African Trypanosomoses

Summary

Introduction

- This note provides a summary of an analysis undertaken by a DISCONTOOLS group of experts on Animal trypanosomoses (AT), including Animal African trypanosomoses (AAT), surra, dourine and human African trypanosomiasis (HAT). The group reviewed the current knowledge of the diseases, considered the existing disease control tools, identified current gaps in the availability and quality of these control tools, and suggested the research necessary to develop new or improved tools. Full details can be downloaded from the website at http://www.discontools.eu/.

Disease profile

- African trypanosomoses are primarily vector-borne diseases caused by trypanosome protozoans that reside in the blood, plasma, lymph, and potentially other tissues of their mammalian hosts. They constitute a group of diseases affecting livestock and humans.
- Animal African Trypanosomosis (AAT), or nagana, is a complex animal disease with a wide host range among domestic and wild animals. It is caused by several African *Trypanosoma* species, chiefly *Trypanosoma vivax*, *T. congolense,* and *T. brucei* subspecies, but may also be due to *T. simiae*, *T. godfreyi,* and *T. suis.* The trypanosomes are pathogenic for animals, but certain species can also be found in humans.
- Human African Trypanosomiasis (HAT), or sleeping sickness, only occurs in sub-Saharan Africa and is caused by two subspecies of *Trypanosoma brucei*: *T.b. gambiense* and *T.b. rhodesiense.* Untreated, the disease is almost always fatal in humans and devastating epidemics have occurred over the last century.
- Trypanosomes causing AAT and HAT are cyclically transmitted through the bites of tsetse flies, *Glossina* species, endemic to sub-Saharan Africa, but some *T. vivax* may be transmitted by mechanical vectors (other biting flies). For this reason, while nagana is present mainly in Africa, it is also found in Latin America, due to the presence of mechanically transmitted *T. vivax*, mostly in Bovinae.
- Surra is an animal disease caused by *Trypanosoma evansi*, a parasite that evolved from *T. brucei brucei* but lost its ability for cyclical transmission by tsetse flies. Primarily spread by biting flies acting as mechanical vectors, surra can also be transmitted perorally (especially to carnivores), iatrogenically, and vertically. Amongst trypanosomoses of African origin, surra has the widest geographic distribution, spanning northern Africa (its distribution within the tsetse belt remains uncertain due to potential confusion with *T. brucei brucei* and other *T. brucei* subspecies), the Middle East, South, and Southeast Asia, and Latin America. While mainly camels and horses are affected in Africa and the Middle East, surra can affect a broad range of mammals, particularly buffaloes and cattle in Asia and Latin America. In rare cases, humans can also be infected.
- Dourine is a disease due to *Trypanosoma equiperdum,* sexually transmitted amongst Equidae. Like *T. evansi*, it is a parasite that derived from *T. brucei brucei*, which has lost its ability for cyclical transmission by tsetse flies and, due to a genital tropism, is mainly transmitted by sexual contact, and occasionally from mare to foal.
- The trypanosomoses transmitted by mechanical vectors, that is surra and nagana due to *T. vivax*, and the sexually transmitted trypanosomosis, that is dourine, can be grouped together under the term NTTAT: “Non-Tsetse Transmitted Animal Trypanosomoses”.

- Animal trypanosomes cause acute to chronic diseases with signs including intermittent fever, anaemia, abortion, anorexia in acute forms, and loss of weight, emaciation and eventually death in chronic forms. Nervous system invasion is also observed with *T. brucei, T. evansi* and *T. equiperdum*. Morbidity and mortality rates can be high. Wild mammals and West-African taurine cattle breeds (humpless *Bos taurus*) possess a certain degree of tolerance to the infection and are able to control anaemia and weight loss. They are called trypanotolerant.
- Vector control is an important way to control AAT and HAT. Several methods can be used to reduce or eliminate tsetse fly populations in order to decrease or stop parasite transmission. These methods include: i) insecticide-treated cattle, ii) insecticide-impregnated systems with attractants to kill the tsetse, i.e. traps and targets and iii) area-wide interventions using aerial spraying or the sterile insect technique (SIT). Control or elimination of the tsetse fly in affected areas is, however, complex and costly and where it has been achieved, preventing reinvasion is a challenge. Control methods for mechanical vectors are not considered efficient so far, due to the very high prolificity of these oviparous biting flies.

