DFID ZOONOSES REPORT 6

'Prioritising the need for new diagnostics, medicine, vaccines and management practices of zoonoses which have significant impact in the developing world'

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Executive Summary

The approach used for the study is based on a rapid appraisal of the literature and use of research tools, expert opinion and workshops to identify priorities for research into interventions for control of zoonoses in low and middle income countries (LMICs). Our analysis was based on detailed studies of 20 zoonotic diseases, selected for their development relevance and to be representative of the diversity of zoonoses generally. Our findings are:

Methodology

- For each of 20 selected zoonoses, literature reviews and expert interviews were undertaken to identify opportunities for innovative technologies and management practices for control of zoonoses, focused primarily but not exclusively on Asia and Africa. We considered diagnostics, drugs, vaccines and management practices for each selected disease.

Disease Selection

- Diseases selected included examples of; the most important zoonotic diseases of development; those likely to become more important due to socio-economic and other changes in low and middle income countries; and the diversity of zoonotic diseases.

The socio-economic and policy context of zoonotic disease management

- Zoonotic diseases are highly diverse in terms of the biological, epidemiological and socio-economic factors that drive disease systems affecting the poor in LMICs. There is growing evidence that zoonotic disease management benefits from an approach involving interventions across animal, health and environment sectors but sometimes it is only feasible or appropriate to intervene in one or other sector. Lack of proof of concept studies for integrated human, animal and environment interventions and few analyses of socioeconomic benefits constrains decisions on investment in this area.
- The environmental association with zoonoses remains the biggest challenge and the most important for long term control or elimination of threats.
- Poor execution or inability to apply management practices, and known solutions for reasons of the underlying poverty, capacity, infrastructure, knowledge and policy has

prevented health services in LMIC to control zoonoses and manage negative externalities and these factors need to be addressed in parallel.

- Zoonotic disease management cross-cuts different health sectors, and therefore faces many barriers in policy and practice arising from their different objectives, procedures and resourcing. The complex relationship between management of zoonotic diseases as agricultural and as health problems can generate negative externalities. For instance, factors that may facilitate economic benefits of livestock production, such as intensification of production and associated movements of animal stocks and feeds, may increase risks of zoonotic disease emergence in humans.
- Reactive and poorly thought out zoonotic disease control campaigns can push poor communities further into poverty. For example, culling programmes to control avian influenza pushed smallholder poultry farmers in affected areas into poverty; direct losses from culling programmes and inadequate compensation averaged US$210 compared to average monthly incomes of US$120
- Pharmaceutical companies will concentrate on producing interventions for human diseases that are more attractive economically, relegating zoonoses to second best treatments and a victim to market failure. This emphasises the need to find public funds for zoonosis research and control.
- Policies on land use, settlement and agriculture fail to consider, for instance, encroachment of communities on wetlands and forests practising new agriculture in high disease risk and vector zones.
- For most, there are problems of counterfeit, access, affordability, storage, or adaptability to local conditions for drugs, vaccines and diagnostics.

Selection of interventions for zoonoses management

- Some success stories in integrative management of zoonoses have been described and suggest this approach will be more effective and cost efficient. In general, good management practices are the core of an integrated strategy for zoonosis control.
- The selection of interventions for research investment should emerge from a process of understanding disease drivers and epidemiology, understanding the local socioeconomic context of the disease, and considering alternate strategies for targeting zoonosis control. These strategies could focus on one or multiple goals including disease elimination from animal hosts, prevention of transmission from animals to humans, and case control in humans.
- Generalization, in terms of control strategies and prioritization of interventions is difficult, and a situational specific approach is recommended to capture disease- and context-specific (human-environment-related) factors which drive disease emergence and persistence.
- An analysis of existing and “in development” diagnostics, drugs, vaccines and management practices for selected diseases show that many diseases have current interventions, particularly management practices, that are effective but not effectively applied. Therefore investing in new interventions is not a guarantee that they will contribute to effective control of zoonoses. However, there are considerable gaps

and opportunities to adapt existing technologies to LMIC contexts and to develop entirely new technologies.

- Recognizing the diversity of zoonotic diseases, which cautions against generalizations, there are nonetheless some patterns across the selected diseases in the use of different technological interventions:
    a. An integrated approach, involving a range of interventions is identified for most diseases
    b. Management practices are the key interventions for most diseases
    c. Drugs have particular application in parasitic infections
    d. Vaccines have particular application in viral diseases
    e. Diagnostics are generally poorly developed, and underpin use of other technologies

Research gaps and opportunities

Management

- The research gaps and opportunities in zoonotic disease management (other than technologies) include;
    a. Constraints on implementing known solutions in LMIC settings.
    b. Biology and epidemiology of poorly-known zoonotic disease systems, including appropriate tools to monitor the impacts of disease control.
    c. Policy, political and professional governance for improved zoonoses control.
    d. Socioeconomics of zoonotic disease control and cost/benefits to different sectors.
    e. Education and awareness methods targeting zoonoses, suitable for application in poor often illiterate communities and in government systems.
    f. Targeted surveillance and sociological surveys of poor communities and high risk environments.
    g. Food safety measures applicable in poor communities to reduce food borne infections.
    h. Role of intensification of livestock production and prioritisation of food security in LMIC, impacts on the emergence and incidence of zoonotic disease.
    i. Drivers of zoonosis emergence and persistence e.g. land use change, settlement patterns, agroecology, transportation links
    j. Benefits of integrative approaches to human, animal (including domestic and wild animals) and environmental health sectors, and clarification of the structural and institutional relationships required for implementation of this approach in LMIC.

Diagnostics

Given that;

- the ability to detect and identify infection and disease is crucial for surveillance and as a prelude to intervention for controlling the disease.
- For all diseases studied access to accurate diagnostic tests was found to be sub optimal, this was due to the unsuitability of the current technology for developing country and field settings or because accurate tests have yet to be developed.
- The lack of regulation for human in vitro diagnostic devices (IVDs) and inadequate evaluation of tests results in the use of tests of uncertain quality and performance.

It was concluded that;

- Development of rapid 'field friendly' diagnostic tests that improve access should be considered a priority for the zoonoses studied.
- New technology has yet to be explored/exploited/evaluated.

Drugs

Given that;

- The ability to treat infection prophylactically or therapeutically is desirable and can form an important component in certain integrated intervention strategies.
- For the majority of the diseases studied a drug intervention approach is not considered to be appropriate relative to the alternatives.

It was concluded that;

- For 6 of the diseases considered there are realistic research and development opportunities with respect to the available drugs or candidates.
- For 6 parasitic diseases studied, we found evidence for potential opportunities to address existing Gaps.
- The risk of antimicrobial resistance and the opportunity to prevent the development of antimicrobial resistance should be considered.

