Human African trypanosomiasis: current status and eradication efforts

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Abstract

Epidemics of human African trypanosomiasis (HAT) in the 20th century led to millions of deaths. However, since the start of the twenty-first century, there is been a continued decline in the number of reported cases, due to increased investment and prioritisation of control efforts. Systematic screening of at-risk areas and widespread access to increasingly advanced diagnostics and treatments, along with much improved vector control, have all helped to make disease elimination achievable in the near future. Despite the progress, the danger of disease resurgence is well-known for HAT and continued surveillance and treatment availability is essential. Additionally, many uncertainties regarding HAT transmission remain and combine to make potential disease eradication a complete unknown.

Keywords: human African trypanosomiasis, elimination, diagnostics, treatment, mathematical modelling

Review methodology: We searched CAB Abstracts and Google Scholar for relevant articles using the keywords human African trypanosomiasis, sleeping sickness, and elimination. We also used references from these articles for additional relevant material.

Introduction

Human African trypanosomiasis (HAT), commonly known as sleeping sickness, is a vector-borne disease affecting humans in sub-Saharan Africa. It is caused by parasitic protists of the species *Trypanosoma brucei*, of which there are two subspecies that can infect humans: *gambiense* and *rhodesiense*. Both types of the parasite are typically transmitted to humans by infected tsetse (genus *Glossina*), a large biting fly that inhabits affected regions. The diseases caused by these infections are generally fatal without treatment [1] and it is estimated that in the last 100 years HAT has been responsible for millions of deaths [2].

Historically HAT was endemic in 36 countries of sub-Saharan Africa, with most *gambiense* human African trypanosomiasis (gHAT) cases occurring in West and Central Africa and most *rhodesiense* human African trypanosomiasis (rHAT) cases occurring in East Africa (see Figure 1) [3]. The disease distribution across these countries is highly focal [2, 4], around locations containing the epidemiological factors conducive for transmission of infection. This spatially heterogeneous clustering of incidence is predominantly attributed to the habitat of the vector (tsetse), but is notable since disease prevalence can vary greatly over short distances and even between neighbouring villages [5]. In general, rHAT

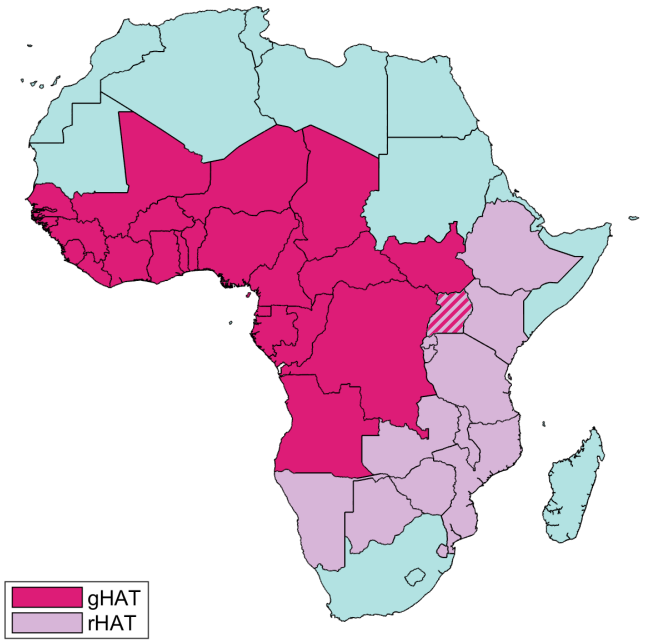

Figure 1: Map of the 36 historically HAT-endemic countries. 24 countries are gHAT endemic and 13 are rHAT endemic, including Uganda, which is endemic with both.

is considered to be a predominantly zoonotic disease with human cases as a result of spill-over from animal infections. In contrast, humans are far more involved with the transmission cycles of gHAT where there is less evidence of zoonotic transmission and the role of animals remains ambiguous [6]. gHAT is the more widespread of the two diseases, causing 98% of all reported infections in the last 10 years of data (2009–2018) [7]; the Democratic Republic of the Congo (DRC) is the country with the highest proportion of gHAT cases with 82% in this period [7].

