The hidden burden of *Bartonella quintana* on the African continent: should the bacterial infection be considered a neglected tropical disease?

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*Bartonella quintana* is a louse-borne gram-negative bacillus that remains a poorly characterized cause of bacteremia, fever and infective endocarditis. Due to the link with pediculosis, *B. quintana* transmission is tied to poverty, conflict, over-crowding and inadequate water access to maintain personal hygiene. Although these risk factors may be present globally, we argue that a substantial burden of undocumented *B. quintana* infection occurs in Africa due to the high prevalence of these risk factors. Here, we describe the neglected burden of *B. quintana* infection, endocarditis and vector-positivity in Africa and evaluate whether *B. quintana* meets criteria to be considered a neglected tropical disease according to the World Health Organization.

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**Key points:** The presence of *Bartonella quintana* human infection and lice positivity throughout the African continent indicate a hidden burden of illness. Here, we describe how *B. quintana* meets criteria to be considered a neglected tropical disease.

*Bartonella quintana* is a louse-borne gram-negative bacillus that remains a poorly characterized cause of bacteremia, fever and infective endocarditis (IE).[1] *B. quintana* is primarily transmitted via the inoculation of infected body louse feces into abraded human skin and mucous membranes.[1] Once in the human host, the bacterium infects erythrocytes, causing chronic bacteremia.[1] Due to the link with pediculosis, *B. quintana* transmission is tied to poverty, conflict, over-crowding and inadequate water access to maintain personal hygiene.[1,2] Although these risk factors may be present globally, we argue that a substantial burden of undocumented *B. quintana* infection occurs in Africa due to the high prevalence of these risk factors.

The first description of *B. quintana* infection was reported among World War I soldiers, causing a syndrome known as trench fever.[3] In the 1990s, *B. quintana* was determined to cause bacteremia and IE among houseless individuals living in cities of high-income countries, leading to the designation “urban trench fever”.[1] While many studies of *B. quintana* focus on urban trench fever in Europe and the United States, some of the first documented epidemics of *B. quintana* occurred in Africa, with Ethiopian and Tunisian outbreaks occurring in 1946 and 1961, respectively.[4–6] Contemporary descriptions of *B. quintana* acquired in Africa are predominantly cases of IE among African inhabitants immigrating to HICs outside Africa and diagnosed there.

IE is *B. quintana*’s most severe clinical syndrome. *B. quintana* IE predominantly affects the aortic valve, causing valvular destruction with large vegetations prone to embolization.[1,7] Before valvular damage occurs, most cases of *B. quintana* IE are associated with months of non-specific symptoms.[1] Consequently, cases of *B. quintana* IE are diagnosed late, after heart failure and embolization occur, if diagnosed at all. Mortality rates due to *B. quintana* IE exceed 10%, even with recommended treatment involving antimicrobials and valvular replacement surgery.[1] In 2023, *Bartonella* test positivity was added as a major update to the modified Duke criteria for IE.[8]

This update reflects the complexity of diagnosing *Bartonella* infections, including those caused by *B. quintana*. Species within the *Bartonella* genus, including *B. quintana*, are difficult to culture from blood and are typically not identified using routine 5-day incubation.[1] The bacillus is thus designated a culture-negative bacterial pathogen and a major cause of culture-negative IE (CNIE).[1] As with the eight other *Bartonella* species known to cause IE, *B. quintana* infection is primarily diagnosed via serologic and molecular techniques.[9] Serology,
such as indirect immunofluorescent antibody testing (IFA), identifies current or previous *Bartonella* infection, but may be limited by cross-reactivity with other pathogens and its inability to identify *Bartonella* to species-level, unless cross-adsorption procedures that are restricted to reference laboratories are used.[1,10] Serologic positivity of different tests using different pathogen antigens may not exclude possible co-exposure to multiple pathogens.[11] Speciating *B. quintana* necessitates molecular techniques such as polymerase chain reaction (PCR) with species-specific primers.[1,12] For cases of IE, sensitivity is highest when testing is performed on explanted cardiac tissue rather than blood samples.[1,9] The reliance on molecular techniques performed on invasive tissue samples undermines the feasibility of diagnosing *B. quintana* in African settings that have limited access to cardiovascular surgery and where 1.3% of the biologic laboratories on the continent perform bacteriologic culture and antimicrobial susceptibility testing.[13,14] Nevertheless, the number of reported cases of *B.quintana* IE acquired throughout the African continent indicate hidden transmission (figure 1, appendix 1 and 2). Here, we describe the neglected burden of *B. quintana* infection in Africa and evaluate whether *B.quintana* meets criteria to be considered a neglected tropical disease.