Vaccines

Given that;

- Progress in vaccine development, epidemiological and economic considerations, vector dynamics and policy issues vary across the 20 priority zoonotic diseases that have been targeted in this study.
- In each case, it is impossible to consider deployment of vaccines in isolation. In no case is it apparent that deployment of a vaccine in isolation would achieve control.
- No option can be effective in the absence of appropriate management measures, which in turn are reliant on sound epidemiological understanding.
- There are several examples where vaccines and therapeutic interventions are complementary, and both depend on reliable diagnostics for effective deployment.

It was concluded that;

- Available vaccines are not always adequate e.g cattle vaccines for bTB are not efficacious and vaccines for leptospirosis or leishmaniasis may not block transmission.

- A vaccine strategy for Human African Trypanosomiasis is extremely unlikely in the short to medium term (and will be costly.
- Candidate vaccines for Lassa fever virus are in the offing with protective antigens identified but translational research is needed.
- The lack of vaccines for cryptosporidiosis is not a significant constraint to control, given its sporadic occurrence and tractability to control by water sanitation and availability of effective therapeutics for humans.
- The lack of human vaccines has greater relevance for those that are endemic - brucellosis, cysticercosis, hydatid disease and fascioliasis. Of these, a compelling case for a human vaccine is apparent only for brucellosis. Vaccines for the sporadic diseases, campylobacteriosis and Rift Valley fever - are more appropriately targeted at the animal reservoirs.
- The gaps in respect of the animal vaccines for endemic diseases relate to efficacy, attenuation and suitability for field conditions. In the case of the sporadic diseases, the utility of available vaccines is constrained by predictive capacity.
- For other of the sporadically occurring zoonotics, utility is also constrained by deficiencies in predictive capability. Hence, avian influenza vaccines are vulnerable to antigenic drift in circulating virus populations and therefore require support of epidemiological monitoring. Further, the available vaccine for Japanese encephalitis in pigs is unsuitable for delivery to roaming/feral pigs, highlighting a need for an oral bait formulation.
- A vaccine against the category 3 pathogen *S. japonicum* in water buffalo is a compelling adjunct to chemotherapy in reducing transmission of the parasite and first generation vaccines are now available commercially in China.

1. Methodology

Overview

This project was undertaken by a multidisciplinary "project team" from the Royal Veterinary College (RVC), London School of Hygiene & Tropical Medicine (LSHTM), Policy Cures and Chatham House, with coordination from the London International Development Centre (LIDC). Individuals were selected from the institutions for their complementary expertise across animal and human diseases in low income countries and specialised knowledge and experience in diagnostic, drug and vaccine technologies, as well as disease management practices.

20 zoonoses were, selected as a focus for this study, on the basis of their potential health and socio-economic impact in the developing world, and to be broadly representative across the total range of zoonoses. We describe how this was done in Section 2. While this report is based on a sample of potential zoonotic diseases in this project, our selection ensured representation of pathogens that are highly relevant to the developing world in terms of burden and risk. We have included diseases likely to pose future threats as well as those with current zoonotic disease contexts. Pathogens were chosen across three taxonomic groups - viruses, bacteria and parasites. We believe that our results on value of investing in different interventions and the prioritization of research will be relevant to a range of zoonotic diseases in the developing world.

For each of these diseases, literature reviews and expert interviews were undertaken to identify opportunities for innovative technologies and management practices for control of zoonoses, focused primarily but not exclusively on Asia and Africa. We considered diagnostics, drugs, vaccines and management practices for each selected disease. These data were collected and integrated into a framework to facilitate analysis and highlight linkages between existing technologies and products in development. The framework also addressed the potential for integration of new technologies and practices. It is presented as a supplement to this report.

Using expert interviews, the literature and the teams' own knowledge, we created for each of our diseases a disease case study, which includes information on the drivers of disease emergence and persistence, current management and interventions and future opportunities. This is "disease by disease" analysis is presented in Appendix 1 as a resource for readers and we have used it, along with the framework, to draw conclusions on prioritizing interventions.

In the body of the report, we begin in Section 3 with a consideration of the complex agricultural and health dimensions of zoonotic diseases and their impact in a development context. Then in Section 4 we consider the drivers which will influence the selection of interventions for research, including biological, socio-economic and cultural factors. A protocol is suggested for selecting interventions, based on these factors and we examine its application to our 20 selected diseases. We then present some cross-cutting analyses drawing case studies from our diseases, identifying patterns of successful control, cross-

cutting gaps and opportunities for research. In the following sections, we examine prioritization from the different perspective of interventions, considering diagnostics (Section 4), drugs (Section 5) and vaccines (section 6) and how these technologies can be used effectively for integrated control.

Prioritising zoonotic diseases for analysis

The selection of our list of 20 zoonoses is described in section 2.

Characterisation of existing and potential interventions

For each zoonosis, current interventions for control in animals (diagnostics, drugs, vaccines and management practices, including vector control) and products and/or practices in development were considered. The team examined interventions in the context of control at the animal-human-environment interface, identifying, where appropriate, when control was best focussed in human populations or on human behaviour in respect of animals or the environment.

Data collection was conducted three stages (i) an expert consultation, (ii) a quality-control stage based on literature review and (iii) development and population of a framework to outline existing and in-development technologies/practices. External groups with similar interests and activities in prioritisation and characterisation of animal and zoonotic diseases and their management options were consulted on methodology. These included WHO, FAO, World Organisation for Animal Health (OIE) and the International Federation for Animal Health (IFAH).

Prior to the expert consultation phase, at least one external expert for each of the prioritised zoonoses was identified through an appraisal of the literature, review of key experts from FAO/ OIE/ WHO documentation and websites, and personal recommendations from team members. A second expert was added where necessary.

Policy Cures developed topic guides for interviews in collaboration with the wider team, based on a standardised protocol, along with a data collection form to obtain preliminary information on current/ in-development interventions from interviewees. These forms also contained scoring criteria for each type of intervention, to assess suitability, efficacy and access within the context of developing countries. However, forms were completed and returned for only 20% of the zoonoses and therefore a detailed analysis of interventions based on scoring criteria was not possible. Interviews with selected experts were led by one team member per interview and supported by the research assistant. They were conducted by teleconference or in-person. A maximum time of one hour was permitted for interviews, each of which was recorded and later summarised for pertinent information. Summaries were analysed to highlight key opportunities for potential innovative technologies/practices or adaptation of current interventions. Experts were sent summaries to verify that the information was accurate, and to enquire about additional literature. With the exception of

Echinococcosis (where only a data collection form was received from the expert), expert interviews were conducted for all diseases (95% coverage). Selection of individual experts introduces a degree of bias into the process. This was balanced by the literature review and taken into account by the team in their analysis. Where concern was raised within the team over bias or agenda driven contributions, further expert interviews were conducted to achieve a more balanced outcome. All interviews were conducted voluntarily with no payment to experts, apart from travel costs in a few instances.

