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Grand challenges in major tropical diseases: Part II

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1 Overview

Tropical diseases pose a significant global health burden, particularly in developing countries. These diseases are caused by a variety of pathogens, including bacteria, viruses, protozoa, and helminths and they remain a major cause of preventable morbidity and mortality, particularly in socially vulnerable populations. The persistence of these diseases is often linked to issues such as overcrowding, lack of access to basic sanitation, inadequate health infrastructure, and uneven distribution of prevention and treatment measures despite considerable advances in these infections management. Even though the risk factors and pathogens involved may vary worldwide, in this article we will especially focus on three important groups of tropical diseases: diarrheal diseases, viral hepatitis, and arboviruses. Herein, we aim to provide an overview of the current state of research on these diseases including definitions, diagnoses, treatments, and prevention methods. We will also discuss the main grand challenges facing researchers and practitioners in this field, as well as outline potential strategies for addressing these challenges. By highlighting those topics, we hope to contribute to the ongoing efforts to control and eliminate tropical diseases. In addition, this article summarizes the priorities that are considered for publication in the journal Frontiers in Tropical Diseases, Section Major Tropical Diseases.

2 Diarrheal diseases

Diarrheal diseases affect an estimated two billion people worldwide and cause approximately 1.57 million deaths each year (1). These diseases disproportionately affect low-income countries or marginalized populations, particularly in African and Southeast Asian regions, with limited access to health care, safe water, and sanitation (2–4). They are

a leading cause of morbidity and mortality, particularly among young children and adults over 70 years old, and are responsible for 74.4 million disability-adjusted life years (DALYs), highlighting their significant impact on premature death and disability (4–6).

Diarrheal diseases are caused by a variety of organisms, including bacteria, viruses, and parasites, and are transmitted through contaminated food, water or person-to-person contact. Examples of these pathogens are *Escherichia coli, Vibrio cholerae, Salmonella* and *Rotavirus* (4, 6). Characterized by an unusually loose or watery stools that occur at least three times within a 24-hour period, the severity of diarrheal episodes can range from mild to severe, depending on the individual's level of dehydration and electrolyte balance, which can lead to hospitalization and death (7). The pathogenicity of the etiologic agent and host characteristics, such as immunodeficiency and age also play a role in the severity of the disease (7, 8).

2.1 Grand challenges

To address the global burden of diarrheal diseases, the WHO/UNICEF's Integrated Global Action Plan for the Prevention and Control of Pneumonia and Diarrhea (GAPPD) aims to reduce deaths from diarrhea to fewer than 1 child in 1,000 live births by 2025. This goal will require targeted approaches, particularly in developing countries and among rural and poor populations where the burden of these diseases is highest. Strategies should focus on prevention, including limiting transmission through the provision of safe water and adequate sanitation facilities, increasing vaccination coverage, and strengthening diarrheal disease control programs for effective case management.

2.2 Treatment

Treatment for diarrheal diseases typically involves supportive therapy and rehydration to replace fluids and electrolytes lost through diarrhea. For mild to moderate cases, oral rehydration therapy (ORT) with low-osmolarity rehydration salts is a cost-effective and widely used approach, and can significantly reduce the need for hospitalization in both developed and developing countries (3, 7, 9). In severe cases, intravenous fluids may be necessary (7, 9). Antibiotics may be prescribed in severe cases of *Salmonella*, *Shigella* or *Vibrio cholera* infections, or for individuals with immunodeficiency, but they are not usually used in mild cases (7, 9). In addition to these specific treatment approaches, it is important to maintain proper hygiene and prevent the spread of the disease through the use of proper handwashing techniques and disinfection of surfaces.

For pediatric patients, zinc sulfate supplementation is recommended as an adjunct to ORT to help reduce the duration and severity of diarrhea (3, 4, 7–12). It is estimated that this treatment prevents approximately 300,000 deaths in children each year, but global coverage of both ORT and zinc supplementation is still less than 50% (7). This low coverage is a multifactorial problem that involves the lack of awareness among care providers on how to implement these treatments, low profit margins for pharmacies, leading to shortages due to low commercial interest, and limited access to low-cost treatment through the public sector. To address these challenges, strategies to improve education and access to treatment, such as the dissemination of training material and hygiene education for health care providers and community members, delivering life-saving treatment kits, pre-packaged sets of essential medications, water purification tablets and personal hygiene supplies, through community-health workers, and addressing the underlying social and economic determinants of health, such as poverty and inequality, may be necessary (12–14).

