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Grand challenges in major tropical diseases

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Overview

Approximately 15 million people die each year due to tropical diseases, which are caused by a variety of infectious agents, such as bacteria, viruses, parasites, or protozoa. Such diseases usually are a result of an intricate relationship between poverty, poor living conditions, malnutrition, and poor healthcare system infrastructure, affecting a large proportion of developing and underdeveloped countries (1–3). Therefore, these diseases are not restricted to infections that are uniquely reported in tropical regions, but also include illnesses that exhibit a very high burden in such zones of the globe.

Despite the great progress in governmental and private initiatives to improve measures to prevent and treat these infections, they remain the world's leading cause of premature death, highlighting the magnitude of this public health problem (4–6). Herein, we summarize top priorities that pose grand challenges to dampen the burden of major tropical diseases worldwide. We will especially focus on the big three pathogens, which are the human immunodeficiency virus (HIV), *Mycobacterium tuberculosis* (*Mtb*), and *Plasmodium* sp. although other important conditions are highlighted. Aspects of disease burden, diagnosis, treatment, and prophylaxis are discussed to define the scope of interest of the Section *Major Tropical Diseases* of the *Frontiers in Tropical Diseases* journal.

HIV

HIV infection is a major global public health problem, as it has been associated with a total of approximately 40.1 million deaths. Moreover, it is estimated that there are 38.4 million people living with HIV (PLWH), and at the end of 2021, 650 thousand people had died from HIV-related causes (7).

Infected individuals gradually diminish the effectiveness of their immunological responses, as the virus invades and destroys lymphocytes, resulting in increased susceptibility to various opportunistic diseases (8). The advanced stage of HIV infection is named acquired immunodeficiency syndrome (AIDS), which is characterized by $CD4^+$ T-lymphocyte counts below 200 cells/mm3 (9).

More than 70% of PLWH reside in low-income countries within the tropics. Most cases are in sub-Saharan Africa, followed by Latin America and the Caribbean (10). Of note, quite often there is an association between HIV and other intercurrent tropical infections. In such cases, HIV infection may deteriorate the natural course of tropical diseases, dampening the accuracy of diagnostic tests and/or the effectiveness of medications. On the converse, tropical diseases can accelerate HIV-associated disease progression and the development of AIDS (11).

Grand challenges

There have been significant advances in the prophylaxis, diagnosis, and treatment of PLWH. Some crucial points in the HIV cascade of care still need to be optimized, from the initial diagnosis to achievement of viral suppression. The cascade of care illustrates the effectiveness of HIV testing services, provide earlier diagnosis and early antiretroviral therapy (ART) initiation, and create policies to increase treatment adherence.

Treatment

The most critical advance in the attempts to control the HIV epidemic was the development and implementation of ART, which has led to significant reductions in morbidity and mortality. The therapeutic effect is based on immune reconstitution which is characterized by improvement on lymphocyte counts and function, and attenuation of homeostatic disruption (12). In addition, PLWH who achieve low levels of viremia are less likely to transmit the virus (13). Thus, more than an effective treatment, ART is also an indispensable prevention strategy.

Currently, 46 ART drugs approved by the US Food & Drug Administration are available to treat HIV infection, and standardized treatment protocols vary depending on the country resources (14). According to the latest WHO bulletin, approximately 70% of PLWH are currently on ART (9). Despite that, ART is not curative, and the viral load usually rebounds within weeks if treatment is interrupted (15). This highlights the need to promote actions that encourage adherence to treatment.

Notwithstanding the significant results obtained from ART, the aspect of controlling but not providing a cure remains a public health concern. The adherence to ART for a lifetime treatment is difficult and therefore it is a big challenge to sustain the patient engaged on therapy. Importantly, the non-adherence to ART appears to be associated with social stigmatization, adverse drug reactions (ADR), bad consumption habits, young age, and low level of education (16–18). Thus, studies with clinical and epidemiological data are needed to understand the risk factors associated with this abandonment of treatment, aiming to direct the creation of effective public health policies to overcome this challenge. Lastly, the development of novel highly effective and/or curative antivirals with less side effects may bring new hope to this field.

Diagnosis

There are different types of tests available to diagnose HIV infection, such as rapid point-of-care tests, serological, and nucleic acid-based assays. Importantly, after obtaining a positive test it is recommended to confirm the diagnosis with another type of test (19).

