) Schistosomiasis – assessing progress toward the 2020 and 2025 global goals. *N. Engl. J. Med.* 381, 2519–2528
37. Toor, J. *et al.* (2018) Are we on our way to achieving the 2020 goals for schistosomiasis morbidity control using current World Health Organization guidelines? *Clin. Infect. Dis.* 66, S245–S252
38. Crellen, T. *et al.* (2016) Reduced efficacy of praziquantel against *Schistosoma mansoni* is associated with multiple rounds of mass drug administration. *Clin. Infect. Dis.* 63, 1151–1159
39. Cecilia, H. *et al.* (2022) Mechanistic models of Rift Valley fever virus transmission dynamics: a systematic review. *PLoS Negl. Trop. Dis.* 16, e0010339
40. Wiegand, R.E. *et al.* (2017) A Persistent Hotspot of *Schistosoma mansoni* infection in a five-year randomized trial of praziquantel preventative chemotherapy strategies. *J. Infect. Dis.* 216, 1425–1433
41. Spencer, S.A. *et al.* (2021) Five-year follow-up on the prevalence and intensity of infections of *Schistosoma mansoni* in a hard-to-reach district of Madagascar. *Am. J. Trop. Med. Hyg.* 104, 1841–1850
42. Omondi, I. *et al.* (2021) Socioeconomic determinants of *Schistosoma mansoni* infection using multiple correspondence analysis among rural western Kenyan communities: evidence from a household-based study. *PLoS One* 16, e0253041
43. Jin, Y. *et al.* (2021) Transmission dynamics of *Schistosoma haematobium* among school-aged children: a cohort study on prevalence, reinfection and incidence after mass drug administration in the White Nile State of Sudan. *Int. J. Environ. Res. Public Health* 18, 11537
44. Trippler, L. *et al.* (2021) Impact of seven years of mass drug administration and recrudescence of *Schistosoma haematobium* infections after one year of treatment gap in Zanzibar: repeated cross-sectional studies. *PLoS Negl. Trop. Dis.* 15, e0009127
45. Civitello, D.J. *et al.* (2022) Transmission potential of human schistosomes can be driven by resource competition among snail intermediate hosts. *Proc. Natl. Acad. Sci.* 119, e2116512119
46. Palasio, R.G.S. *et al.* (2019) Diversity of *Biomphalaria* spp. freshwater snails and associated mollusks in areas with schistosomiasis risk, using molecular and spatial analysis tools. *Biota Neotrop.* 19
47. Théron, A. (1984) Early and late shedding patterns of *Schistosoma mansoni* cercariae: ecological significance in transmission to human and murine hosts. *J. Parasitol.* 70, 652–655
48. Fryer, S.E. and Probert, A.J. (1988) The cercarial output from three Nigerian bulinids infected with two strains of *Schistosoma haematobium*. *J. Helminthol.* 62, 133–140
49. Woldegerima, E. *et al.* (2019) Prevalence and reinfection rates of *Schistosoma mansoni* and praziquantel efficacy against the parasite among primary school children in Sanja Town, Northwest Ethiopia. *J. Parasitol. Res.* 2019, 3697216
50. Senghor, B. *et al.* (2015) Efficacy of praziquantel against urinary schistosomiasis and reinfection in Senegalese school children where there is a single well-defined transmission period. *Parasit. Vectors* 8, 362
51. Leger, E. and Webster, J.P. (2017) Hybridizations within the genus *Schistosoma*: implications for evolution, epidemiology and control. *Parasitology* 144, 65–80
52. Berger, D.J. *et al.* (2022) Genomic evidence of contemporary hybridization between *Schistosoma* species. *PLoS Pathog.* 18, e1010706
53. World Health Organization (2020) *Considerations for implementing mass treatment, active case-finding and population-based surveys for neglected tropical diseases in the context of the COVID-19 pandemic: interim guidance*, WHO Published online July 27, 2020. https://iris.who.int/bitstream/handle/10665/333499/WHO-2019-nCoV-neglected_tropical_diseases-2020.1-eng.pdf?sequence=1
54. World Health Organization (2020) Neglected Tropical Diseases: Impact of COVID-19 and WHO's Response – Maladies tropicales négligées: impact de la COVID-19 et réponse de l'OMS. *Wkly Epidemiol. Rec.* 95, 461–468
55. Borlase, A. *et al.* (2022) Evaluating and mitigating the potential indirect effect of COVID-19 on control programmes for seven neglected tropical diseases: a modelling study. *Lancet Glob. Health* 10, e1600–e1611
56. NTD Modelling Consortium (2020) The potential impact of programmes interruptions due to COVID-19 on 7 neglected tropical diseases: a modelling-based analysis. *Gates Open Res.* 4, 115
57. Kura, K. *et al.* (2021) Disruptions to schistosomiasis programmes due to COVID-19: an analysis of potential impact and mitigation strategies. *Trans. R. Soc. Trop. Med. Hyg.* 115, 236–244