Literature reviews were conducted for each disease - this was seen as a vital quality control step to cross-check information obtained from expert consultation. It also provided an opportunity to examine wider opinion within the literature. A range of review articles and original research articles (capturing specific technologies and cutting-edge research) were collected from major databases (including PubMed, Web of Science etc.) and centralised into a collaborative referencing programme to enable access across the team. Over 950 publications were sourced and those which contributed to the study are referenced in the Appendices. Grey literature was also captured and analysed; an initial process of contacting relevant institutions/organisations (e.g. WHO/FAO/OIE /IFAH/GALVmed). Consultation with these groups enabled us to identify key reports for review.

An interventions framework, developed by Policy Cures, enabled us to collect both quantitative and qualitative data on existing interventions and products in development. The tool is based on similar frameworks developed and utilised to characterise new and existing technologies for neglected diseases in humans. It brought together data characterising technologies and included criteria such as suitability, efficacy and access for each intervention considered. Specific technologies were grouped into product classes under diagnostics, medicines, vaccines and disease best management practices. Further detail was included in the framework for each technology under a qualitative information column, including evidence from the literature (referenced) and expert consultations. The framework has been adapted specifically for technologies and interventions targeting zoonotic diseases with capacity to highlight opportunities at the animal-human health interface.

With the limited time available, we did not seek to characterize every available and in-development technology, but to represent of the key interventions in wider use, and the most promising future technologies.

Once the framework had been populated, it was distributed to the project team for comment and feedback, to ensure quality control and consensus in respect of identified opportunities.

Evaluating the strength of the evidence base

Two kinds of evidence are presented in this report: that of specific interventions and that of gaps/opportunities. For the former, it is important to stress that our data gathering was limited by time – absence of evidence should not be interpreted as evidence of absence. A

blank cell of our Framework (Supplementary document 1) does not mean that no interventions exist for that pathogen, but simply that these were not reported in the literature we examined or by experts interviewed. Evidence of gaps/opportunities is based on subjective judgement. To maximise the strength of this, we added expert opinions to the information available from the literature. Therefore, where the literature reported a lack of, or need for, a vaccine in the case of a particular disease, information from the expert interview that supported this strengthened the evidence base. We indicate in the framework those gaps and opportunities that are supported by the literature, by experts interviewed and by both.

Analysis of constraints and opportunities

The final step of our analysis was to identify feasible opportunities for research from information in the framework and the relevant socio-economic, cultural and ecological context. Opportunity gaps at the animal-human health interface, as highlighted in the framework, were carefully considered. The project team convened to discuss research opportunities for each disease. In addition to these specific judgements, we sought to extrapolate our analysis beyond our selected 20 zoonoses to highlight general gaps and broader opportunities across disease groups, and to relate these to the wider barriers/policy options that may exist.

2. Zoonotic disease selection

In order to evaluate constraints to identification of solutions for zoonotic diseases that affect the developing world, the project team had first to select a set of diseases for examination.

It was not possible to include in our study all potential zoonotic diseases affecting the developing world. Therefore, a set of 20 diseases was selected that (i) includes the most important zoonotic diseases of development, (ii) in addition to currently relevant diseases, includes those likely to become more important due to socio-economic and other changes in low and middle income countries, and (iii) reflects the diversity of zoonotic diseases, so that our general conclusions about technical gaps and research opportunities might apply to diseases not analysed. Below we explain these selection criteria in more detail.

Identifying important zoonoses in the developing world

Zoonotic diseases affect the poor in two important ways (ILRI, 2002; Molyneux et al, 2011). Firstly, like all animal diseases, they have a socio-economic effect by reducing the productivity and income of poor households that depend on animals for their livelihoods, or by affecting income at a national level through impacts on food value chains, markets and trade (Shaw, 2009; Rushton et al, 1999). Secondly, because these diseases affect humans, they reduce health, contributing to morbidity, mortality and, where the ability to work is affected, they reduce income and livelihoods, with possible consequences for health (Meslin, 2006). There is an additional effect of zoonotic diseases that relates particularly to households or local communities that are dependent on producing their own animal-based foods for consumption (Perry & Grace, 2009). For these groups, animal diseases limit access to and consumption of important nutrients associated with these foods, particularly

micronutrients, with particular implications for child health (Murphy & Allen, 2003; Tacher et al, 2000). Rural farming communities, which comprise the majority of households living in poverty, are particularly affected in this way (Thornton et al, 2002). In our prioritisation, we include this as an additional socio-economic effect.

It is these potential effects that make the evaluation of zoonotic diseases and their impacts complex. While there is strong evidence for independent socio-economic or health effects of zoonotic diseases, there has been little examination of their combined effects; this has been limited particularly by a lack of common metrics for agriculture and health outcomes (Shaw, 2009). However, the potential additive nature of the agricultural and health effects of zoonoses is highlighted by a well-known cost-benefit analysis of brucellosis control in Central Asia which showed the cost of control to be economical relative to the combined effects of the disease on human health and livestock productivity (Roth et al, 2003).

The changing landscape for zoonotic diseases of the poor

Recent changes in low and middle income countries (LMICs) with respect to human and animal populations will affect the nature and importance of zoonoses (Casico et al, 2011). Population and economic growth in these countries is leading to an extension of agriculture and human populations into natural ecosystems, creating greater contact between people, livestock and wildlife, which will facilitate movement of zoonotic diseases (Wilcox et al, 2005; Tomley et al, 2009). At the same time, demand for animal-based foods, associated with growing incomes in LMICs, is stimulating intensification of livestock production and the emergence of more complex food chains linking production with consumers (Schlundt et al, 2004). New productions systems and food value chains may lead to a change in the importance of zoonotic diseases, as exemplified by a growing importance of food-borne diseases, relative to diseases associated with direct animal-human contact (Delgado et al, 1999). These changes will affect zoonotic risks to the poor in rural settings, but will have a particular effect on growing urban and peri-urban poor populations, with their increasing livestock production, where consumers sit at the end of increasingly long food chains (Slingenbergh et al, 2004; Kang'Ethe et al, 2007; Schelling et al, 2007).

Another anticipated trend is the emergence of entirely new zoonotic diseases in LMICs (Jones et al, 2008). Studies of the emergence of new zoonotic diseases suggest that this is associated with the overlap of dense human populations with areas of high mammalian biodiversity ('hot spots'), which are particularly associated with LMICs (Kleczkowski et al, 2012; Grace et al, 2012 *In Press*). While much research has focused on emerging zoonotic diseases as global threats, and their potential impact on global economies and high income countries, it is likely that poor populations in their countries of origin will be particularly affected due to a lower capacity to manage zoonotic diseases generally (Coleman, 2002). Further, the effect of zoonotic disease emergence on cross-border trade can have dramatic impacts on local and national economies, which may in turn affect livelihoods of the poor in those countries (WHO, 2006).