Risk

- AAT occurs in thirty-eight sub-Saharan countries covering about 9 million km^2 and threatens an estimated 50 million head of cattle in tsetse-infested areas. Surra is found in the arid and semi-arid regions of the northern and eastern half of Africa, and widely spread in South America, the Middle East, and South and Southeast Asia, while mechanically transmitted *T. vivax* is found in South America and has been recently reported in the Middle East. Surra caused outbreaks in Europe (Spain, France), and *T. evansi* and *T. vivax* have the potential to spread and cause outbreaks in non-endemic areas. Dourine has no geographic boundaries and was even reported in Italy and Mongolia in the last decade.
- HAT affects mostly poor populations living in remote rural areas of Africa. Travellers visiting the sub-Saharan part of the continent may also become infected when they travel through tsetse-infested zones. WHO reported a total of 802 cases of Human African Trypanosomiasis in 2021 and 837 in 2022, with around 94% of the cases caused by *T.b. gambiense*. Ongoing and systematic mapping of HAT cases has enabled estimating the population at risk (41.5 million for 2018–2022), with 6% of the population at risk of rhodesiense HAT (r-HAT). Under-reporting occurs mainly in r-HAT areas because of a lack of surveillance and diagnostic expertise in remote regions.

Diagnostics

- There are currently no Rapid Tests to detect active trypanosome infections in animals. The VerY Diag RDT developed and commercialised by CEVA (Libourne, France) (still under evaluation) detects specific antibodies directed against *T. vivax* and *T. congolense*, and as such is more geared towards epidemiological survey than towards decision of treatment, at least in highly endemic areas, due to the persistence of antibodies after treatment or self-cure. One serological analysis kit is available for surra, the Card Agglutination Test for Trypanosomes, CATT/*T. evansi*.
- Different diagnostic methods are used by research laboratories, reference laboratories and veterinary laboratories. Several parasite detection techniques can be applied, including the microscopic examination of wet and stained thick or thin blood films or examination of the buffy coat following blood centrifugation. Parasitological techniques are specific (sub-genus level) but are poorly sensitive. PCR techniques are highly specific and moderately sensitive and can identify parasites at the genus, sub-genus, species, subspecies or type level. Nevertheless, PCR is often not sensitive enough to distinguish parasites among the *T. brucei* subspecies, especially not to distinguish *T.b. gambiense* from *T.b. brucei* in animals.
- Indirect fluorescent antibody tests and ELISAs are used for the detection of antibodies, especially in cattle and camels. They have high sensitivity and specificity (for

trypanosomoses as a whole) but as antibodies persist for weeks or months after clearance of trypanosomes from an animal, a positive result is no proof of active infection. The infective species cannot be determined by ELISA. In addition, ELISAs are not sufficiently standardized among laboratories. Cross-reactivity among trypanosomatids is a limitation for serological diagnosis in regions endemic for leishmaniosis or American trypanosomiasis (Chagas disease) as it could lead to false positivity.

A compendium of standard diagnosis protocols is available on the WOAH website: (https://www.woah.org/nttat/Attached%20files/A16-REC-COMPENDIUM_PROTOCOLES_TRYPANO-En.pdf).

- For HAT due to *T.b. gambiense*, tests for serological screening include a card agglutination test for trypanosomiasis (semi-commercial CATT/*T.b. gambiense*) and two rapid diagnostic tests, HAT Sero *K*-Set (Coris Bioconcept, Gembloux, Belgium) and Abbott Bioline HAT 2.0 (Abbott, Seoul, South Korea). Parasitological examinations are mainly carried out on screening test-positive patients. Immune trypanolysis has so far been used as a reference test for the presence of specific antibodies against *T.b. gambiense,* but it is carried out in a few reference laboratories only. For r-HAT, no simple screening test is available, and microscopy is directly applied to clinical suspects for its diagnosis. The development of rapid tests for *T.b. rhodesiense* is considered a priority by the WHO. For both *T.b. gambiense* and *T.b. rhodesiense*, the detection of DNA or RNA could be used as a reference test. As for AT, PCR may lack sensitivity, in particular for *T.b. gambiense*.

There is an urgent need for rapid diagnostic tests for AT, especially for nagana and surra. Ideally, such tests need to pick up active infections, based on antigen or DNA/RNA detection of trypanosomes. Such test(s) would allow targeting treatment on actually infected animals and would improve the management of animal health considerably while reducing the use of drugs. There is also a need for a standardized and easy to-use test for surveillance and monitoring of AT.

Vaccines

- Currently, no effective vaccines are available for African trypanosomoses. Vaccine development faces significant challenges due to the parasite's ability to evade the host immune system through antigenic variation, where they constantly change their surface proteins. Although advancements in biotechnology and computational capacity offer promising avenues for identifying novel vaccine candidates, the prospects of developing a vaccine in the near future remain poor.