2.3 Diagnosis

Diagnosis of diarrheal diseases is typically clinical, based on the presence of its characteristic symptoms of watery or loose stools and abdominal cramps, as well as the individual's medical history and potential exposure to contaminated food or water. In mild cases of acute diarrhea, laboratory evaluation is typically not necessary due to the self-limited and quick resolution of the condition (15, 16). However, for severe cases, with fever or bloody stools, or in cases where the etiology is unknown and there is a need to control the spread of the disease, testing may be necessary to identify the specific cause and guide treatment. These tests may include stool cultures to detect bacteria or parasites, viral testing, or serologic assays. Rapid diagnostic tests can also be used as an alternative, but their accuracy may vary depending on the specific test and the etiologic agent. In cases evolving with dehydration, blood tests may be helpful in guiding the replacement of fluid and electrolytes (3, 6, 9, 17).

However, access to laboratory testing can be limited in resource-poor settings, and RDT's may not accurately determine all causes of diarrhea. Improving access to and the accuracy of diagnostic tests is an ongoing challenge that requires funding, for the development of new easy-to-use technologies, and advancements in the distribution of resources in underserved areas. In addition to their role in patient care, diagnostic tests can be useful for controlling population exposure to causative agents and preventing disease transmission. Therefore, improving access to high-quality tests is also important, not only for disease control, but also to enable government agencies to restrict the movement of animals and products exposed to specific agents (17).

2.4 Prevention/Vaccine

Preventive measures for diarrheal diseases include handwashing promotion, provision of safe drinking water and basic sanitation services, and vaccination. Handwashing promotion alone or in combination with other hygiene education interventions has been shown to reduce the risk of diarrhea by 30% in children of lower-middle-income countries (6, 18). Similarly, providing safe drinking water and basic sanitation services is crucial and can be achieved through the protection of water sources, improvement in infrastructure and water treatment with chemicals. These

interventions can result in a nearly 50% reduction in diarrheal diseases (12, 18). However, despite progress in areas such as vitamin supplementation, measles immunization, and access to safe drinking water, the implementation of these strategies, especially for the vulnerable population, has been inadequate or non-existent, resulting in nearly 1 billion people without access to these services (6). Is also important to increase demand for toilets and stop open defecation, while subsidizing households to acquire their sanitation facilities (12).

Vaccination is another effective means of preventing diarrheal diseases. The introduction of rotavirus vaccines has contributed to a 7% reduction in mortality among children under 5 years old due to diarrhea and a 96% reduction in hospitalizations (6, 19). Currently, the US Food and Drug Administration (FDA) has approved two rotavirus vaccines, RotaTeq® (RV5) and Rotarix® (RV1), and the Centers for Disease Control and Prevention (CDC) recommends their use. There is also a cholera vaccine available for adults in the United States who plan to travel to areas where cholera is endemic (17). Despite the recommendation to include these vaccines in national immunization programs, they are still underused globally (12, 17). To address this, it is important to prioritize investments to accelerate the introduction of these vaccines in Africa and Asia, where the burden of diarrheal disease is greatest, and to conduct media campaigns to improve knowledge about the importance of completing the vaccination schedule (with all 2 or 3 doses).

3 Viral hepatitis

The study of viral hepatitis is an active and rapidly evolving field, with ongoing research focused on improving prevention, diagnosis, and treatment of the disease. In recent years, the best understanding of the genetics and molecular biology of viral hepatitis has led to the development of more targeted and effective treatments. In addition, advances in imaging techniques and diagnostic tests have made it possible to identify and monitor hepatitis in its early stages, which can help prevent complications and improve outcomes. Although, viral hepatitis remains a significant public health issue responsible for approximately 3,000 preventable deaths daily.