In our selection process, therefore, we sought to ensure inclusion of food-born zoonotic diseases likely to be associated with changing production systems, and emerging zoonotic diseases associated with wildlife-livestock-human interactions. This meant including some zoonotic diseases that presently have very little impact on population health, e.g. avian

influenza, along with the more traditional neglected zoonoses of livestock such as brucellosis, bovine TB and human African trypanosomiasis.

Capturing the diversity of zoonotic diseases and interventions

This study examined a range of interventions for management of zoonotic diseases, including diagnostics, drugs, vaccines and management practices. For any disease, the relevance and importance of each intervention type depends very much on the biology and epidemiology of the disease itself (Woolhouse et al, 1997). For instance, vector-borne diseases pose particular opportunities for the use of management practices (Lambrechts et al, 2009), while diseases characterised by livestock-human transmission pose more opportunities for the use of vaccines than those characterised by wildlife-human transmission (Zinsstag et al, 2007). In selecting diseases for inclusion, therefore, we sought to ensure that the 20 diseases captured a range of biologies and epidemiologies typical of the full spectrum of zoonotic diseases and the circumstances in which they might exist or arise amongst poor populations (WHO, 2009; Maudlin et al, 2009).

Methods for disease prioritisation

Disease prioritisation was undertaken by a team comprising experts in both animal and human disease in LMICs, selected particularly for their experience in the development and use of diagnostics, medicines, vaccines and management practices. The team drew upon their own expertise and a set of recent publications on the distribution of animal, zoonotic and human diseases of the poor.

A long-list of 61 zoonotic diseases was selected, based on Jones et al (2011). The team was asked to consider these diseases and any others that they felt should be included, guided by the need to reflect currently important diseases and those that might arise through the trends described above. They were then asked to score these diseases in terms of a range of characteristics that reflected:

- socio-economic impact on poor populations
- health impact on poor populations

The listed diseases were then ranked according to the cumulative scores given by team members. The team then examined the list to confirm the significance of these diseases relative to the criteria. Particular attention was paid to diseases with similar rankings around the cut-off point of 20, and a reserve list of 10 was made for further consideration.

The entire list was then checked to ensure that it had a representation of zoonotic disease diversity that would well capture a broad range of potential interventions for analysis as described above (Taylor et al, 2001). This involved, for instance, considering the balance of taxa, disease transmission pathways and wildlife and livestock origins. Where necessary, some changes were made to replace diseases at the bottom of the top 20 list with those in the next 10 which improved this diversity.

Features of the priority disease list

The list of selected diseases is presented in the Framework (Supplementary document 1).

Table 1 and Figures 1 and 2 illustrate some properties of these 20 diseases. Table 1 illustrates features of the viruses, bacteria and parasites selected. There is considerable biological diversity between and within taxa but also some strong similarities within taxa in respect of biological and epidemiological features. The frequency and characteristics of different taxa in our selection are typical of the broader group of known zoonoses (Taylor et al, 2001; Woolhouse et al, 2005; Jones et al, 2008). Figures 1 and 2 present results to show how epidemiological factors (sources of infection for humans and importance of reservoirs) are distributed across the 20 zoonoses analysed. The table/figures where based on discussion within our expert team and review of the literature (i.e. general background articles on the epidemiology of the 20 zoonoses- see Appendix 1 for specifics). Figure 1 shows the proportion of the 20 diseases associated with different sources of infection for humans, where environmental sources include natural, domestic and food sources. For Figure 2, each disease was considered in terms of the hosts and factors shown, and a ranking was given for the importance of each factor in its epidemiology. These ranks were then summed across all diseases, such that the area of the sector associated with a particular host/factor indicates its overall importance across the selected diseases. These data provide a quick overview and support the general messages provided in the main text.

Several lists of priority zoonotic diseases have been made in recent years. Differences in selection criteria make direct comparison of these lists difficult, but we note that our top list of 20 includes:

- 8 priority zoonotic diseases identified for action by the WHO/ FAO/ IOE Interagency Meeting on Planning the Prevention and Control of Neglected Zoonotic Diseases (2011);
- 10 of the top 15 zoonotic diseases rated by the International Livestock Research Institute (ILRI) on the basis of their importance in pro-poor development (Perry et al, 2002).
- 11 priority zoonotic diseases identified by the Roadmap to Combat Zoonoses in India Initiative (Sekar et al, 2011);
- 10 of the 11 zoonotic diseases targeted by the WHO-UNDP-World Bank Special Programme's Disease Reference Group on Zoonotic Diseases and Other Marginalised Infections of Poverty (WHO, 2009).

Finally, we note that the inclusion of veterinary and medical experts in our team broadened the selection of diseases, with veterinary specialists ensuring inclusion of diseases with socio-economic impact, and medical specialists ensuring inclusion of some diseases with little economic impact but potentially high health impact.

Characteristics	Viruses	Bacteria	Parasites
% Representation in list of 20 zoonoses	**35%**	**30%**	**35%** (15% protozoa & 20% helminths)
% Representation in total list of 868 known zoonoses (Taylor et al, 2001- 13% Fungi)	**19%**	**31%** (bacteria or rickettsia)	**37%** (5% protozoa & 32% helminths)
Biological classification & evolutionary characteristics	• All are RNA viruses- mixture of single-stranded +ve/-ve and segmented/non-segmented • High nucleotide substitution rate and reduced error-proofing capabilities- increased plasticity & ability to infect new hosts (Taylor et al, 2001; Woolhouse et al, 2005; Cleaveland et al, 2001)	• Wide range of bacterial species responsible for zoonoses (Meslin et al, 2005)	• Mixture of protozoan and helminthic zoonoses
Disease patterns	• Feature prominently among emerging zoonoses (e.g. ebola, lassa fever, RVF) (Jones et al, 2008)	• More stable, endemic zoonoses transmission dynamics (Bovine Tb & brucellosis) • Drug resistant bacteria responsible for proportion of emerging zoonoses (food-chain related)- Jones et al, 2008	• Protozoan zoonoses more likely to be linked emerging infections (Taylor et al, 2001)- e.g. cryptosporidiosis
Transmission & life cycle characteristics	• Predominant mixture of vector-borne and direct transmission pathways	• Food chain - increasing use of industrialised livestock systems to feed slum populations in developing countries with poor management practices (salmonella and campylobacter spp.)- consequently environment contamination important	• Representative across vector borne, human exposure through environmental contamination and food-borne zoonoses • Complex lifecycles involving intermediate hosts (e.g. snail- fascioliasis, schistosomiasis) • Environment contamination importance
Reservoir hosts	• Wildlife non-pathogen reservoir component important (JE virus, H5/H7 influenza subtypes, lassa fever, ebola)	• Livestock central to bacterial zoonoses: often livelihood related (changing dynamics between human-livestock and livestock-livestock) populations (e.g. bovine tb/brucellosis)	• Production and companion animals important

Table 1. Highlights the key characteristics across the list of 20 zoonoses analysed. Segregating the list into viruses, bacteria and parasites gave a clear set of categories across the list, and mirrored the classification of main biological groups of zoonoses from Taylor et al.- wherever the literature on the characteristics of the wider zoonoses list shared characteristics with our list, references have been indicated.