During an infection, antibodies are produced by the immune system to eradicate the pathogen. The serological test for HIV identifies this production, which usually occurs within a period of up to 28 days. An important limitation of the diagnosis is the time from viral exposure to serologic conversion, defined as immunity gap (20).

Rapid diagnostic tests, which uses blood from a fingerstick or saliva, can identify HIV infection in as fast as 30 minutes. However, for specific populations at risk, such as babies born from mothers living with HIV, this tool is less accurate to detect HIV infection. Therefore, new technologies are warranted to be developed and implemented to carry out the point-of-care approaches (9). In fact, development of rapid and accurate diagnostic tests for at risk populations is one of the major challenges to overcome. Molecular methods are essential for the identification of HIV nucleic acid, which can provide logistical, financial, and human resource difficulties (21). The creation of an easy and highly accurate test is crucial to identify HIV infection in vulnerable populations. Also, novel approaches to exposed patients who were still in the gap of 28 days are needed, aiming to improve the application of the post-exposition therapy. For those who are tested and diagnosed with HIV, access to HIV treatment and an efficient cascade of care without stigma must be as simple and affordable as well as conceivable to obtain the favorable outcomes.

Prevention/vaccine

HIV can be transmitted through unprotected sex, blood transfusion, and contact with the various body fluids of infected people, such as blood and breast milk. Of note, HIV can also be transmitted from a mother to child during pregnancy and delivery (8, 9). Critical approaches are needed, such as condom use, pre and post-exposure prophylaxis, reduced use of injecting drugs, prevention of vertical transmission through use of antiretrovirals during pregnancy, and permanent

advocacy for screening for HIV and other sexually transmitted infections (7, 9).

Overall, the lack of political commitment, the hesitancy to widely adopt sex education and family planning, and the exclusion of minorities that are most at risk for HIV all contribute to inability to achieve desirable level of HIV prevention. The lack of a vaccine that could control the worldwide dissemination of HIV disease completes the list of targeted challenges.

Tuberculosis

TB was responsible for around 1.6 million deaths worldwide in 2021 (22). Approximately ¼ of the world's population is estimated to be infected with *M. tuberculosis*, and about 10 million new cases are registered annually. The main regions related to high TB burden are found in South-East Asia, followed by Africa and the Western Pacific (22). Moreover, higher TB burdens pointing to underdeveloped countries characterize TB as a disease of poverty, economic distress, and vulnerability (22).

From a clinical perspective, the disease presentations are divided, in a simplified way, into TB infection (TBI), previously named latent TB infection, and active TB (23). TBI is characterized by the clinically silent infection, with an apparent effective immune response against the bacilli and control of immunopathology. On the other hand, active TB can be stratified according to the site of the bacillus infections, such as pulmonary (PTB), extrapulmonary (EPTB) or disseminated (PTB+EPTB) (24). PTB patients may manifest a variety of symptoms such as cough, weight loss, appetite loss, fever, and night sweats. The EPTB presentation varies depending on the system/organ affected by the infection or exacerbated immune responses, such as, TB lymphadenitis, pleural TB, meningitis, as well as Pott disease, where bones and joints of the spine are affected (25).

Some factors are associated with worse TB disease outcomes. The bacterial load exposure, host comorbidities, and the integrity of the immune system, both at the cellular level and systemic level, are directly related with unfavorable outcomes, such as treatment failure, and death (26–29). Notably, pregnant women, PLWH and children under five years-old are considered populations with a higher risk of both developing active TB and presenting poor outcomes (30–32).

Grand challenges

To achieve the goals set by the WHO aiming at ending TB by 2035, we still need to optimize some key points in the prevention/vaccination, diagnosis, and treatment of this disease. The big challenge in this scenario is in developing tools with high effectiveness, low cost and easy application. These three characteristics are important to implement each technology in underdeveloped countries.

Treatment

TB is currently treated on a minimum six-month standard of four antibiotics (Rifampin, Isoniazid, Pyrazinamide, and Ethambutol - RIPE), regardless of the clinical form of TB. RIPE regimens for treating TB disease have an intensive phase of two months, followed by a maintenance phase of at least four months with just rifampin and isoniazid (33). Although recommended, the standard treatment is not yet applied in all countries in its proposed format. In addition, some *Mtb* strains are resistant to standard therapy, making it necessary to use alternative methods, with different combinations of antibiotics, according to the sensitivity of the strain (33).