Historical cases and control strategies

The first accurate medical report of HAT was published in 1734 [8]. In 1896–1906 a large-scale epidemic of HAT was recorded which caused an estimated 800,000 deaths across the Congo basin and Uganda [9], which was coincident with European colonisation of the region and severe droughts. However, it was not until the early twentieth century that cases were routinely recorded [10] (Figure 2).

Historical control of HAT utilised three main mechanisms that, although much refined, still form the basis of modern control. In 1905, the first drugs effective in treating HAT were discovered. These were organic arsenicals, which had mixed benefits: while successful in reducing parasitaemia, they were less effective for patients in Stage 2 of the disease and were also relatively toxic to the patients [11]. In the 1920s Eugène Jamot devised the test and treat principle, using mobile teams to cover the highest possible proportion of the population at risk [12]. Finally, as early as 1911 systematic vector control was also introduced to the island of Principe, using primitive tsetse traps [10]. Despite this early progress, control measures declined after 1953, and through to the end of the twentieth century, leading to a resurgence of cases.

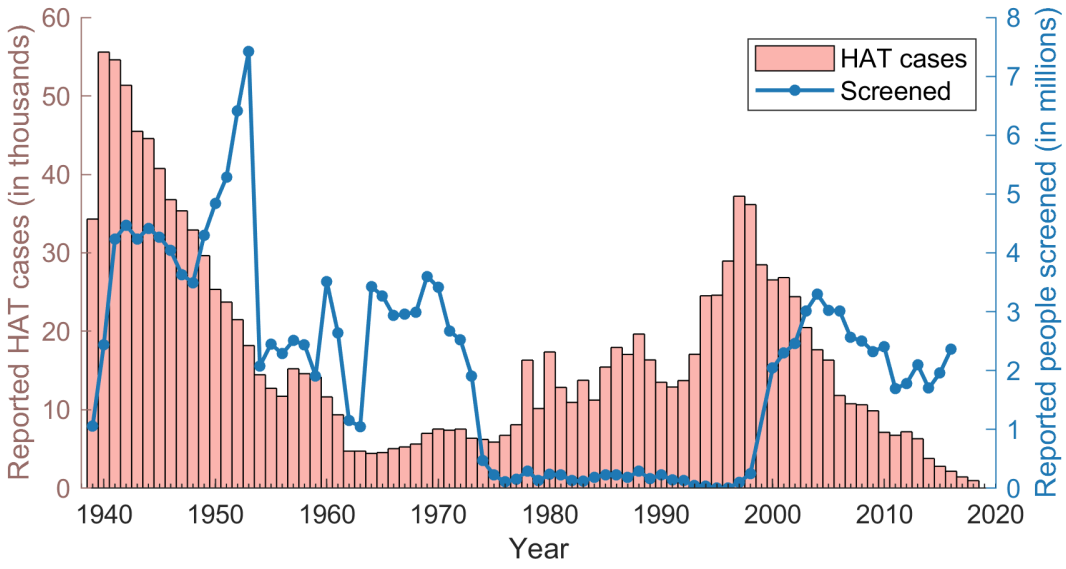

Figure 2: Cases and number of people screened for HAT reported to the World Health Organization between 1939 and 2018. Data is collated from WHO reports and WHO's Global Health Observatory data repository (cases and screening 1939–1998 [13], cases 1999–2018 [7], and screening 2000–2016 [15]).

Current epidemiology and elimination targets

The number of annual reported HAT cases has varied dramatically in the last century as a consequence of different levels of investment in control [13] (Figure 2). However, since the late 1990s, HAT control has been more actively prioritised, with coordination between the World Health Organization, national HAT control programmes, funding agencies, industrial partners, and non-governmental organisations [14]. This has improved the support of control activities within HAT-endemic countries with better surveillance and access to diagnostic tools and treatments [2]. This reinvestment, coupled with advancements in diagnostics and drugs to treat the infection, as well as plausible elimination strategies, has led to a steep decline in gHAT cases (Figure 2). In 2018, the number of reported HAT cases dropped below 1,000 cases, from a recent peak of 38,000 cases in 1998 [7].

The Neglected Tropical Diseases (NTD) Roadmap, published in 2012, identified HAT as a candidate for elimination as a public health problem [16]. The was formalised as a goal in 2013, with the elimination definition, comprising of two global indicators, updated in 2017 to: (i) fewer than 2,000 reported cases per year, and (ii) reducing the area at risk of reporting more than 1 case per 10,000 people per year by 90% as compared to the baseline for 2000–2004. The Roadmap is due to be updated in 2020 and is proposed to include the goal of zero reported gHAT cases by 2030 [3, 17, 18].