Pharmaceuticals

- Trypanocidal drugs for use in cattle and other animals affected by nagana are limited to three compounds: diminazene aceturate, isometamidium chloride, and homidium salts. The latter is rarely used due to its toxicity for humans. Diminazene aceturate is used as a therapeutic compound, while isometamidium chloride is used both therapeutically and prophylactically. Prophylactic use of trypanocidal drugs to prevent the disease in animals can also protect people since in many r-HAT areas, domestic cattle are now the main reservoir of the human infective *T.b. rhodesiense.* Trypanocidal drugs are becoming more expensive, and their efficacy is reduced by the existence of counterfeit drugs, inappropriate dosage, and the appearance of chemoresistance. No new animal trypanocides have been developed in the past 60-70 years. Despite these limitations, trypanocidal drugs remain the main mean of control used by resource-poor livestock keepers to manage AAT.
- Two drugs, quinapyramine salts and melarsomine hydrochloride, are used to treat surra in camels and horses. To ensure fully curative treatments, it is advisable to treat an animal at least twice at 3-month intervals. Melarsomine hydrochloride is sometime used to treat

dourine in horses but without proof of a total cure, culling of infected animals is recommended.

- Vector control used in combination with diagnosis and treatment can efficiently stop transmission.
- Drugs to treat HAT are not commercially available but can be obtained through WHO. For HAT, huge progress has been made with new, safe, oral treatments that are effective in all disease stages. Detailed recommendations have been published by WHO in the "Guidelines for Treatment of Human African trypanosomiasis" (https://www.who.int/publications/i/item/9789240096035). Similar recommendations are available for AAT (https://www.cirdes.org/wp-content/uploads/2018/12/F03-Trypanocides-Ang.pdf).

Knowledge Gaps

- Significant knowledge gaps remain concerning the complex interplay of factors that determine the course and spread of trypanosomosis across different host species. Our understanding of the host immune response to trypanosome infections in livestock is particularly limited, requiring further investigation. Moreover, a more comprehensive understanding of parasite-host interactions at the cellular and molecular levels is crucial for advancing our knowledge of this disease.
- It is unknown how long mammals can remain healthy carriers of trypanosomes in the absence of treatment, and what is the epidemiological role and potential risk of animals carrying *T.b. gambiense*.
- The impact of global change, including climate change, on the vectors (both tsetse flies and other biting flies), AAT and HAT is largely unknown. Positive side effects of global changes could make AAT and HAT control easier through a strong negative impact on tsetse flies' habitat, as reported in some areas. However, there could also be new opportunities for tsetse to colonize areas where they were not occurring in the past, or, for other biting flies, to increase their range and activities.
- Knowledge of both parasites and vector interactions including vector microbiota, and of the bases of vector competency, is lacking.
- Optimal intervention strategies are not established for all tsetse vectors and agro-ecological settings**.**
- Critical and quantitative analyses of the impact on productivity and the socioeconomic costs of nagana, as well as of the costs and benefits of controlling these diseases, have been undertaken but they vary greatly between locations, study quality and protocols. Such studies are scant for surra, mechanically transmitted *T. vivax* and dourine.

Conclusions

- African trypanosomoses act as a constant drain on livestock productivity and livestock keepers' livelihood, contributing to poverty, food insecurity and inequality. Those affecting cattle are the most important economically since they are a major cause of reduced meat and milk production and limit the use of draught power for agricultural production.
- Due to their biological nature and their links with agro-ecological settings, these diseases constitute a complex and vast problem to be solved, particularly in sub-Saharan Africa, though other parts of Africa and the world should not be neglected. Investments in AT control have to spread over five main areas: (i) human resource development; (ii) improved technology for diagnosis and disease treatment, global surveillance and monitoring; (iii) improved vector control; (iv) increased exchange of information and (v) international, regional, national and local institutional support, commitment and awareness. To support the development of new tools and policies, a better understanding of the complex interactions between main hosts, parasites, vectors in different agro-ecological settings is needed.

- Due to intensive control efforts in the last two decades, the target of eliminating HAT due to *T.b. gambiense* as a public health problem has now been reached in several endemic countries. Gambiense HAT is now targeted by WHO for elimination of transmission by 2030, while r-HAT, due to difficulties inherent to its zoonotic nature, is only targeted for elimination as a public health problem by 2030.
- Novel funding models are urgently needed to provide long-term funds for AAT, surra, dourine and HAT management.