58. Mwinzi, P.N. *et al.* (2012) Integrated community-directed intervention for schistosomiasis and soil transmitted helminths in western Kenya – a pilot study. *Parasit. Vectors* 5, 182
59. Binder, S. *et al.* (2020) Lessons learned in conducting mass drug administration for schistosomiasis control and measuring coverage in an operational research setting. *Am. J. Trop. Med. Hyg.* 103, 105–113
60. Knopp, S. *et al.* (2016) Praziquantel coverage in schools and communities targeted for the elimination of urogenital schistosomiasis in Zanzibar: a cross-sectional survey. *Parasit. Vectors* 9, 5
61. Onkanga, I.O. *et al.* (2016) Impact of two rounds of praziquantel mass drug administration on *Schistosoma mansoni* infection prevalence and intensity: a comparison between community wide treatment and school based treatment in western Kenya. *Int. J. Parasitol.* 46, 439–445
62. Coulibaly, J.T. *et al.* (2018) A rapid appraisal of factors influencing praziquantel treatment compliance in two communities endemic for schistosomiasis in Côte d'Ivoire. *Trop. Med. Infect. Dis.* 3, 69
63. Adriko, M. *et al.* (2018) Low praziquantel treatment coverage for *Schistosoma mansoni* in Mayuge District, Uganda, due to the absence of treatment opportunities, rather than systematic non-compliance. *Trop. Med. Infect. Dis.* 3, 111
64. Tallo, V.L. *et al.* (2008) Is mass treatment the appropriate schistosomiasis elimination strategy? *Bull. World Health Organ.* 86, 765–771
65. Gebreyesus, T.D. *et al.* (2023) Efficacy and safety of praziquantel preventive chemotherapy in *Schistosoma mansoni* infected school children in Southern Ethiopia: a prospective cohort study. *Front. Pharmacol.* 14, 968106
66. Utzinger, J. *et al.* (2000) Efficacy of praziquantel against Schistosoma mansoni with particular consideration for intensity of infection. *Tropical Med. Int. Health* 5, 771–778
67. Landouré, A. *et al.* (2012) Significantly reduced intensity of infection but persistent prevalence of schistosomiasis in a highly endemic region in Mali after repeated treatment. *PLoS Negl. Trop. Dis.* 6, e1774
68. Booth, M. *et al.* (2004) Hepatosplenic morbidity in two neighbouring communities in Uganda with high levels of *Schistosoma mansoni* infection but very different durations of residence. *Trans. R. Soc. Trop. Med. Hyg.* 98, 125–136
69. Tanabe, M. *et al.* (1997) Occurrence of a community with high morbidity associated with *Schistosoma mansoni* infection regardless of low infection intensity in north-east Brazil. *Trans. R. Soc. Trop. Med. Hyg.* 91, 144–149
70. Wiegand, R.E. *et al.* (2021) Control and elimination of schistosomiasis as a public health problem: thresholds fail to differentiate schistosomiasis morbidity prevalence in children. *Open Forum Infect. Dis.* 8, ofab179
71. French, M. and Evans, D. (2019) Adaptive strategies for schistosomiasis control. *Lancet Glob. Health* 7, e1302–e1303
72. Li, E.Y. *et al.* (2019) Improving public health control of schistosomiasis with a modified WHO strategy: a model-based comparison study. *Lancet Glob. Health* 7, e1414–e1422
73. Knopp, S. *et al.* (2019) Evaluation of integrated interventions layered on mass drug administration for urogenital schistosomiasis elimination: a cluster-randomised trial. *Lancet Glob. Health* 7, E1118–E1129
74. Pennance, T. *et al.* (2022) Potential drivers for schistosomiasis persistence: population genetic analyses from a cluster-randomized urogenital schistosomiasis elimination trial across the Zanzibar islands. *PLoS Negl. Trop. Dis.* 16, e0010419
75. Shen, Y. *et al.* (2020) Modeling approaches to predicting persistent hotspots in SCORE studies for gaining control of *Schistosomiasis mansoni* in Kenya and Tanzania. *J. Infect. Dis.* 221, 796–803
76. Ouattara, M. *et al.* (2021) Effectiveness of school-based preventive chemotherapy strategies for sustaining the control of schistosomiasis in Côte d'Ivoire: results of a 5-year cluster randomized trial. *PLoS Negl. Trop. Dis.* 15, e0008845
77. Tushabe, J.V. *et al.* (2020) Does intensive treatment select for praziquantel resistance in high-transmission settings? parasitological trends and treatment efficacy within a cluster-randomized trial. *Open Forum Infect. Dis.* 7, ofaa091
78. Ouattara, M. *et al.* (2021) Effectiveness of four different interventions against *Schistosoma haematobium* in a seasonal transmission setting of Côte d'Ivoire: a cluster randomized trial. *Clin. Infect. Dis. Off. Publ. Infect. Dis. Soc. Am.* 74, 2181–2190