Hepatitis consists in an inflammation of the liver that has several causes, including viral agents such as hepatitis A virus (HAV), hepatitis B virus (HBV), hepatitis C virus (HCV), hepatitis D virus (HDV) and hepatitis E virus (HEV) (20, 21). While all types of hepatitis can cause symptoms such as nausea, vomiting, abdominal pain, fever, and jaundice, the transmission, incubation period, potential for chronic infection, and methods of diagnosis and treatment can vary significantly depending on the specific virus involved (20–23). Among them, HAV and HEV typically have an acute and self-limited clinical course, while HBV and HCV tend to become chronic, leading to cirrhosis and liver cancer (22, 23). Together, HBV and HCV are responsible for the majority of the global burden and mortality of this disease, with more than 3 million people newly infected and accounting for 1.4 million deaths in 2019 (23–25). Thus, this review focuses primarily on these two viral agents and their impact on global health.

3.1 Grand challenges

Eliminating viral hepatitis is a major goal for the World Health Organization (WHO), with a target of achieving this by 2030. Vaccines are available for hepatitis A and B and there is viral control for hepatitis B and cure for C, therefore provide an early detection is crucial to prevent advanced stages of the disease, that include a risk of decompensated cirrhosis, hepatocellular carcinoma, and all-cause mortality (23, 24). One of the major challenges in addressing viral hepatitis is the lack of widespread awareness about the disease. Many people are unaware that they are infected and do not seek testing or treatment until they develop serious complications. This lack of awareness can be exacerbated by stigma and discrimination faced by people with viral hepatitis, which can prevent them from seeking testing and treatment and negatively impact their quality of life (24, 26). Another challenge is the limited access to testing and treatment in many parts of the world due to a lack of resources, trained healthcare workers, and funding (24). This can lead to an unequal burden of diseases and contribute to the spread of the viruses, which are concentrated in low and middle-income countries. The emergence of drug-resistant strains of hepatitis C is also a growing concern, as current treatment options may not be effective against them. To address these challenges, it is important to implement targeted hepatitis C screening programs for high-risk groups, such as injection drug users and incarcerated individuals, with a focus on the risk of infection or reinfection.

3.2 Treatment

Treatment for viral hepatitis depends on the specific type of virus and the stage of infection. For patients with acute HBV infection, treatment is typically supportive, as more than 95% of immunocompetent adults recover spontaneously (27). Antiviral therapy, such as nucleotides analogs and peginterferon, are reserved to severe cases and for subgroups of patients with comorbidities that worsen the disease course (27). In chronic cases of HBV, tenofovir alafenamide has been recommended for treatment in adults ever since the *2016 American Association for the Study of Liver Diseases Hepatitis B Guideline*, due to the high risk of liver complications otherwise (24, 27). Despite this, an effective cure for HBV remains a challenge, as there is currently no treatment that can completely eradicate the virus and its biomarkers or eliminate the risk of further liver damage (28, 29).

Chronic hepatitis delta virus (HDV) infection still has limited treatment options. Interferon alfa (IFNα) is currently the only available drug shown to be effective for patients with detectable HDV-RNA and active liver disease (30). Nevertheless, novel drugs, including specific inhibitors of HDV prenylation (Lonafarnib), HDV entry inhibitors (Bulevirtide) and inhibitors of virion secretion (REP 2139) have all demonstrated promising results in phase 2 clinical trials (31–33). Of note, the European Medicines Agencies (EMA) has provided a conditional marketing authorization to Bulevirtide (34).

Importantly, HCV can be cured and it is recommended that patients with acute infection start treatment at the time of diagnosis, rather than waiting for spontaneous resolution, and following a treatment strategy similar to chronic infections (35, 36). The goal of this approach is to effectively eradicate HCV-RNA from the blood and to reduce progression to chronicity (35, 36). The latest therapeutic proposal for these patients involves the use of direct-acting antivirals (DAA), which target specific nonstructural proteins of the virus and disrupt viral replication and infection. There are four categories of DAAs, which are defined by their mechanism of action and therapeutic target, namely nonstructural proteins 3/4A (NS3/4A) protease inhibitors (PIs), NS5B nucleoside polymerase inhibitors (NPIs), NS5B non-nucleoside polymerase inhibitors (NNPIs), and NS5A inhibitors. While the selection of an appropriate regimen for HCV treatment depends on factors from host and pathogen, newer DAAs are pan-genomic, making genotype testing less critical in making treatment decisions. Additionally, this therapy is highly effective, well-tolerated, and easier to administer than older treatments (37). Although, the high cost of these therapies can be a barrier to access for some patients and strategies to help improve access to DAA therapies are needed.