The first indicator for elimination as a public health problem is very likely to be met by 2020, since it is currently being achieved, with 977 cases reported to WHO (of which 953 were gHAT) in 2018, well below the target of 2,000 [7]. The second indicator is more challenging to assess; in 2012–2016, 280,000 km^2 of land was estimated to be at moderate risk or higher of HAT, a reduction of 61% compared to the baseline 790,000 km^2 from 2000–2004 [15]. Therefore, the 90% reduction was not met by 2016, but the progress is encouraging, with a continued decline in the at-risk area; the size of this area was close to the milestone aim of 230,000 km^2 for 2012–2016 [16]. It is expected that these downward trends are indeed reflecting a real decline in transmission, rather than simply under-reporting, since the number of health facilities providing HAT surveillance, diagnosis and treatment is increasing [15].

There is less evidence that the 2030 elimination of gHAT transmission target [17] will be met, but

it remains an important aspirational goal to ensure that progress is sustained and that the previous mistakes of early cessation of HAT programmes are not repeated in the twenty-first century [19].

Intervention approaches

To attain the targets set by WHO and break the transmission cycle, HAT interventions need to be applied effectively at all levels, understanding the geography, the community and field workers, the technology, and the governance [20]. However, to be able to implement intervention strategies successfully, there also needs to be adequate surveillance; this allows both for long-term disease monitoring and early identification of outbreaks [21]. HAT surveillance is recorded as screening and incidence data by the WHO in the Atlas of Human African Trypanosomiasis [22, 23]. This is a systematic approach of collating the number of new cases in villages across the endemic areas in each year, as well as the number of people screened for HAT and a census estimate. This data allows for the production of disease-risk maps, monitoring, planning of future surveillance and data for modelling and making future predictions [24].

Active Screening

Since there is no vaccine or chemoprophylaxis for HAT [25], case control for gHAT is primarily through direct case detection by mass screening, followed by confirmation and treatment [26]. This has widely been considered to be the most effective method of control, even since the early twentieth century [27–29]. Its impact on reducing the underlying number of infections is also supported by mathematical modelling [30].

Active screening is implemented by the operations of small mobile teams including microscopists, secretaries, drivers, messengers, guards, and health workers, who travel directly to villages in the HAT-endemic areas in four-wheel drive vehicles (or boats) and aim to test full populations for the infection through mass screening [31]. The region a mobile team can cover may include a population of up to 800,000, and teams typically travel for twenty days each month to conduct active screening, staying for multiple days in some large villages to ensure the available population is screened [31]. The choice of villages visited is dependent on the history of screening and cases in the village and area, cases from nearby health centres and local information [31]. Other predictive methods to identify at-risk villages are being devised [32].

For active screening programmes to be effective a high screening coverage is important in all villages to ensure the detection and treatment of those infected and prevent onward transmission. This requires a detailed knowledge of the area with sensitisation ahead of an active screening, to ensure that the village is ready for the maximum possible number of people willing and available to be screened and not on an inconvenient day, such as when there is a market [33]. There also needs to be low drug toxicity, low cost to the patients and some level of privacy to achieve high attendances and treatment uptakes [29, 34, 35].

There is limited evidence for how frequently these active screenings should occur and when they should stop if no cases are found. Van Nieuwenhove [36] recommends three repeated screening rounds with one year intervals, while Simarro et al. [37] used six month intervals. The current WHO recommendation is for yearly screening with three years of zero case reporting before stopping active screening in the village [26]. There have been many calls for the need to maintain active screening, even when no cases are observed [38, 39], particularly given the feedback between surveillance and control [40]. Recent mathematical modelling has suggested that infection is expected to persist for long periods, with no new infections detected for multiple years to have any certainty of local elimination [41]. Indeed, multiple years of active screening without case detections is a valuable measure of the likelihood that elimination of transmission has been achieved [42].

In low-prevalence settings, due to consistent under-representation of certain demographics [35], targeted door-to-door screening can be more cost-effective and less labour-intensive if there is knowledge

of suspected cases, alongside the availability of diagnostic tests and treatments for individuals suffering symptoms. Indeed, door-to-door screening has been found to detect significantly more HAT cases than standard active screening [43]. In locations where the terrain is difficult to traverse, active screening is also carried out by light mobile teams using motorbikes [44].