Patient consent statement: This study exclusively uses existing published data and thus does not include factors necessitating patient consent or ethical committee approval.

*Bartonella quintana* in Sub-Saharan Africa:

The first documented outbreak of *B. quintana* in Sub-Saharan Africa occurred in Ethiopia in 1946 and the Horn of Africa continues to be endemic for *B. quintana.*[4] In 2017, among five Ethiopian children undergoing cardiovascular surgery for IE in Israel, *B. quintana* was found to be the main agent, in 4/5 patients.[15] In 2023, an additional Ethiopian case of *B. quintana* endocarditis was added to this series.[16] While the sample size remains small, *B. quintana* was the predominant cause of IE in this cohort despite testing for alternate aetiologies.[15] In 2021, *B. quintana* endocarditis was diagnosed in an Eritrean man living in the Netherlands after presenting with fatigue, renal failure and weight loss.[17] One year later, an additional case of *B. quintana* endocarditis was reported from a 31-year-old Eritrean woman soon after immigrating to Canada.[7]

*B. quintana* is common in louse vectors in the Horn of Africa. *B. quintana* is the most common pathogen identified in Ethiopian lice, identified in over 9% of 65 head lice pools.[18] While body louse transmission of *B. quintana* is well-established, entomologic and epidemiologic studies suggest that head lice may occasionally transmit *B. quintana*, especially in resource-poor contexts, as highlighted by a recent review article and a *B. quintana* outbreak associated with head lice in Senegal.[19,20] In a separate study of 271 head and 424 body lice collected from 134 Ethiopian individuals, *B. quintana* was identified in 6.7% and 12.7% of individuals with head and body lice, respectively.[21] *B. quintana* positivity in Ethiopian lice and the pathogen’s
presence among cases of IE acquired in Ethiopia and Eritrea suggest a burden of undiagnosed \textit{B. quintana} infection in the Horn of Africa.

Regions of Sub-Saharan Africa outside the Horn of Africa have long been known to harbour \textit{B. quintana}. Cases of \textit{B. quintana} were recognized during a 1995 outbreak of epidemic typhus in Burundi.[22] IE in the region was previously characterised by high rates of CNIE, but recent results from the Tygerberg Endocarditis Cohort suggest that \textit{B. quintana} may be the predominant cause CNIE in South Africa. The Tygerberg Endocarditis Cohort is a cohort study of endocarditis patients treated at Tygerberg Academic Hospital, Cape Town, South Africa.[23] This study included 140 patients, of which 65 were recruited prospectively. In the prospective arm, patients with suspected IE were subjected to a set protocol for organism detection, including serology for \textit{Bartonella} species and routine tissue PCR at time of surgery.[23] This study identified \textit{B. quintana} as the most common cause of CNIE and the second most common cause of IE after \textit{Staphylococcus aureus}.[23] This finding supports the notion that \textit{B. quintana} may be a major contributor to the high rates of CNIE in Southern Africa.

In 2022, an outbreak of febrile illness due to \textit{B. quintana} was reported from the Senegalese village of Ndiop.[20] Of the 228 patients whose blood sample was tested for \textit{B. quintana}, 4.4\% (n=10) were positive by real-time PCR.[20] Previously, three cases of \textit{B. quintana} IE acquired in Senegal were diagnosed in Europe, including a pediatric case in a 13 year-old girl and a fatal case in a 50 year-old man.[24,25] In 2019, a case of \textit{B. quintana} IE was reported in a 37-year-old school teacher after immigrating from the Democratic Republic of Congo (DRC) to the United States of America.[26] Here too, the authors maintained that the infection was acquired in the DRC. In 2023, \textit{B. quintana} IE was reported in an 11 year-old patient from Rwanda who underwent valve replacement surgery in Israel.[16] These descriptions exemplify cases of \textit{B. quintana} endocarditis acquired in Africa but diagnosed and treated outside the African continent.