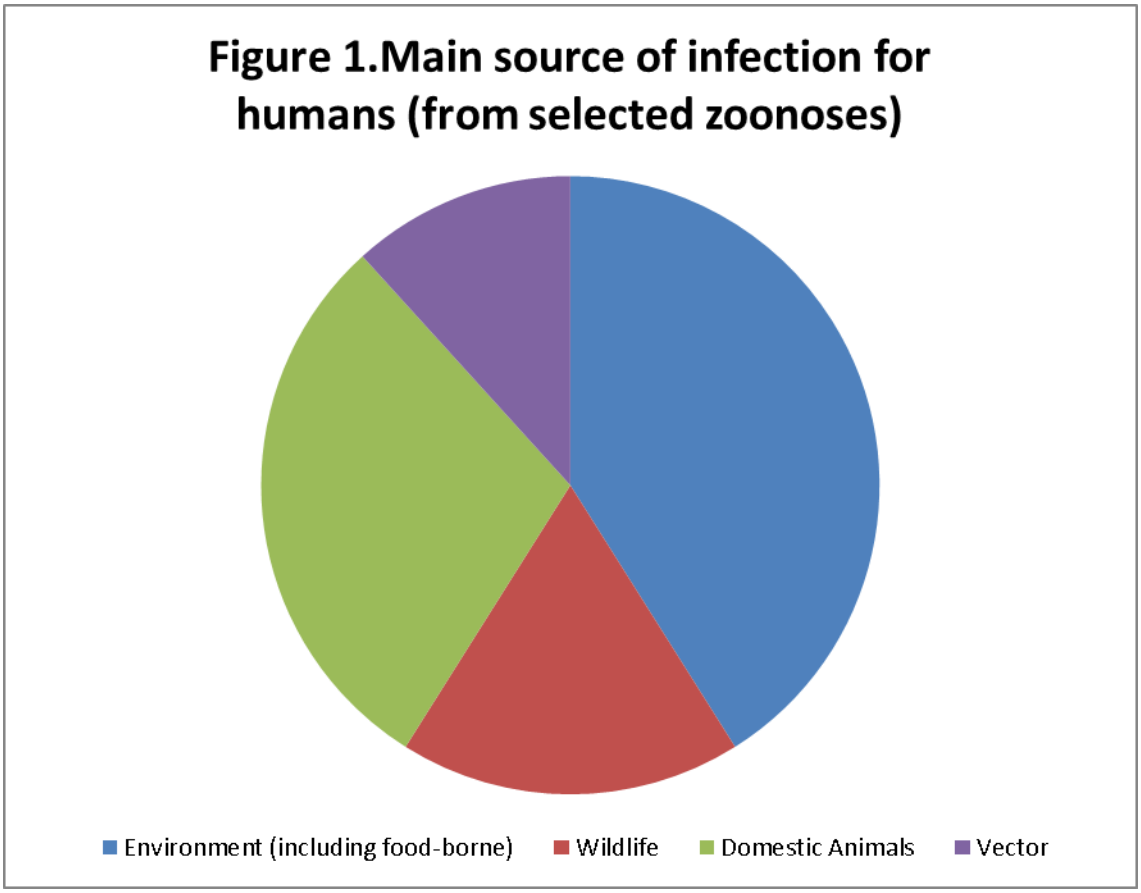


Figure 1.Main source of infection for humans (from selected zoonoses)
Environment (including food-borne)
Wildlife
Domestic Animals
Vector

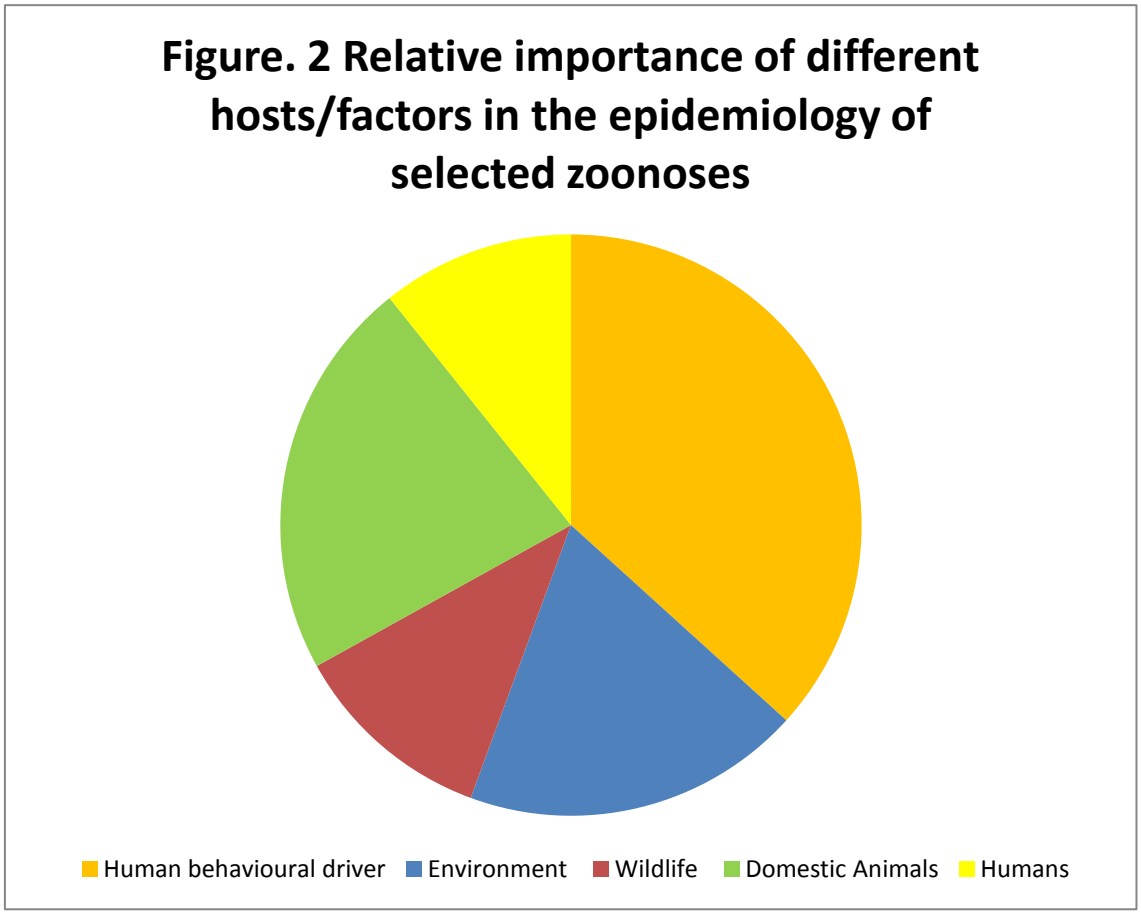


Figure. 2 Relative importance of different hosts/factors in the epidemiology of selected zoonoses
Human behavioural driver
Environment
Wildlife
Domestic Animals
Humans