Passive Detection

To better detect cases, there needs to be additional support for those that are not reached by active screening. As such, passive surveillance provides fixed health centres with the capacity and tools required to test and treat for HAT [45]. This is crucial in areas with low transmission intensity that will not be targeted in active screening [46], which will become more common as total case numbers fall [14]. It also ensures that individuals who miss active screening events or receive a false negative result in previous active screening, can still access diagnosis and treatment. These facilities need to be suitably equipped, such that infections are recognised promptly [47, 48]. Since passive surveillance relies of individuals to self-present to these health centres, a high proportion of them will be in the late stage of the disease, with significant symptoms [49]. The ability to access facilities where HAT can be rapidly diagnosed shortens the time between infection and treatment, reducing potential transmission opportunities. Indeed modelling has suggested there is great potential in improving rates of passive case detection [50].

Vector Control

Since gHAT is largely considered an anthroponosis, control has heavily relied on active and passive surveillance rather than considering the tsetse [14]; however, if vector control can reduce the number of tsetse, there will be fewer flies able to become infected, and hence a reduction in HAT transmission [51]. Vector control is frequently a staple component of other vector-borne disease intervention strategies, such as malaria and dengue, due to its potential to avert transmission. Modelling has supported this hypothesis for gHAT, predicting that in many areas including vector control would consistently avert more infections that other intervention strategies [52, 53] and strategies without vector control may be insufficient to meet the 2030 elimination of transmission target [30, 54, 55].

Tsetse control can be implemented by traps, targets, insecticide-treated cattle, aerial spraying, or sterile insect release [56]. One current strategy showing considerable potential is the use of 'tiny targets' [25]. These are small blue squares of cloth attached to a square of mesh impregnated with the insecticide, deltamethrin. They are attached to a frame and either planted in the ground or hung from vegetation. Tsetse are attracted to the blue colour, circle the cloth and come into contact with the insecticide, resulting in their death [57–61]. These targets are both highly effective and easier to deploy that traditional devices [51] in settings where livestock density is low. In regions with higher cattle ownership, restricted application of insecticides can also be a cost-effective approach to reduce tsetse populations [62].

The two main drawbacks of vector control until recently were the expense [25] and the associated logistics of repeatedly deploying multiple control. However, with developments in insecticide-treated targets and traps [25, 59, 63], tsetse control can now be considered more cost-effective [64]. The small size has helped reduce costs, while remaining effective [25]. Furthermore, tsetse control is species-specific to tsetse and does not negatively impact the environment, since tsetse are not a key species in the food chain. Therefore, it can be considered ethically defensible, as human deaths are averted [65]; the objective is for local reduction of tsetse in HAT foci to interrupt transmission, rather than global eradication of the fly [66].

'Tiny targets' have been introduced in several HAT foci, such as Guinea, Uganda Chad where reductions in the tsetse population of 80% in 18 months [67], 90% in 12 months [66], and 99% in 4 months [53] have been observed respectively. Furthermore, no gHAT cases have been found in areas where 'tiny targets' were deployed in North West Uganda [68]. When challenges are presented to health services, tsetse control is often easier to maintain than traditional medical interventions. For

example, when active screening was postponed in Guinea due to the 2014–2016 Ebola outbreak, a rise in gHAT prevalence was observed; however, in the area where tsetse control had been implemented, no cases were found. Vector control is also now part of HAT control strategy in some high-burden areas in the DRC, the country with the highest HAT burden [7, 69].

Diagnostics

Medical treatment of HAT patients can cure them of the infection and so prevent suffering and potential death, however, early detection of the infection will also reduce the duration a person is infectious and able to transmit the infection to biting tsetse. Therefore, accurate diagnostic tools are essential to identify early stages of the infection and both prevent the severe symptoms for the individual and reduce further transmission to the population. Different diagnostics are available as field-applicable and laboratory-bound tests.

The most commonly used and reliable test for gHAT infection in the field is the card agglutination test for trypanosomiasis (CATT) [70]. This is a serological test developed in the 1970s, which uses blood collected from a finger prick, plasma, or serum [71]. The test is most suited to be carried out by mobile teams in active screening since it is relatively quick, inexpensive and reliable. However, the test does require an electricity supply, a cold chain and trained personnel [72]. A positive CATT test requires additional parasitological validation to visibly detect the presence of parasites by microscopy for HAT confirmation [73].