The Sub-Saharan African presence of infection due to \textit{Bartonella} species and \textit{B. quintana} was further demonstrated in a 2021 multicenter study of febrile illness in African children: \textit{Bartonella} species were among the first and second most common origin of bacterial DNA found in the blood of febrile patients in Madagascar and Burkina Faso, identified in 2.5\% and 2\% of all acute fever cases, respectively.[27] Of the nine \textit{Bartonella} cases from Madagascar, four were further speciated to \textit{B. quintana}.[27] No other \textit{Bartonella} species were identified.[27] While this study did not identify to species-level all \textit{Bartonella}-associated febrile illness, the only \textit{Bartonella} cases that underwent sequencing were identified as \textit{B. quintana}, supporting the notion that \textit{Bartonella} species, and \textit{B. quintana} specifically, likely remain common and under-recognized causes of fever in Sub-Saharan Africa.

\textit{Bartonella quintana} in North Africa

Many of the first reported cases of \textit{B. quintana} IE were acquired in North Africa and recent cohorts from the region identify \textit{B. quintana} as a common cause of CNIE. The first African case
of *B. quintana* IE was reported in 1996 in a 34-year-old Algerian farmer, only three years after the first publication on *B. quintana* IE in 1993.[5,28] As the Algerian farmer denied houselessness, alcohol use and ectoparasitosis, this description provided the first suggestion that risk factors for *B. quintana* “may be different in western Europe or North America and in Africa.”[28] Subsequently, 14 other Algerian cases of *B. quintana* IE were described and 12 cases were reported from Tunisia, leading the authors to conclude that the disease “seems to be very common in Tunisia.”[29,30] While specific risk factors for *B. quintana* infection in North Africa have not been explicitly studied, the majority of *B. quintana* IE from Algeria and Tunisia were among individuals with “poor living conditions” who lived in crowded households “of at least 10 persons”.[29,30] This suggests that over-crowding and poverty are risk factors for *B. quintana* infection, independent of houselessness and alcohol use disorder.

**Estimating the hidden burden of *Bartonella quintana* in Africa**

The available evidence on human *B. quintana* infection acquired in Africa is disproportionately based on cases of IE treated in high-income countries outside Africa and regions within Africa with access to cardiovascular services. This reflects bias due to the unequal availability of cardiovascular surgery and molecular diagnostics.[14,31] Estimating the burden of *B. quintana* in Africa is limited by the compound difficulties of identifying *B. quintana* infection microbiologically and diagnosing endocarditis clinically. Estimating *B. quintana* prevalence is problematic as infected individuals may have subclinical disease and may not seek care. These difficulties are further exacerbated by the fact that the disease is not notifiable.

Studies of houseless populations in high-income countries suggest that more than 15% of individuals had prior *B. quintana* infection and 5-14% of houseless individuals had *B. quintana* bacteremia.[1,32] Applying these figures to African jurisdictions where *B. quintana* IE has been reported would suggest a burden of undiagnosed infection, even if the risk would be several fold lower in this context. Considering that 20% of individuals with *B. quintana* bacteremia may develop IE, a substantial number of *B. quintana* IE may be overlooked.[1,33] This issue is further complicated by the chronicity of *B. quintana* bacteremia, which may persist well over a year despite minimal symptoms.[6,34]

While large studies of heart failure and IE in Africa are scant, the existing data suggests a hidden burden of CNIE, possibly consistent with *B. quintana*.[14,31] In a cross-sectional study of 106 Ethiopian children admitted with acute heart failure, IE was the most common cardiac etiology.[35] In a systematic review of IE in Africa, half of the cases were culture-negative.[14,23] While direct evidence of *B. quintana* IE in large prospective African studies is limited to TEC and the studies described above, it is possible that many of the CNIE are due to undiagnosed *B. quintana*. This systematic review also characterizes IE in Africa as a disease of young patients, a finding reflected in the cases of *B. quintana* IE described above.[14]

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Does *B. quintana* meet criteria to be considered a neglected tropical disease?