Despite the importance of early diagnosis and treatment for hepatitis C virus (HCV), a significant proportion of infected individuals remain undiagnosed and untreated. According to estimates, only 5% of those who need treatment for chronic HCV receive it. This is especially problematic in countries with limited infrastructure and resources to provide testing, vaccination, and treatment for hepatitis patients (38, 39). To address these issues, it may be helpful to decentralize and fund HCV testing and treatment, as well as hepatitis B virus (HBV) prevention, in primary healthcare and drug-use prevention institutions (23, 24).

3.3 Diagnosis

The diagnosis of viral hepatitis can be confirmed through various methods. In acute infections of both HBV and HCV, the detection of immunoglobulin (IgM) antibodies to the viruses' core antigen (anti-HBc and anti-HCV, respectively) can indicate a current or past resolved infection. To diagnose HBV, the surface antigen HBsAg can be used, while HCV requires RNA-PCR tests (40). Additionally, the chronic infections of both diseases can be confirmed by the persistence of these active markers of infection for more than six months (27, 36, 41).

Importantly, point-of-care (POC) testing tools are being developed and used to more easily diagnose HBV. Through these tests, the diagnostic process can start to move away from established healthcare settings, aiding diagnosis in resource-poor locations and high-risk communities (42). Despite these advancements, hepatitis infection is still largely underdiagnosed, with approximately 80% of HBV and HBC cases remaining unidentified. This is partly due to the low political priority given to these viruses, which slows progress in epidemic control (43, 44). To address this issue, it is essential to substantially increase HBV and HCV testing in order to identify infected individuals who remain undiagnosed, allowing them to initiate medical treatment and enabling the development of local strategies based on reliable data (23, 24).

3.4 Prevention/Vaccines

Currently, only HAV and HBV have vaccines approved by the United States Food and Drug Administration (FDA), and efforts to develop vaccines for HCV and HEV are ongoing (24, 29, 45–47). Regarding HAV, there are two officially licensed vaccines: HAVRIX and VAQTA. Two doses of either are recommended for children and for adults who have not been previously vaccinated (45, 46, 48). For HBV, single antigen vaccines such as Engerix-B and Recombivax HB, as well as combination vaccines such as Pediatrix, Vaxelis and Twinrix (a combination of HAV and HBV vaccines) are available (45, 46). Children typically receive 3 to 4 doses over a period of 6 to 18 months, depending on the type of vaccine, scheduling, and specific characteristics such as the gestational age and birth weight of the child, as well as the HBsAg status of the mother (22, 49, 50). For adults, two doses are usually given one month apart, or three doses over a six-month period, depending on vaccine type and manufacture (22, 51). Although infant HBV vaccination rates are high, with three-dose coverage being 85% worldwide, access to birth doses remains low in countries where antenatal coverage is minimal (24). Therefore, a combined intervention in certain core areas, including effective production and distribution of preventive vaccines for HAV and HBV, is one of the key strategies included in the first WHO Global Health Sector Strategy (GHSS) to combat this disease as a major public health challenge (23, 24). Immunoglobulin can also be used to prevent Hepatitis B virus infection in high-risk individuals, such as newborns of mothers who are positive for HBsAg and in individuals who have been exposed to the virus (52).

Other prevention measures should also be prioritized, including harm reduction for patients who use illicit drugs and prevention of mother-to-child transmission, particularly for types of hepatitis without a current vaccine. This issue can be addressed with educational interventions in those targeted populations, as minimizing exposure to the viruses is the most effective way to prevent infection. Research into the development of effective vaccines for other viral agents such as HCV and HEV is also an important proposal in reducing the global burden of viral hepatitis.