More recently, rapid diagnostic tests (RDTs) have been available to screen for gHAT. These tests have an important role in the fixed passive detection health centres, since they do not require electricity and are instrument-free [74]. This means rural hospitals, that are often ill-equipped, can still screen for HAT, and hence RDTs have been widely distributed in remote endemic areas [74–76]. While these tests are being developed to have both high sensitivity and specificity (comparable to CATT) [77–82], in areas where the infection numbers are low, the number of false positives from RDTs can far outweigh the number of true positives, resulting in a very low positive predictive value [2, 83]. Cost-effectiveness analysis has suggested RDTs could be more cost-effective than CATT in both mobile and fixed health facilities [74].

For laboratory-bound tests, the trypanolysis test is a confirmatory test with extremely high specificity, such that positives from other tests can be verified and thus the patients treated. However, this test is expensive to perform and can only be done in selected laboratories in Europe and Africa [26]. Notwithstanding this, the trypanolysis test is particularly useful in the context of elimination since its high specificity means it can be used as a surveillance tool to identify areas which are disease-free [84, 85]. Enzyme-linked immunosorbent assays (ELISAs) can also be used as confirmatory tests with high specificity, but are time-consuming, expensive and need to be performed in large batches [86]. Molecular tests have also been developed to detect *T. b. gambiense* [87] and exhibit high sensitivities and specificities. The fact these tests are not directly applicable in the field yet, however, means the direct benefit remains limited [75, 88].

Rhodesiense HAT currently has no field-applicable serodiagnostic test [2], however the more obvious symptoms and high levels of parasitaemia make this less crucial for detection of the infection [26].

Treatment

Classically, because of the very different severity of symptoms and location of trypanosomes in the two stages of HAT, treatments are generally stage specific [89]. The earlier HAT is treated, the better prospects for the patient; drugs for Stage 1 will not cure a patient in Stage 2, and drugs for Stage 2 are unnecessarily toxic for patients in Stage 1. Hence staging is traditionally an important first step in determining whether the parasite has passed the blood–brain barrier into the central nervous system. This relies on a lumbar puncture to collect cerebrospinal fluid for the counting of white blood cells and to ascertain whether trypanosomes are present [90].

Until recently, the drugs used to treat Stage 1 infection were pentamidine or suramin [91]. Pentamidine has a high effacacy in treating gHAT and is administered intramuscularly for seven days, with generally minimal ill-effects [2]. Suramin is effective too, but is only used for rHAT as the slow intravenous infusion is more difficult to manage and the side-effects more frequent [2].

For Stage 2, the first-line treatment is nifurtimox–eflornithine combination therapy (NECT) (nifurtimox is delivered orally and eflornithine delivered intravenously) [92, 93]. This is an agressive treatment with common side-effects including abdominal pain, vomiting and headaches, with a high probability of a successful treatment [2]. The alternative, melarsapol, is now restricted to Stage 2 rHAT, due to the frequency of life-threatening reactions it can induce [94].

All five of the drugs are donated by manufacturers to WHO, who is able to freely who are able to freely distribute them across HAT-endemic countries [2].

In addition to these drugs, fexinidazole [95], an oral drug that is taken for ten days, was recently included in WHO guidelines for gHAT treatment [96] and approved for use in the DRC in December 2018 [97]. This drug is effective in treating both stages of gHAT, when the symptoms are not overly severe [98]; so eliminating the need for a painful lumbar puncture to determine the infection stage, and simplifying the treatment process whilst improving access to care [69, 97]. However, it is notable that a lack of stage determination provides less information for subsequent surveillance and can reduce the accuracy of recommendations from predictive models [99]. Fexinidazole appears less effective than NECT in treating late Stage 2 patients however [96], and the effect on parasites in the skin is still unknown [100]. The safety profile of fexinidazole is not sufficient to consider treatment without parasite confirmation as part of the diagnostic algorithm.

Another drug, acoziborole [101] is currently being trialled as a one-day, one-dose oral treatment for all gHAT patients. This could potentially revolutionise treatment due to the ease with which it would be delivered and has the potential to be administered to all at-risk populations based on RDT results, or even given to all high-risk individuals if suitable safety standards are met [100].