Neglected tropical diseases are a diverse grouping of diseases united by their association with poverty and their disproportionate burden in tropical and subtropical areas.[36] The World Health Organization (WHO) has four criteria for designating a condition as a neglected tropical disease (table 1).[36] Existing evidence suggests that *B. quintana* may meet these criteria, though additional research is needed.

*B. quintana* disproportionately affects populations experiencing poverty

*B. quintana* causes morbidity and mortality among populations experiencing houselessness, displacement and lack of access to running water to maintain personal hygiene.[1,2] Within Africa, *B. quintana* positivity in lice is correlated to country Gross Domestic Product (GDP).[2] Countries with lower GDP have a higher prevalence of lice with *B. quintana*, though specific risk factors for *B. quintana* infection in the African context have not been thoroughly investigated.[2] *B. quintana* IE causes morbidity in the form of heart failure, renal dysfunction and embolization.[1] As access to cardiovascular surgery is limited in many African contexts, mortality due to *B. quintana* IE may be simultaneously amplified and under-reported. Stigma occurs via the association with ectoparasitosis. Individuals with pediculosis may be shunned due to fears of transmission, pruritis and the development of skin abrasions. As illustrated by the cases above, *B. quintana* acquired in Africa disproportionately affects a younger population, adding an additional economic burden on families, though cohort studies that incorporate an economic analysis are needed to better elucidate the cost of *B. quintana* infection in Africa.

*B. quintana* primarily affects populations living in tropical and sub-tropical areas

While *B. quintana* was historically described as being localized to Northern Europe, the disproportionate burden of *B. quintana* infection in Africa has long been postulated, including a gradient of increasing *B. quintana* infection from Northern Europe to African countries.[29] This likely reflects an economic gradient rather than a climactic one.[2] The preponderance of *B. quintana* cases reported from high-income countries in non-tropical areas likely reflects the combined availability of cardiovascular surgery and molecular diagnostics to speciate *B. quintana*, rather than a large burden of disease, as indicated by the cases of *B. quintana* endocarditis reported from Northern high-income countries where the pathogen was determined to be acquired in Africa.[26,37–40]. The single largest description of *Bartonella* endocarditis is a French study where *B. quintana* was detected in 48 (53%) of cases.[39] A recent systematic review of *B. quintana* endocarditis identified 105 (62.9%) of cases to be acquired in a high-income country.[40] More studies are needed to determine the true burden of *B. quintana* infection in low and middle income countries, including those on the African continent.
B. quintana is immediately amenable to broad control

B. quintana infection may be eliminated by applying a combination of four of the five public health strategies adopted by the WHO for control of NTDs.[36] Oral antimicrobials, such as doxycycline, may be used as chemotherapy to prevent B. quintana disease in areas with elevated B. quintana infection, as occurs with mass-drug administration for other neglected infections, though studies involving B. quintana are lacking.[41] Intensified case management and household contract tracing may use existing technology, such as IFA, to screen individuals for infection prior to endocarditis-related morbidity and mortality. Vector control is feasible using existing pediculicidal agents such as permethrin and ivermectin and interventions to improve access to water to maintain personal hygiene. The latter may be integrated into existing Water, Hygiene and Sanitation (WASH) interventions that are known to be indispensable components of NTD control.