4 Arboviruses

With approximately 11.6 million cases between 2008 and 2019, the emergence and resurgence of the arboviruses, such as Dengue virus (DENV), Chikungunya virus (CHIKV), and Zika virus (ZIKV) are considered a public health problem in the world (53, 54). These viruses are primarily found in tropical and subtropical regions, where they can cause significant morbidity and mortality, with around 7,043 deaths annually (55, 56). Arboviruses are transmitted through interactions between arthropod vectors, such as the *Aedes aegypti* mosquito, and susceptible vertebrate hosts, with

the environment also playing a role in transmission (57, 58). Although caused by viruses previously considered to be controlled or of little public health importance, CHIKV and ZIKV are emerging diseases in the Americas, and DENV is still the most prevalent arthropod-borne virus in the world (57–59).

The majority of arboviral infections result in either asymptomatic or non-specific mild illness, with a short incubation period that typically lasts three to ten days (60, 61). During the acute phase, the clinical presentation is often similar and can include fever, flu-like symptoms, and possibly rash, myalgia, arthralgia, and headache (60, 62). However, it is important to note that DENV can cause a significant proportion of case fatalities associated with hemorrhagic fever, ZIKV infection in pregnant women can lead to microcephaly in the infant, and CHIKV infection can cause debilitating chronic sequelae (53, 54, 56, 58).

The majority of arboviral infections are either asymptomatic or cause mild, non-specific symptoms, such as fever and flu-like illness, with short incubation periods. However, DENV can lead to fatal hemorrhagic fever, ZIKV infection in pregnant women can cause microcephaly in infants, and CHIKV can cause chronic sequelae.

4.1 Grand challenges

The challenges in addressing emerging and re-emerging arboviral diseases are numerous and complex. Despite significant progress in understanding these diseases and the ways in which they are transmitted, efforts to eliminate or significantly reduce mosquito populations have remained difficult (60, 63). This is due, in part, to the dynamic interaction between various factors, such as human travel, unplanned urbanization, climate change, and changes in viral genetics, that can facilitate the spread of these diseases. To address these challenges, it is important for governments to provide support and enforcement for effective control measures, such as promoting community engagement and understanding of these diseases, as well as imposing penalties on residents who fail to eliminate larval container habitats (i.e., standing water where *A. aegypti* mosquitoes can lay their eggs). It is also crucial to invest in research to better understand the transmission and epidemiology of these diseases, as well as to develop and evaluate new interventions for their prevention and control.

4.2 Treatment

There are currently no specific antiviral treatments for ZIKV, DENV, or CHIKV infection, so management is primarily focused on providing symptom relief and supportive care, such as rest and adequate hydration to prevent dehydration (53, 57). Furthermore, it is also important to avoid the use of aspirin and other nonsteroidal anti-inflammatory drugs (NSAIDs) while the etiology of the infection is unknown (53, 64). Early recognition is particularly important for DENV, as it can progress to dengue hemorrhagic fever, a potentially life-threatening condition. In addition, overuse of paracetamol (also known as acetaminophen), a drug commonly used to relieve fever and pain, has been reported to cause toxic complications in the liver, which can be severe (65). If left untreated or treated improperly, dengue hemorrhagic fever can have a mortality rate of up to 20%, but this can be reduced to less than 1% with proper management (64).

Given the limited options for treatment of arboviral infections, there are ongoing efforts to develop specific therapies for severe dengue, as well as preventative vaccines. One promising approach is the use of monoclonal antibodies, which have shown promise in clinical trials for the treatment of severe dengue (66). Additionally, research is being conducted on the use of other antiviral agents, such as ribavirin and interferon, for the treatment of severe dengue. It is essential to provide close monitoring and patient education to ensure that patients receive appropriate follow-up care and prevent complications from arising (67, 68). It is also important to invest in research to identify potential antiviral therapies that can prevent the progression of symptoms and disease evolution in all cases of arboviral infections. It is crucial to emphasize the importance of seeking medical attention at the first sign of symptoms, as early recognition and treatment can greatly improve outcomes.