Considering eradication

There are many reasons to be optimistic about the eventual elimination of HAT: the declining trend in reported cases; the availability of accurate diagnostics; effective drugs that are freely donated; new diagnostics and drug being developed; and continuing operations to reduce infection numbers through both active and passive surveillance and tsetse control. However, as the case numbers decrease to very low levels, there will be more competition for funding with other diseases [102, 103] and activities will have to continue to avoid resurgence [14]; in addition other factors may emerge that were undetectable at high prevalences but could pose problems for elimination and eventual eradication.

Firstly, all figures for HAT infections are based on reported case numbers and it is expected that the true number infected will be much higher. For rHAT in particular, with very low case numbers, there has been a decrease in HAT-skilled staff, causing a decrease in awareness and hence reporting as a consequence [15]. There is also an issue with systematic non-participation in screening for gHAT, where sections of the population are likely to avoid being screened [35]. Data on the age and gender of screened participants could be used to determine which groups are not attending screening, although this is not routinely collated in an electronic format. Anecdotal evidence suggests working age individuals are the least likely to participate, as they may be away from the village working when active screening teams visit. From the perspective of elimination, this is particularly troubling since this group is also more likely to be working in the tsetse habitat, close to vegetation surrounding river. Hence, there could be a high-risk (core) group for infection never being tested – a hypothesis supported by fitting models to longitudinal active and passive case data to regions in DRC and Chad [30, 53]. If screening stops in areas where there are no identified cases, transmission could be sustained by such a core maintenance population, which could re-infect those who have partaken in active screening [6, 104].

Without active surveillance that can reach high proportions of the at-risk populations, there is also the danger that gHAT could sustain itself in low numbers due to a possible asymptomatic reservoir of

humans [105]. It has been observed that some individuals infected with gHAT do not present symptoms for a long time and so will not seek medical attention or be detected, as they are unaware of the infection [1]. These individuals may have the trypanosomes surviving in their skin with no blood parasitaemia, which is difficult to screen for in large numbers [100]. However, the parasite can still be ingested by tsetse and so transmitted [6, 106, 107]; modelling has suggested treatment of these asymptomatic cases should be considered [108]. Gaps in active screening coverage for at-risk populations may also hinder elimination programmes [109], with high coverage needed to be maintained to prevent a decrease in detected cases being due to a decrease in screening effort [110].

Movement of infected people into disease-free areas should also be considered in intervention planning [111], as this can lead to recrudescence [41]. This is especially important in former-endemic areas, where HAT control is no longer considered a priority and high influxes of refugees, could be a perfect environment for parasite transmission [112].

Finally, even if the *gambiense* form of the infection was eliminated from humans, there is the possibility that the transmission cycle could be preserved through animal reservoirs [113]. This is certainly the case for rHAT [2], but while *T. b. gambiense* infection exists in animals, it remains unclear if animal hosts able to sustain infection or are likely to re-infect human populations [114]. Modelling has suggested that the existence of an animal reservoir was a requirement for continued transmission in a gHAT focus in Cameroon [115], while other studies have demonstrated there is lack of evidence to draw definite conclusions [30, 105]. Spraying livestock could prevent some transmission in domestic animals, but pockets of infected wild animals could still pose a problem. The existence of a *T. b. gambiense* infected animal on the island of Luba, where there have been no reported human cases since 1995 [116], also provokes wider questions about persistence in the absence of human cases and potential reintroduction from the animal reservoir [6, 117]. To achieve rHAT elimination, there will need to be multisectoral (One Health) cooperation, with impetus for improved surveillance of infection in both humans and animals [118].

Conclusion

HAT cases have declined substantially in the twenty first century due to considerable efforts to eliminate the diseases [7]. Elimination of transmission of gHAT has also been shown to be cost-effective, with economic benefits greater than the costs [102, 119]. Efforts need to be maintained to sustain the current decline in cases, with continued investment in diagnostics and treatment, as well as their implementation in active and passive surveillance, and tsetse control; even recent interruption of interventions has been known to lead to an increase in cases [120]. For rHAT, there are now only tens of cases, but completely eliminating transmission could be less achievable due to substantial zoonotic transmission. Despite over a century of study and data, there still remain key unknowns concerning the biology and epidemiology which influence the likely success of the proposed elimination of these diseases [6, 15].

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