Treatment adherence is a substantial challenge to combat TB. The long duration of treatment and related ADR are associated with nonadherence and loss to follow up (34, 35). Thus, it is crucial to invest in shortening the treatment duration and/or in less toxic drugs to reduce the risk of ADR. Moreover, treatment interruption may facilitate the emergence of multidrug-resistant strains, which represent an important obstacle in the management of TB patients. The necessity to develop an efficient treatment is related with the prerequisite of updating the knowledge on the molecular basis for evolution of *Mtb* drug resistance.

Diagnosis

Despite of the clinical form of TB, the diagnosis remains a public health problem. First, the diagnosis of TBI is rather indirect and relies on evidence of cellular immune response against mycobacterial antigens. The low tissue bacterial burden associated with TBI works against any microbiology-based diagnostic strategy focused on identifying the bacteria or its components (36).

The most currently used tests for TBI diagnosis are the Interferon-Gamma Release Assays (IGRA) and tuberculin skin test (TST) (36). Aside from the higher accuracy of IGRA, the high cost and the need for infrastructure for execution (37) make it difficult to implement in developing countries. On the other hand, the diagnosis of active TB is well established by the isolation of *Mtb* or fragments from a body secretion, tissue, or fluid. Most of the available active TB tests were developed to be performed using a sputum sample, such as the acid-fast bacilli (AFB) identification in smears by microscopy and GeneXpert (38). However, these methods present a limiting factor in patients with low bacillary load, such as children, PLWH, and those with only EPTB forms (39).

To expand the TB diagnosis, it is key to develop tests that can diagnose TB in easily accessible samples, such as blood and urine. Furthermore, the possibility of applying the tests on a large scale and at a low cost is indispensable. Tests that can

diagnose TB independent of the site affected can potentially make the diagnosis of EPTB in populations at risk with low bacillary load more reliable. To fulfill this objective, it is imperative to increase investment in research focused on biomarkers and molecular signatures of TB. Additionally, another challenge is to develop tools that permit to identify patients with high risk to progress from TBI to active TB, as well as to recognize the patients who present increased risk of unfavorable TB treatment outcomes. This reinforces the need of investments in precision medicine on tropical diseases.

Prevention/vaccines

The available prophylaxis for TB is the Bacillus Calmette-Guérin (BCG) vaccine. This vaccine was formulated using a live-attenuated strain of *M. bovis*. However, the BCG vaccine prevents only severe forms of the disease, such as miliary and meningeal TB in children. Importantly, BCG does not prevent other TB presentations such as the primary pulmonary infection or activation of TBI (40). It is vital to encourage the development of an effective and specific vaccine against *Mtb*, which can prevent not only severe forms of the disease, but also the development of active pulmonary TB. There are a few vaccines currently been tested in clinical trials, but no candidate has been formally implemented in clinical practice.

Malaria

The world has made considerable progress in the fight against malaria. This disease is transmitted by mosquitoes infected with *Plasmodium* sp. In the past 20 years, the incidence reduced by 27%, and the mortality rate decreased by 50.8% (41). Of note, due to service disruptions caused by the coronavirus disease (COVID-19) pandemic, increases of 14 million cases of malaria and 47 thousand deaths were estimated in 2020 compared to 2019 (41).

Despite all advances in the last years, malaria remains with high burden worldwide, notably in resource-limited, tropical countries, with most cases and deaths occurring in sub-Saharan Africa. In 2020, approximately 241 million cases of malaria and 627 thousand malaria-related deaths were reported worldwide, accounting 7.8% of the global diseases burden (41).

Some population groups are at higher risk of acquiring malaria and developing the severe disease presentations, such as children under five years of age, pregnant women, and PLWH (41). Among the most important clinical presentations of public health relevance are severe anemia and cerebral malaria, which are associated with elevated risk of death if not treated. Parasitic and host factors are involved in the development of the severe clinical forms, and the associations between clinical parameters and the outcomes have been largely explored in recent years.

Grand challenges

New perspectives in the research field are required to better understand the dynamicity between *Plasmodium* fitness and the host immune response. Development of vaccines, new malaria drugs and mosquito intervention strategies are necessary to achieve the WHO goals and minimize the malaria burden, decreasing the devastating impact of this parasitic disease in the world.