3. The socio-economic and policy context of zoonotic disease management

Summary of main messages

- Zoonotic diseases are highly diverse in terms of the biological, epidemiological and socio-economic factors that drive disease systems affecting the poor in LMICs.
- There is growing evidence that zoonotic disease management benefits from an approach involving interventions across animal, health and environment sectors but sometimes it is only feasible or appropriate to intervene in one or other sector. The environmental association with zoonoses remains the biggest challenge and the most important for long term control or elimination of threats.
- Zoonotic disease management cross-cuts different health sectors, and therefore faces many barriers in policy and practice.
- The complex relationship between management of zoonotic diseases as agricultural and as health problems can generate negative externalities. For instance, factors that may facilitate economic benefits of livestock production, such as intensification of production and associated movements of animal stocks and feeds, may increase risks of zoonotic disease emergence in humans.
- Reactive and poorly thought out zoonotic disease control campaigns can push poor communities further into poverty. For example, culling programmes to control avian influenza pushed smallholder poultry farmers in affected areas into poverty; direct losses from culling programmes and inadequate compensation averaged US$210 compared to average monthly incomes of US$120
- Pharmaceutical companies will concentrate on producing interventions for human diseases that are more attractive economically, relegating zoonoses to second best treatments and a victim to market failure. This emphasises the need to find public funds for zoonosis research and control.
- Lack of proof of concept studies for integrated human, animal and environment interventions and few analyses of socioeconomic benefits constrains decisions on investment in this area.

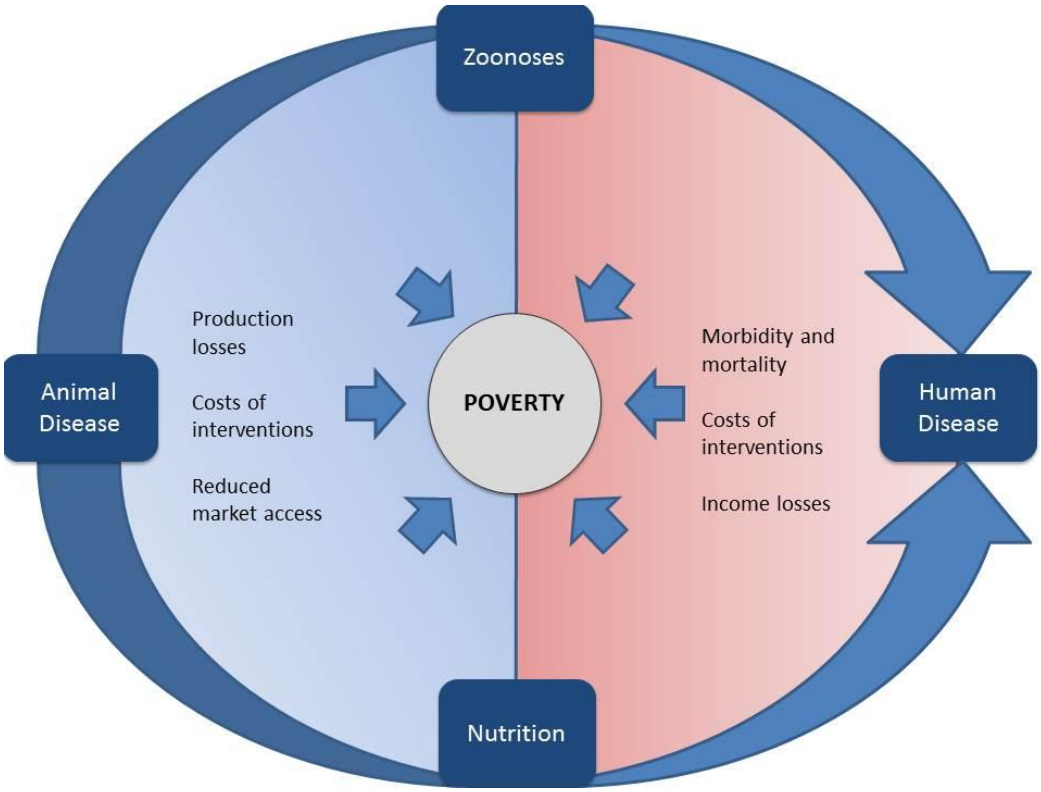
Socioeconomics of Zoonoses

The World Bank estimates that zoonotic diseases have cost over $20 billion to global economies in direct costs over the past decade, with a further $200 billion in indirect costs (World Bank, 2010). Quantifying impacts of zoonoses requires assessing the disease costs across multiple sectors, including human health, livestock production, as well as tourism and other sectors.

The complex relationship between zoonotic disease and poverty is illustrated in Figure 3. This illustrates that, as diseases of livestock, zoonoses affect production and reduce market access. Interventions against these diseases, whether they are aimed at reducing losses or reducing human health effects, may be expensive to producers. All of these may contribute to maintaining producer communities in poverty. Moving to the right of this diagram, animal diseases may also affect health, by reducing the nutritional benefits of animal products,

whose micronutrients are particularly important in child development, and by causing disease in humans, with its consequences of morbidity and mortality, reduced labour and income, and the costs of treating these diseases. Both agricultural effects and health effects therefore may contribute to the persistence of poverty in poor populations associated with animal production. These effects are considered in more detail below.

Figure 3: Impacts of animal disease on human health



The burden of disease in humans includes morbidity and mortality, (commonly measured as Disability Adjusted Life Years (DALYs)), as well as monetary losses due to income reduction and the costs of treatment and prevention. Determining accurate human health costs, particularly in poor settings, is complicated by the frequent under-reporting and misdiagnosis of zoonotic diseases. Although zoonotic diseases were largely excluded from previous World Health Organisation Global Burden of Disease studies, the 2010 study was expanded to include zoonotic diseases such as trichinellosis, echinococcosis, cysticercosis and rabies. Further assessments have attempted to quantify monetary costs of disease in people. Canine rabies has been estimated to cause 1.74 million DALYS per year in Africa and Asia as well as costing over US$500 million per year in lost income and control and treatment costs, US$485 million of which relate to post exposure prophylaxis treatment of humans (Knobel et al., 2005).

