A Reality Cheque – Tackling a Neglected Disease

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Impact of Trypanosomiasis in sub-Saharan Africa

- Affects 37 countries and over 9 million km$^2$.
- Kills around 3.5 million cattle each year with a further 46 million at risk.
- Causes losses in productivity of between $3 and $5 billion annually.
- About 50,000 people are infected annually (sleeping sickness) and over 50 million are at risk (a zoonosis).
Impact Influences Funding – BUT How Good are the Figures?

- Country reports are unreliable.
- Economic impact is a guesstimate based on weak data
  - From the ‘70’s to the ‘90’s it was $5 billion estimated by Cees de Haan
  - In 1999 Brent Swallow estimated $1.3 billion using questionable methods.
  - More recent estimates are around $2.5 billion
- Estimates on the number of people infected annually ranges from 50,000 to 300,000 with similar ranges in deaths.
A Misconception Propagated by Many European and North American Researchers

“Trypanosoma brucei causes a severe debilitating disease in cattle (Nagana) and inhibits agricultural development in large regions of sub-Saharan Africa”

– Almost all scientific publications!

<table>
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<th>Species</th>
<th>Description</th>
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<tr>
<td><em>T. brucei</em></td>
<td>In east and southern Africa <em>T. brucei rhodesiense</em> causes human African trypanosomiasis. <em>T. brucei brucei</em> is pathogenic to camels, horses and dogs. <em>T. b. brucei</em> and <em>T. b. rhodesiense</em> are also found in cattle, sheep, goats and pigs but cause mild or no clinical disease, and in a wide range of wildlife species. <em>T. b. gambiens</em> causes human African trypanosomiasis in west and central Africa and has also been reported in pigs and several wildlife species.</td>
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<td><em>T. congoense</em></td>
<td>Most important as a pathogen of cattle but can also cause disease in other species, including sheep, goats, pigs, horses and dogs [53,54]. Has been identified in a wide range of wildlife species, including Bovidae and Suidae [7,26,28]. Three groups – savannah, riverine forest and Kenya coast or Kilifi [42].</td>
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<td><em>T. vivax</em></td>
<td>Most important as a pathogen of cattle but also causes disease in sheep, goats, horses and camels. Found in a wide range of wildlife species including Bovidae and Suidae [28,55].</td>
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<td><em>T. simiae</em></td>
<td>Causes acute, fatal disease in pigs [53], and mild disease in sheep and goats. Predominantly associated with wild suids [26,56]. Subspecies <em>T. simiae</em> Tsavo isolated from tsetse [2], causes mild disease in domestic pigs experimentally [57] and has been reported in warthogs [26].</td>
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<td><em>T. godfreyi</em></td>
<td>Only isolated from tsetse but causes chronic, occasionally fatal disease in pigs experimentally [3].</td>
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http://www.plosntd.org/article/info:doi/10.1371/journal.pntd.0001828
The Focus of the Research (and its funding) Propagates Other Misconceptions

- During tsetse fly transmission, all African trypanosomes develop in the fly midgut and then migrate to the salivary glands of the tsetse fly – **untrue**.
- All African trypanosomes invade the central nervous system (CNS) – **untrue**.
- Parasitaemias are high in infected animals – **untrue**.
- The VSG repertoire is essentially endless – **untrue, at least for Trypanosoma vivax**.
Where is the Research Focus and Funding?

Pubmed Search
– *Trypanosoma brucei* – 8,444 hits
– *Trypanosoma congoense* – 1,365 hits
– *Trypanosoma vivax* – 744 hits
The ‘70’s “Experiment” to Tackle Animal Trypanosomiasis

- The International Laboratory for Research on Animal Diseases (ILRAD) established in 1973.
- Began operations at Kenyatta hospital in 1975.
- ILRAD's research and support facilities inaugurated in 1978 on a 70 hectare site on outskirts of Nairobi.
- Donors: World Bank, UNDP, Rockefeller Foundation, Australia, Belgium, Canada, Germany, Ireland, the Netherlands, Norway, Sweden, Switzerland, the UK and USA.
ILRAD (ILRI) – Part of the Consortium of 15 CGIAR Centres
Mandate:
To develop effective control methods for trypanosomiasis and theileriosis.

Approach:
• Attract the best international scientists possible to apply cutting-edge technologies to tackling the mandate.
• Operate in the region where the problem occurs.
• Choose a site within an affected country that is free of the disease.
• ILRAD would apply a risky “blue skies” research approach using <2% of the Agricultural Development funding for livestock – the other >98% would be for application and strengthening of national systems and veterinary services.
ILRI mandate

- To measurably and sustainably improve the livelihoods of resource-poor livestock keepers, make animal products more affordable and accessible for the poor and to conserve natural resources in developing countries through partnerships and alliances for innovative livestock research, training and information exchange.
Early Successes

- *In vitro* cultivation of *Trypanosoma brucei* initially and then extended to *Trypanosoma congolense*.
- Cloning of VSG genes from African trypanosomes in collaboration with Kenyan scientists.
- Application of monoclonal antibodies to parasite characterisation (and diagnostics).
- Established that MHC type was not responsible for an animal’s ability to resist disease.
- Established a vibrant research institute in Africa that had an international reputation for cutting edge research.