Treatment

Malaria treatment depends on the parasite species, severity of infection, endemicity of the area, and drug-resistance profile. The drugs used range according to the local guidelines and include various possible combinations (42).

Antimalarial drugs are used in the treatment and prevention of *Plasmodium* infection (43). The erythrocytic stage, that causes symptomatic diseases, is the main target in the current treatment model. However, the lack of a highly effective therapy and the emergence of drug-resistant parasite strains lead to challenges in the malaria burden control. Currently, several new options have been studied, focusing on novel targets, such as proteins and enzymes associated with lipid metabolism and parasite DNA replication, with less side effects.

A valuable tool in malaria control is the development of vaccines, with potential to drastically reduce the disease's global burden. Despite the relevance of the intervention, the creation of new vaccine options has led to the discovery of several challenges to an effective strategy and include antigenic polymorphism and loss of immunological memory. Several vaccine models at different stages of development are candidates to prevent infections due to *P. falciparum* and *P. vivax* [reviewed in (44)].

Diagnosis

Due to the non-specific nature of the signs and symptoms, which overlap with other frequent tropical diseases, diagnosis is based in microbiologic techniques (45). Laboratory diagnosis of malaria can be made through parasite identification by microscopic examination of thick or thin blood smears or by parasite nucleic acid detection using polymerase chain reaction (PCR). PCR is more sensitive than microscopy and is useful for confirmation of species as well as drug resistance (46).

Importantly, the urgency of simple, quick, accurate, and cost-effective diagnostic tests for determining the presence of malaria parasites has foster development of numerous rapid diagnostic tests (RDTs). RDTs are used as a screening test and must be validated with other methods, such as microscopic diagnosis and serological and molecular tests, to confirm the infection (45). It is necessary to offer resources more quickly and efficiently to patients at risk of severe illness. Better understanding of the interaction between the host and parasite

is the key to the development of prediction models of severe disease.

Prevention/vaccines

Prophylactic approaches include individual protection measures against mosquito exposure and vector control (47). Regarding vector control, there are several methods considered effective, such as community education for surveillance and reduction of breeding sites, sanitary improvements, behavioral measures (use of repellents and insecticides in spray versions or impregnated with materials) and vaccination (48, 49).

There is currently only one WHO-approved malaria vaccine: RTS,S/AS01. This vaccine was implemented in endemic countries in 2019. Nonetheless, it is only 36% effective in a population highly exposed to *Plasmodium* (50). Therefore, it is necessary to encourage new studies to develop an effective vaccine that can be widely applied to the entire population. Furthermore, long-term sustainable preventive measures as well as large scale availability of malaria tests, rapid notification of results, and possibility of geolocation of notified cases in a timely fashion are critical, to combat possible outbreaks of the disease.

Concluding remarks

The major tropical diseases listed here still represent tremendous public health and socioeconomic burden is several countries worldwide. Such diseases share common challenges, such as poverty, timely access to proper diagnosis, clinical care, effective prophylaxis and treatments. To overcome these problems, aside from increased investments from governmental and public sectors, it is necessary to design decision making strategies, based on science, that can be reliably implemented in the tropical regions. This also needs to consider the peculiarities of each region, including weather, geopolitics, and genetics for example. Our journal was launched to serve as a forum to discuss such strategies and help accelerating new policies to reduce the burden of these diseases.

Author contributions

BB-D, MA-P, GR, CV, MM-B, IF, JM-P, KV-S, RM and BA wrote the manuscript. All authors contributed to manuscript revision, read, and approved the submitted version of the manuscript. All authors contributed to the article and approved the submitted version.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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References

1. Zumla A, Ustianowski A. Tropical diseases: Definition, geographic distribution, transmission, and classification. *Infect Dis Clin North Am* (2012) 26:195–205. doi: 10.1016/j.idc.2012.02.007

2. Camargo EP. Doenças tropicais. *Estud av* (2008) 22:95–110. doi: 10.1590/S0103-40142008000300007

3. Pujara P, Parmar M, Rupakar P, Asawa K, Patel S. An introduction to tropical disease: A review article. *IP Int J Med Microbiol Trop Dis* (2021) 2:81–3. doi: 10.5958/2455-6807.2016.00011.8