Zoonoses also impose economic costs which fall largely on animal keepers, through losses in animal productivity, costs of veterinary interventions and lower prices. Cystic echinococcosis cases in humans cause estimated annual losses of 285,000 DALYs and

US$194 million, rising to 1 million DALYs and US$764 million when factoring in underreporting (Budke, Deplazes, & Torgerson, 2006). However, the majority of monetary losses were losses to global livestock production, estimated at US$1.3 billion annually, rising to US$2.2 billion with underreporting (Budke, Deplazes, & Torgerson, 2006). Livestock diseases can also affect other stakeholders in the value chain. The 2007 outbreak of Rift Valley Fever outbreak in Kenya cost an estimated US$32 million to the national economy, negatively impacting livelihoods of livestock traders and butchers, as well as casual labourers, caterers and other sectors supplying services and goods to livestock sectors (Rich & Wanyoike, 2010).

The complex relationship between management of zoonotic diseases as agricultural and as health problems can generate negative externalities. For instance, factors that may facilitate economic benefits of livestock production, such as intensification of production and associated movements of animal stocks and feeds, may increase risks of zoonotic disease emergence in humans. On the other hand, actions to reduce human health risks, such as the culling of livestock or wildlife populations carrying zoonotic diseases, can have serious economics effects on producers, or dramatic effects on biodiversity and associated ecosystem services, respectively.

The agricultural and health impacts of zoonotic diseases, and their associated externalities, will generally be more severe in low and middle income countries where producers and consumers are poor, veterinary and human health services are limited and good policy and regulatory instruments to manage zoonotic disease risk are lacking or difficult to enforce. Access to diagnostics, medicines, vaccines and the means to apply best practices have always been difficult to ensure in those rural and poorer populations that are often at greatest risk from infections at the animal/human interface (Kizito et al, 2012; Hargreaves et al, 2011; Sheik-Mohamed & Velema, 1999; Marcotty et al, 2009).

Successful zoonotic disease management often requires a combination of interventions. For instance, management of rabies in domestic animals in Europe and North America has involved movement controls, vaccination campaigns and surveillance and test and slaughter programmes (Velasco-Villa 2008; Wandeler 2008). These complex interventions are difficult to achieve in resource poor settings where governments lack necessary finances and human resources. Surveillance may be limited, as may be public awareness of zoonotic risks. In a poorly regulated environment, producers may not be motivated to reduce disease risk. Penalties in formal markets may be avoidable or relatively inexpensive, while much trade goes through unregulated, informal markets.

Reactive and poorly thought out zoonotic disease control campaigns can push poor communities further into poverty. For example, culling programmes to control avian influenza pushed smallholder poultry farmers in affected areas into poverty; direct losses from culling programmes and inadequate compensation averaged US$210 compared to average monthly incomes of US$120 (Hancock and Cho 2008).

Poor communities may therefore experience higher levels of zoonotic disease infection. Besides direct health effects, disease may cause a reduction in employability and resulting loss of short term or long term income, depending on clinical outcomes. Diseases from

livestock, such as anthrax, tuberculosis and brucellosis, most commonly infect active adults. The loss of income from a primary earner in the household can drive the household into poverty. Similarly, diseases affecting primarily children may place large financial and time burdens on other household members (WHO 2006).

The value of an intersectoral approach

There is growing evidence that zoonotic disease management benefits from an approach involving interventions across animal, health and environment sectors. An example would be Japanese B encephalitis virus, where attention to rice crop cycles (favouring dry rice schemes as a critical intervention to break the insect vector life cycle), reducing the risk of exposure of humans to pigs and vaccination of humans.

For other zoonoses, the most cost effective approach may involve intervention at just the human or the animal level. For instance, Ebola and bat lyssavirus infections are rare and sporadic zoonoses associated with extensive wildlife reservoir populations and highly specialised occupations such as hunting. Managing these diseases in wildlife populations is difficult, and interventions to change human behaviour or otherwise to protect humans from exposure may be the only practical option. Human health benefits from control of zoonotic diseases in animal populations alone can be substantial – some examples are given in Table 2.

Table 2: cost effectiveness of animal interventions on human health (WHO, 2006):

Disease	Intervention	Cost Effectiveness (Cost per DALY averted)
Brucellosis	Mass vaccination of livestock in Mongolia	US$ 19
Rabies	Dog vaccination in Tanzania	US$ 10
Echinococcosis	Deworming dogs	US$ 10- 12
Zoonotic Human African Trypanosomiasis	Treatment of cattle and vector control	US$ 9-18

In still other cases, the greatest benefit relative to cost may involve balancing interventions in both animals and humans. For instance, with rabies control in humans, post exposure vaccine prophylaxis is provided to those who have been bitten by animals that are thought to be, or are confirmed as infected with the rabies virus. At the same time, preventive vaccination is provided to dogs and in some instances to wild animals such as foxes, in order to prevent animal infection. Were the cost effectiveness of these strategies to be compared, it may be that placing greater emphasis on one strategy (in this case, vaccination of the primary reservoir host of human rabies - domestic dogs) would provide more cost effective prevention in both sectors (Knobel et al. 2005; Canning, 2006; Molyneux et al. 2011).

An cross-sectoral approach may involve more than interventions at the animal and human level. In China, an integrated control programme for *Schistosomiasis japonica* included human and livestock chemotherapy as well as health education programmes, molluscicide treatments and habitat modification to reduce snail vector populations. Although the project yielded low benefit cost ratios initially, the net benefit cost ratio equated to US$6.20 per every US$1 spent (Zhou et al., 2005).

By thinking across sectors, it may also be possible to identify situations where the combined agricultural and health benefits of zoonotic disease management justify the cost of intervention. For example, in Mongolia, where brucellosis is a significant public health problem, cost benefit analysis found brucellosis vaccination was not economically efficient for the livestock sector. However, when the costs of the vaccination campaign were distributed between health and veterinary sectors according to the benefits received, animal vaccination was a highly cost effective veterinary intervention at $19 per DALY averted (Roth et al., 2003).

Table 3 examines this relationship between where a zoonotic disease has impact and where interventions may best be targeted for some of the diseases selected for this study. Impact and intervention points include human health, wildlife populations, animal production, food chains and markets and the environment. As is suggested in the table, negative externalities are most likely to arise where the point of greatest impact is not the point of optimal intervention. It is here than an integrated approach to zoonotic disease management may be most important and effective.