4.3 Diagnosis

Diagnosis of DENV, CHIKV, and ZIKV, can be challenging due to the clinical overlap with other viruses and the difficulty in distinguishing them based on clinical evaluation alone. Thus, laboratory testing is necessary for an accurate diagnosis, and some methods are available, including viral cultures, polymerase chain reactions (PCR), electron microscopy, and antigen and antibody detection (57). These methods can be divided into two categories: direct methods, which provide a definite diagnosis, and indirect methods, which rely on the host's immune response and are used for confirmation after the first few days of illness (69). Of the direct methods, viral isolation using the real-time PCR method in the early days of infection is considered the gold standard, but its high cost and need for specialized resources limit its widespread use (60, 69). As an alternative strategy, indirect methods such as rapid tests or enzyme-linked immunosorbent assay (ELISA) in combination with clinical presentation could be performed and encouraged. At the same time, it is important to implement communication strategies that educate individuals, families, and communities, allowing them to detect signs and symptoms of these infections in order to reduce time to care (70).

4.4 Prevention/Vaccines

The current best prospects for controlling most vector-borne diseases depend on reducing contact between vectors and susceptible humans (60). There are several strategies that, if applied consistently and sustainably, can effectively control and even eliminate mosquito populations, including the elimination of common oviposition and larval sites (such as standing water in containers and used tires), and the fumigation of larvicides and adulticide in households. Personal prevention measures, such as

using insect repellents, wearing protective clothing, and using mosquito netting and traps, are also recommended (64, 70). The CDC recommends the use of Environmental Protection Agency-registered insect repellents, such as DEET or picaridin, for personal protection (64).

In recent years, there has been a growing interest in using new technologies for *A. aegypti* control (71). One approach is to reduce the mosquito's ability to reproduce or transmit the viruses. Sterile insect technique (SIT) involves breeding of large numbers of male mosquitoes that are sterilized by radiation or chemical means before being released into the wild. The sterile males mate with wild females, but their eggs do not hatch, leading to a reduction in the mosquito population over time (72). Wolbachia-based control, also known as endosymbiotic control, involves releasing mosquitoes infected with Wolbachia, a genus of obligate intracellular bacteria that while colonizing *A. aegypti* mosquitoes, these insects become less susceptible to variety of arboviruses infection, thereby reducing the potential for disease transmission (73, 74). In addition to these techniques, wearable devices and smartphone apps are being explored as tools for outbreak tracking and prediction, as well as, the use of drones and other aerial vehicles to deliver insecticides and other control measures has been explored (71). While these technologies offer exciting possibilities for vector control, there are also challenges and limitations that must be considered. These include the costs and logistics of large-scale implementation, public perception and acceptance, and potential unintended consequences.

Efforts to develop vaccines for arboviruses have been ongoing worldwide, given the potential for mutability in these viruses. These vaccines are currently in various stages of clinical trials, and the goal is to provide long-term protection against homotypic and heterotypic serotypes of infection (51). The CYD-TVD (ChimeriVax-Dengue/Dengvaxia®) tetravalent vaccine, which was first licensed in 2015, is the first vaccine for DENV and is currently approved in 19 countries for patients with confirmed primary infections. Moreover, the vaccine TAK-003 (QDENGA®), which is based on a live-attenuated dengue serotype 2 virus, has been recently approved in the European Union for use in individuals regardless of previous dengue exposure (75, 76). Many institutions are also working on developing vaccine candidates for ZIKV and CHIKV using different strategies (53, 54).

As vaccine coverage for arboviruses is currently limited, it is important for governments and health systems to be aware of this growing public health problem (60). Actions should be taken to increase local capacity for early detection and response to arboviral diseases emerge. It is crucial to emphasize the importance of personal protection in endemic areas, both as an issue of personal safety as well as a public health measure. In addition, investments should be made to improve epidemiological, virological, and vector surveillance efforts, as well as to continue efforts to develop safe vaccines.

5 Concluding remarks

Overall, the emergence and re-emergence of diarrheal diseases, viral hepatitis, and arboviruses pose significant public health challenges globally, particularly in low- and middle-income countries. These diseases can only be controlled through the rigorous application of vigilant prevention measures in combination with epidemiological surveillance and solid laboratory support. In addition, it is essential to invest in research, prioritizing potential therapies and interventions that can prevent the progression of symptoms and disease evolution, and to use this research to inform decision-making and the development of efficient prevention and control actions and programs. By prioritizing these efforts, it is possible to make significant progress in reducing the morbidity and mortality associated with these diseases.

Author contributions

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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.

Publisher's note

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