4. Hotez PJ, Molyneux DH, Fenwick A, Kumaresan J, Sachs SE, Sachs JD, et al. Control of neglected tropical diseases. *N Engl J Med* (2007) 357:1018–27. doi: 10.1056/NEJMra064142

5. Shetty N P, Shetty P S. Epidemiology of disease in the tropics. *Manson's Trop Dis* (2009) 1:19–34. doi: 10.1016/B978-1-4160-4470-3.50007-0

6. Holmes KK, Bertozzi S, Bloom BR, Jha P, Gelband H, DeMaria LM, et al. Major infectious diseases: Key messages from disease control priorities, third edition, in: *Major infectious diseases* (2017). Washington (DC: The International Bank for Reconstruction and Development / The World Bank. Available at: http://www.ncbi.nlm.nih.gov/books/NBK525197/ (Accessed August 19, 2022).

7. UNAIDS. *UNAIDS DATA 2021* (2021). Available at: https://www.unaids.org/sites/default/files/media_asset/JC3032_AIDS_Data_book_2021_En.pdf.

8. Deeks SG, Overbaugh J, Phillips A, Buchbinder S. HIV Infection. *Nat Rev Dis Primers* (2015) 1:1–22. doi: 10.1038/nrdp.2015.35

9. World Health Organization. *Consolidated guidelines on HIV prevention, testing, treatment, service delivery and monitoring: Recommendations for a public health approach* (2021). Available at: https://www.who.int/publications-detail-redirect/9789240031593 (Accessed March 12, 2022).

10. UNAIDS. *UNAIDS fact sheet 2022* (2022). Available at: https://www.unaids.org/sites/default/files/media_asset/UNAIDS_FactSheet_en.pdf.

11. Harms G, Feldmeier H. The impact of HIV infection on tropical diseases. *Infect Dis Clin North Am* (2005) 19:121–35. doi: 10.1016/j.idc.2004.10.002

12. Broder S. The development of antiretroviral therapy and its impact on the HIV-1/AIDS pandemic. *Antiviral Res* (2010) 85:1. doi: 10.1016/j.antiviral.2009.10.002

13. Quinn TC, Wawer MJ, Sewankambo N, Serwadda D, Li C, Wabwire-Mangen F, et al. Viral load and heterosexual transmission of human immunodeficiency virus type 1. *N Engl J Med* (2000) 342:921–9. doi: 10.1056/NEJM200003303421303

14. Food & Drug Administration. HIV And AIDS: Medicines to help you, in: *FDA* (2020). Available at: https://www.fda.gov/consumers/free-publications-women/hiv-and-aids-medicines-help-you (Accessed July 30, 2022).

15. Davey RT, Bhat N, Yoder C, Chun T-W, Metcalf JA, Dewar R, et al. HIV-1 and T cell dynamics after interruption of highly active antiretroviral therapy (HAART) in patients with a history of sustained viral suppression. *Proc Natl Acad Sci* (1999) 96:15109–14. doi: 10.1073/pnas.96.26.15109

16. Ahmed A, Dujaili JA, Jabeen M, Umair MM, Chuah L-H, Hashmi FK, et al. Barriers and enablers for adherence to antiretroviral therapy among people living with HIV/AIDS in the era of COVID-19: A qualitative study from Pakistan. *Front Pharmacol* (2022) 12:807446. doi: 10.3389/fphar.2021.807446

17. Soares Rd, de Brito AM, Lima K, Lapa TM. Adherence to antiretroviral therapy among people living with HIV/AIDS in northeastern Brazil: A cross-sectional study. *Sao Paulo Med J* (2020) 137:479–85. doi: 10.1590/1516-3180.2019.0212170919

18. van Wyk BE, Davids L-AC. Challenges to HIV treatment adherence amongst adolescents in a low socio-economic setting in cape town. *South Afr J HIV Med* (2019) 20:1002. doi: 10.4102/sajhivmed.v20i1.1002

19. HIV Testing, in: *HIV/AIDS* (2022). CDC. Available at: https://www.cdc.gov/hiv/testing/index.html (Accessed August 19, 2022).