After five years of operation ILRAD is on its way to accomplishing this mandate.

*ILRAD Annual Report - 1980*
Peter Doherty, 1996 Nobel Laureate in Medicine or Physiology, who from 1986 to 1992 chaired the program committee of the board of trustees of ILRAD.

Reputation

- Attracted top-level scientists to the board of management to oversee the research and set priorities
Problems with the “Experiment” (1)

- Over promised on delivery of mandate.
- Strong and influential personalities in international science community were sceptical of results and voiced this loudly.
- ILRAD was different to all other centres – it focussed almost exclusively on fundamental research and had no products being applied in the field.
- The expectation was that National Research Centres would take the products of ILRAD’s research and apply them in the field.
- All other CGIAR centres were plant-based with a negative attitude to animal agriculture.
Problems with the “Experiment” (2)

- Money for agricultural research was being continuously cut.
- Some research groups felt ILRAD was too expensive and research could be conducted more effectively in Europe and North America.
- Donors wanted a larger say in how funding was spent and started directing the research for short-term gains (what the >98% funding should have been doing).
- Long-term core funding removed – became project-based.
- National Research Centres wanted to do the “sexy” upstream research” rather than doing the more applied work (unequal partnerships).
Example Where ILRAD Might have Pursued its Mandate

Wildlife – “Resistant” to Trypanosomiasis
Trypanocidal Factor in Cape Buffalo Sera (innate resistance mechanism)

A collaborative project between the University of Massachusetts at Amherst, ILRAD/ILRI, and the Kenya Agricultural Research Institute

- Cape buffalo sera and (that of other wildlife ungulates) is trypanocidal for ALL African trypanosome species.
- The active factor is an enzyme that produces hydrogen peroxide.
- Production is induced in response to trypanosome infection.
- Trypanosomes are highly sensitive to the hydrogen peroxide as they lack an enzyme to break it down.
The mechanism suppresses parasitaemia, but doesn’t clear the infection.

The mechanism is short–lived, therefore other mechanisms must be invoked to account for longer-term suppression of parasitaemia.
Antibody Responses of Cattle and Wildlife Infection Sera to Trypanosome “Surface” Proteins

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<td>Cape Buffalo</td>
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kDa

1  97  69  21  21
2  69  46  30  30
3  21  21  21  21
4  21  21  21  21
Antibody Responses of Wildlife Infection Sera
Mimicking Similar Responses in Susceptible Animals

- Two groups of age-matched animals were immunised with two different antigen preparations.
- Controls were immunised with an irrelevant antigen.
- All animals were challenged – a group of age-matched non-infected animals were maintained and monitored throughout the trial.

Results

All animals became infected.
4/5 controls succumbed.
3/6 of one immunised group succumbed.
1/7 of the second immunised group succumbed.
Antibody Responses of Immunised Cattle

Pre-challenge  Post-challenge
Last Remaining Control and Matched Immunised Animal
All Surviving Animals from the Trial

Funding had stopped at this stage so no possibility of testing the validity of the results or bringing it to a conclusion.
Further Problems in Bringing Positive Research Results to Fruition

Anderson Wambugu

- Trained with CDPC from January to May 2009
- Involved in developing easy to use, low cost, rapid and at point tests for animal diseases.
- Contagious Caprine Pleuropneumonia, a rampant and highly contagious respiratory disease of goats.
- Mortality rates of 60 to 90% and morbidity as high as 100% in susceptible goat populations.
- Major disease impacting on resource-poor pastoralist communities.
- Developed a prototype rapid diagnostic with Kieran Walshe, NUIM, formerly Tridelta Ltd.
- The same technology can be applied to other important infectious diseases.
LATERAL FLOW TEST ON FIELD SERA OF CCPP CARRIED OUT ON RETURN TO KENYA (Anderson Wambugu)

Challenges

• Funding to further develop the test for application in the field.
• Funding to apply this technology to other important infectious diseases (e.g. CBPP)
How to Make Effective Use of the Research – Some Lessons?

- Requires greater understanding among researchers of the problems being addressed.
- Need partnerships and collaboration – North-South, South-South, scientists, practitioners and clients.
- Partnerships need to be equal and beneficial for all.
- Requires stable, long-term funding and trust between the funders and researchers.
- Requires training and capacity building in the North as well as the South.
- Requires a separate group of skill sets and expertise that can put the research results into practice.
The London Declaration Scorecard for Neglected Tropical Diseases (NTD)

Compiled by the Uniting to Combat NTDs coalition of private and public sector organizations.

www.unitingtocombatntds.org

Estimated Implementation Funding Gap for NTD Programs

- Estimated Domestic Resources Available
- Estimated International Resources Available
- Estimated Resources Needed

US$ Millions

Of the $34.2 million allocated for Human African Trypanosomiasis, about $3 million is used to purchase drugs and $2 million goes to African Institutes.
Thank You!