Research on B. quintana is neglected

All aspects of B. quintana research are neglected. B. quintana epidemiology is poorly described with most studies focusing on houseless populations in high-income countries, as exemplified by studies of B. quintana bacteremia among houseless individuals in the United States and France.[1,5,6,42] Seroprevalence studies in Africa are lacking. No large studies describe the prevalence of B. quintana infection among individuals living on the African continent and presenting with fever, heart failure or symptoms of embolization. Diagnosis of B. quintana is complex, relying on expensive equipment and specialized personnel. IFA, the main serologic test for B. quintana, has low throughput and necessitates a fluorescent microscope, which may not be available in laboratories in certain low-resource settings. Interpretation of IFA requires specific training. Many of the diagnostic companies that produce commercial B. quintana IFA kits do not distribute to certain African countries where B. quintana is endemic.[18] Isolating B. quintana from blood culture samples necessitates specific techniques, such as lysis centrifugation, freeze-and-thaw, subculturing, and prolonged incubation up to 45 days.[1,43] If growth occurs, the pathogen is excluded from many commercial databases for interpreting Matrix-Assisted Laser Desorption/Ionization Time-Of-Flight Mass Spectrometry results, requiring the inclusion of additional spectra limited to specific international reference laboratories.[44,45] PCR from whole blood has limited sensitivity compared to its performance on invasive tissue samples and there is no consensus on the best molecular target to use.[46,47] Even in high-income countries, B. quintana testing is often centralized in reference laboratories. B. quintana serology and PCR are not available in most African countries, despite the capacity of many national laboratories to perform these tests. Rapid diagnostic tests, such as immunochromatographic tests, do not exist and none are in development. Treatment for B. quintana is largely based on a small open trial of gentamicin and doxycycline versus placebo for treatment of chronic bacteremia.[48] As gentamicin is associated with significant toxicity, drug
level monitoring is recommended but is rarely available in low-resource settings where the infection is endemic. American resources recommend treatment with rifampin and doxycycline based on limited data.[49] There are no published or registered randomized controlled trials comparing the efficacy of different antimicrobial regimens.

**Public health recommendations**

While *B. quintana* may meet all four WHO NTD criteria to be considered for elimination, the current state of research on *B. quintana* is so severely deficient that further research is needed to confidently define the condition as a NTD (table 2). We believe that a few modest measures may substantially improve awareness of this neglected disease. We advocate for *B. quintana* to be considered a national notifiable disease to ensure that data on existing cases are reported. We suggest making *B. quintana* testing available at national reference laboratories capable of performing serology and PCR, as this would use existing infrastructure and trained personnel to avoid significant financial costs. We suggest that initial surveillance testing occur in batch among high-risk patients with an elevated pre-test probability of *B. quintana* infection, such as those with CNIE. For countries without capacity to perform *B. quintana* testing, we propose that samples be sent to regional reference laboratories with dedicated *B. quintana* diagnostic capacity, as occurs with other infections.[50] We encourage the development of immunochromatographic tests to facilitate surveillance in low-resource settings. Lastly, we advocate for randomized controlled trials to identify safer alternatives to gentamicin. Early detection and treatment of subclinical *B. quintana* infection may prevent avoidable morbidity, mortality and cost.

The inverse care law states that the availability of care “tends to vary inversely with the need of the population served.”[51] *B. quintana* predominantly affects individuals experiencing substantial need, with a concealed burden on the African continent. Recognizing that *B. quintana* meets many NTD criteria is a first necessary step.
LEGEND FIGURE 1:

Figure 1. Map of *B. quintana* infective endocarditis and louse positivity on the African continent. IE: infective endocarditis. References for this map are available in appendix 1 and 2.
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A.M.: Writing (review & editing), methodology, resources/ investigation

H.A.: Writing (review & editing), investigation

P.E.F.: Writing (review & editing), supervision

N.G.: Writing (review & editing), project administration

J.v.G: Conceptualization, writing (review & editing), supervision
References:


Table 1. WHO criteria for classifying a condition as a neglected tropical disease and applicability to Bartonella quintana

<table>
<thead>
<tr>
<th>WHO criteria for NTD classification</th>
<th>Applicability to B. quintana</th>
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</table>
| 1. Disproportionately affect populations living in poverty; and cause important morbidity and mortality – including stigma and discrimination. | - B. quintana infection is associated with conditions of severe deprivation (eg: houselessness, living in a refugee camp, lacking running water to maintain hygiene).  
- B. quintana endocarditis causes morbidity (heart failure, renal dysfunction, cerebral embolization causing neurologic impairment) and mortality (>10% despite treatment).  
- Pediculosis associated with stigma. |
| 2. Primarily affects populations living in tropical and sub-tropical areas. | - Europe-Africa gradient with greater burden in Africa.  
- Reliance on molecular testing and cardiovascular surgery creates bias against reporting in LMICs. |
| 3. Is immediately amenable to broad control, elimination or eradication by applying one or more of the five public health strategies adopted by the Department for Control of NTDs. | - 1. B. quintana infection may be treated with preventable chemotherapy (eg: doxycycline).  
- 2. Intensified case management may prevent ongoing household transmission (eg: via shared bedding). |
3. Vector control: treatment of pediculosis (eg: washing clothing/bedding, pediculicidal therapy with permethrin or ivermectin).