20. Kucirka LM, Sarathy H, Govindan P, Wolf JH, Ellison TA, Hart LJ, et al. Risk of window period HIV infection in high infectious risk donors: Systematic review and meta-analysis. *Am J Transplant* (2011) 11:1176–87. doi: 10.1111/j.1600-6143.2010.03329.x

21. Mofenson LM, Cohn J, Sacks E. Challenges in the early infant HIV diagnosis and treatment cascade. *J Acquir Immune Defic Syndr* (2020) 84 Suppl 1:S1–4. doi: 10.1097/QAI.0000000000002366

22. World Health Organization. *Global tuberculosis report 2021*. Switzerland: Geneva (2021). Available at: https://www.who.int/publications-detail-redirect/9789240037021.

23. Esmail H, Barry CE, Young DB, Wilkinson RJ. The ongoing challenge of latent tuberculosis. *Philos Trans R Soc Lond B Biol Sci* (2014) 369:20130437. doi: 10.1098/rstb.2013.0437

24. Pai M, Behr MA, Dowdy D, Dheda K, Divangahi M, Boehme CC, et al. Tuberculosis. *Nat Rev Dis Primers* (2016) 2:1–23. doi: 10.1038/nrdp.2016.76

25. Rodriguez-Takeuchi SY, Renjifo ME, Medina FJ. Extrapulmonary tuberculosis: Pathophysiology and imaging findings. *Radiographics* (2019) 39:2023–37. doi: 10.1148/rg.2019190109

26. Narendran G, Andrade BB, Porter BO, Chandrasekhar C, Venkatesan P, Menon PA, et al. Paradoxical tuberculosis immune reconstitution inflammatory syndrome (TB-IRIS) in HIV patients with culture confirmed pulmonary tuberculosis in India and the potential role of IL-6 in prediction. *PloS One* (2013) 8:e63541. doi: 10.1371/journal.pone.0063541

27. Barreto-Duarte B, Araújo-Pereira M, Nogueira BMF, Sobral L, Rodrigues MMS, Queiroz ATL, et al. Tuberculosis burden and determinants of treatment outcomes according to age in Brazil: A nationwide study of 896,314 cases reported between 2010 and 2019. *Front Med (Lausanne)* (2021) 8:706689. doi: 10.3389/fmed.2021.706689

28. Demitto FO, Araújo-Pereira M, Schmaltz CA, Sant'Anna FM, Arriaga MB, Andrade BB, et al. Impact of persistent anemia on systemic inflammation and tuberculosis outcomes in persons living with HIV. *Front Immunol* (2020) 11:588405. doi: 10.3389/fimmu.2020.588405

29. Kornfeld H, Sahukar SB, Procter-Gray E, Kumar NP, West K, Kane K, et al. Impact of diabetes and low body mass index on tuberculosis treatment outcomes. *Clin Infect Dis* (2020) 71:e392–8. doi: 10.1093/cid/ciaa054

30. Nguyen HT, Pandolfini C, Chiodini P, Bonati M. Tuberculosis care for pregnant women: A systematic review. *BMC Infect Dis* (2014) 14:617. doi: 10.1186/s12879-014-0617-x

31. Lewinsohn DA, Gennaro ML, Scholvinck L, Lewinsohn DM. Tuberculosis immunology in children: Diagnostic and therapeutic challenges and opportunities. *Int J Tuberc Lung Dis* (2004) 8:658–74.

32. Demitto FO, Schmaltz CAS, Sant'Anna FM, Arriaga MB, Andrade BB, Rolla VC. Predictors of early mortality and effectiveness of antiretroviral therapy in TB-HIV patients from Brazil. *PloS One* (2019) 14:e0217014. doi: 10.1371/journal.pone.0217014

33. WHO. Consolidated guidelines on tuberculosis, module 4, in: *Treatment - drug-susceptible tuberculosis treatment*. Available at: https://www.who.int/publications-detail-redirect/9789240048126 (Accessed August 7, 2022).

34. Forget EJ, Menzies D. Adverse reactions to first-line antituberculosis drugs. *Expert Opin Drug Saf* (2006) 5:231–49. doi: 10.1517/14740338.5.2.231

35. Lorent N, Sebatunzi O, Mukeshimana G, den Ende JV, Clerinx J. Incidence and risk factors of serious adverse events during antituberculous treatment in Rwanda: A prospective cohort study. *PloS One* (2011) 6:e19566. doi: 10.1371/journal.pone.0019566

36. Carranza C, Pedraza-Sanchez S, de Oyarzabal-Mendez E, Torres M. Diagnosis for latent tuberculosis infection: New alternatives. *Front Immunol* (2020) 11:2006. doi: 10.3389/fimmu.2020.02006

37. Costa AG, Carvalho BKS, Araújo-Pereira M, Ibiapina HNS, Spener-Gomes R, Souza AB, et al. Lessons learned from implementation of an interferon gamma release assay to screen for latent tuberculosis infection in a Large multicenter observational cohort study in Brazil. *Microbiol Spectr* (2021) 9:e0116321. doi: 10.1128/Spectrum.01163-21

38. Kabir S, Parash MTH, Emran NA, Hossain ABMT, Shimmi SC. Diagnostic challenges and gene-xpert utility in detecting *Mycobacterium tuberculosis* among suspected cases of pulmonary tuberculosis. *PloS One* (2021) 16:e0251858. doi: 10.1371/journal.pone.0251858

39. Jacob ST, Pavlinac PB, Nakiyingi L, Banura P, Baeten JM, Morgan K, et al. *Mycobacterium tuberculosis* bacteremia in a cohort of HIV-infected patients hospitalized with severe sepsis in Uganda–high frequency, low clinical sand derivation of a clinical prediction score. *PloS One* (2013) 8:e70305. doi: 10.1371/journal.pone.0070305

40. Lange C, Aaby P, Behr MA, Donald PR, Kaufmann SHE, Netea MG, et al. 100 years of *Mycobacterium bovis* bacille calmette-guérin. *Lancet Infect Dis* (2022) 22:e2–e12. doi: 10.1016/S1473-3099(21)00403-5

41. *World malaria report 2021* Available at: https://www.who.int/publications-detail-redirect/9789240040496 (Accessed August 7, 2022).

42. Malaria treatment, in: *Medicines for malaria venture* . Available at: https://www.mmv.org/malaria-medicines/malaria-treatment?gclid=CjwKCAjw6fyXBhBgEiwAhhiZsheuUPwXO3Hkkbog-ccx-l2kS_SfwgsXfNATyz3uyt6CKoFyPgU_YhoChHsQAvD_BwE (Accessed August 19, 2022).

43. Zani B, Gathu M, Donegan S, Olliaro PL, Sinclair D. Dihydroartemisinin-piperaquine for treating uncomplicated plasmodium falciparum malaria. *Cochrane Database Syst Rev* (2014) 1:CD010927. doi: 10.1002/14651858.CD010927

44. Hassan AO, Oso OV, Obeagu EI, Adeyemo AT. MALARIA VACCINE: PROSPECTS AND CHALLENGES. *Madonna Univ J Med Health Sci ISSN: 2814-3035* (2022) 2:22–40.

45. Tangpukdee N, Duangdee C, Wilairatana P, Krudsood S. Malaria diagnosis: A brief review. *Korean J Parasitol* (2009) 47:93–102. doi: 10.3347/kjp.2009.47.2.93

46. Kyabayinze DJ, Tibenderana JK, Odong GW, Rwakimari JB, Counihan H. Operational accuracy and comparative persistent antigenicity of HRP2 rapid diagnostic tests for *Plasmodium falciparum* malaria in a hyperendemic region of Uganda. *Malar J* (2008) 7:221. doi: 10.1186/1475-2875-7-221

47. World Health Organization. Diseases UBSP for r and T in T, in: *Global vector control response 2017-2030* (2017). World Health Organization. Available at: https://apps.who.int/iris/handle/10665/259205 (Accessed August 19, 2022).

48. World Health Organization. *Seasonal malaria chemoprevention with sulfadoxine–pyrimethamine plus amodiaquine in children: A field guide* (2013). World Health Organization. Available at: https://apps.who.int/iris/handle/10665/85726 (Accessed August 19, 2022).

49. Messenger LA, Furnival-Adams J, Pelloquin B, Rowland M. Vector control for malaria prevention during humanitarian emergencies: Protocol for a systematic review and meta-analysis. *BMJ Open* (2021) 11:e046325. doi: 10.1136/bmjopen-2020-046325

50. Laurens MB. RTS,S/AS01 vaccine (Mosquirix™): An overview. *Hum Vaccin Immunother* (2019) 16:480–9. doi: 10.1080/21645515.2019.166941