5. Safe water, sanitation and hygiene: Access to water to maintain hygiene is essential to interrupt transmission.

4. Is relatively neglected by research – i.e., resource allocation is not commensurate with the magnitude of the problem.

- Diagnostics: No new development of diagnostics. No rapid diagnostic tests. Current diagnostics (eg: IFA, qPCR) not available in many low-resource settings.
- Treatment: Antimicrobial therapy based on limited evidence (single open trial of gentamicin and doxycycline vs. placebo). Toxicity associated with gentamicin. Elevated mortality despite treatment. Anecdotal reports of success with other regimens.
Table 2. Key *Bartonella quintana* knowledge gaps and associated WHO criteria for classifying a condition as a neglected tropical disease

<table>
<thead>
<tr>
<th>WHO criteria for NTD classification</th>
<th>Key knowledge gaps</th>
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<tbody>
<tr>
<td>1. Disproportionately affect</td>
<td>- Risk factors for <em>B. quintana</em> infection in LMICs are poorly defined and largely extrapolated from studies in HICs (case-control studies in LMICs are lacking).</td>
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<td>populations living in poverty; and</td>
<td>- Morbidity and mortality due to <em>B. quintana</em> infection and endocarditis are poorly characterized in LMICs (long-term cohort studies of <em>B. quintana</em> infection and IE are lacking as well as prevalence studies among individuals with heart failure and embolization such as stroke).</td>
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<td>cause important morbidity and</td>
<td>- Qualitative research on pediculosis-related stigma and discrimination are absent (the effect of ectoparasitosis on employment, social mobility and marriageability is not well studied).</td>
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<tr>
<td>mortality – including stigma and</td>
<td>- While a Europe-Africa gradient has been proposed, comparative prevalence studies between different countries do not exist.</td>
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<td>discrimination.</td>
<td>- With few exceptions (eg: TEC), existing data predominantly relies on diagnostics performed outside LMICs, reflecting the need for diagnostic capacity in referral laboratories in LMICs.</td>
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<tr>
<td>2. Primarily affects populations</td>
<td>- Studies evaluating the role of oral chemotherapy to prevent the progression from infection to endovascular disease are lacking.</td>
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<td>living in tropical and subtropical</td>
<td>- Environmental stability of <em>B. quintana</em> on shared bedding/clothing and its role in transmission is poorly defined.</td>
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<tr>
<td>areas.</td>
<td>- Transmission in LMICs is poorly characterized. Many case reports of patients with <em>B. quintana</em> IE acquired in LMICs deny previous pediculosis, suggesting alternate forms of transmission (case-control, contact tracing and additional vector studies are required).</td>
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<tr>
<td>3. Is immediately amenable to</td>
<td>- Little to no investment in most aspects of <em>Bartonella</em> research (The Steven &amp; Alexandra Cohen Foundation being a recent exception).</td>
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<td>broad control, elimination or</td>
<td>- <em>Bartonella</em> research need, stakeholders and existing projects have not been mapped.</td>
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<td>eradication by applying one or</td>
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<td>more of the five public health</td>
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<td>strategies adopted by the</td>
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<td>Department for Control of NTDs.</td>
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<td>4. Is relatively neglected by</td>
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<td>research – i.e., resource allocation is not commensurate with the magnitude of the problem.</td>
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LMICs: low- and middle- income countries, HICs: high-income countries, IE: infective endocarditis, NTDs: neglected tropical disease. TEC: Tygerberg Endocarditis Cohort (South Africa).