	Humans		Livestock/ domestic		Wildlife		Food (Markets)		Environment		Point at which an negative externality occurs
Disease	**Economic Impact**	**Importance of Intervention point**	**Economic Impact**	**Importance of Intervention point**	**Economic Impact**	**Importance of Intervention point**	**Economic Impact**	**Importance of Intervention point**	**Economic Impact**	**Importance of Intervention point**	
Rabies	**	*	*	***	*	*	-	-	-	-	Human population (health)
Ebola virus	-	***	-	-	*	*	*	***	*	*	
Lassa Fever	***	**	-	-	-	***	*	*	*	***	
Rift Valley Fever	*	*	**	**	*	*	-	*	-	*	Livestock keepers, human health & environment
JEV	**	*	**		-	-	*	-	*	***	Human Population (health)
Zoonotic Hepatitis E	*	*	*	*	-	*	-	-	-	-	
HPAI H5N1	-	*	***	***	-	-	***	***	*	*	Livestock keepers and Human health
Brucellosis	**	**	**	**	-	-	*	***	-	-	Livestock keepers, human health
Leptospirosis	***	**	*	*	-	-	-	-	*	***	
Campylobacter	**	***	*	*	-	-	**	**	*	*	Human population (health)
Anthrax	-	*	**	***	*	-	*	*	-	*	No strong externalities some impact on slaughter workers
Salmonellosis	*	***	**	***	-	-	**	***	-	*	Poultry keepers, human health
Fascioliasis	*	**	*	***	-	-	*	***	*		Environment
HAT	*	***	-	**	*	-	-	-	*	*	Environment and wildlife
Cryptosporidosis	***	***	-	*	-	-	-	**	-	***	Human population (health)
Zoonotic Leishmaniasis	**	**	-	*	-	-	-	-	*	*	Human health
Cysticercosis	*	*	**	***	-	-	*	**	-	-	Pig keepers, pig traders, human health
Echinococcosis	*	*	*	*	-	-	*	**	-	-	Livestock keepers, livestock processing, human health
Zoonotic Schistosomiasis	***	**	**	***	-	-	-	-	*	*	Human health

Table 3: Heatmap of economic impact and key intervention point for each "host" of selected zoonotic pathogens.

Barriers to a cross-sectoral approach

Zoonotic diseases are usually not priorities amongst human disease targets, not even neglected disease targets, although this may be changing. The WHO report on Global Health Risks shows that in LMIC the third highest percentage of disability-adjusted life years (DALYs) in 2004 was from unsafe water, sanitation, hygiene, a cause of many zoonoses (WHO 2009). The recent publication of a report on neglected tropical diseases (WHO 2012a) lists 7/20 priority diseases globally as zoonoses: cysticercosis, echinococcosis, HAT, fascioliasis, leishmaniasis, rabies and schistosomiasis.

Pharmaceutical companies will concentrate on producing interventions for human diseases that are more attractive economically (Moran et al, 2011; WHO, 2010). While it is estimated that zoonotic diseasese are responsible for about 50% of economic losses due to animal diseases worldwide (World Bank, 2011), only a few zoonotic diseases are priorities for development of veterinary products (IFAH, personal communication).

Despite their significance, Interventions for zoonotic diseases in the developing world may be constrained by market failure in both relevant sectors. This problem is compounded by barriers to cooperation between animal and health sectors represent a key constraint to the management of zoonoses (Coker et al, 2011, Seimenis, 2008; Perry et al, 2011; Pappaioanou, 2010), and arise from their different objectives, procedures and resourcing. They lead to missed opportunities for integration of policy, strategy and implementation of research and development for diagnostics, drugs, vaccines and best practices across sectors. For example, many existing products do not have maximum benefit for zoonoses control because they have been developed independently with only one sector in mind (Zinstag et al, 2007). There is considerable irony in finding a product with utility in both humans and animals but which is licensed in only one sector, usually for marketing reasons. The international development community provides funding for control of some zoonotic diseases, but often in only one sector. In-country financing structures could play an important potential role in sustainable zoonoses control, for example through mechanisms for cross-sectoral financing between different ministries (Schelling et al, 2007; Okello et al, 2011).

The value of an cross-sectoral approach to zoonotic disease management is frequently cited in arguments for a “one health” approach (Zinsstag 2010). However, there remains little evidence of success. A recent systematic review of the literature (One Health Initiative, 2011-*Draft*) using strict criteria was enlightening in this respect. The approach was to consider publications where the following were considered: animal health (including relevant wildlife species), human health, and other abiotic and biotic environmental factors that may be determinants of a health issue; assessed health outcomes of the intervention in: humans and at least one non-human animal species and the health of the ecosystem in terms of the disease ecology, such as status of host parasite relationships, degree of toxic contamination, sustainable agricultural practices, biodiversity etc. and which involve human health, animal health, and environmental health/science sectors in the intervention. Whilst ignoring; studies that do not have a definable intervention, or that deal only with animal health or human health, studies that do not consider ecosystem health in any way and studies of interventions for which no outcome data are available. From this extensive work,

out of 6 million potentially "one health" related citations only 2 papers exist which test the efficacy of "one health" interventions (integrating human, animal and environmental approaches) using scientifically controlled study designs and validated analyses. These examples included a study on schistosomiasis control in China (Gray et al 2009, cited earlier) and the other campylobacteriosis in Peru (Oberhelman et al. 2006). In the first example the integrated intervention generated health benefits, which in the second it did not. The campylobacter intervention involved conventional disease control methods based on separation of chickens from people through penning. The failure to get a significant effect was unexplained. It may possibly relate to increased disease levels associated with penning and the concentration of birds.

4. Selection of interventions for zoonoses management

Summary of main messages

- The selection of interventions for research investment should emerge from a process of understanding disease drivers and epidemiology, understanding the local socioeconomic context of the disease, and considering alternate strategies for targeting zoonosis control, including elimination from animal hosts, prevention of transmission from animals to humans, and case control in humans.
- An analysis of existing and "in development" diagnostics, drugs, vaccines and management practices for selected diseases shows that many diseases have current interventions, particularly management practices, that are effective but not effectively applied. There are also considerable gaps and opportunities to adapt existing technologies to LMIC contexts and to develop entirely new technologies.
- Generalization, in terms of control strategies and prioritization of interventions is difficult, and a disease- and context-specific approach is recommended, i.e. the value of developing or improving specific interventions will be strongly related to the particular disease system, and situation, specifically to human-, pathogen- and environment-related factors which drive disease emergence and persistence.
- Recognizing the diversity of zoonotic diseases, which cautions against generalizations, there are nonetheless some patterns across the selected diseases in the use of different technological interventions:

    - An integrated approach, involving a range of interventions is identified as best practice by expert opinion for most diseases
    - Management practices are the key interventions for most diseases
    - Drugs have particular application in parasitic infections
    - Vaccines have particular application in viral diseases
    - Diagnostics are generally poorly developed, and underpin use of other technologies

The framework created for this study (supplementary document 1) identifies currently available technologies for diagnosis, drugs, vaccines and management practices for each selected disease and provides information on technologies in development. It shows that

there is a range of potential technologies appropriate to zoonotic diseases in the developing world. These may have different targets, animal populations, human populations, environmental interventions, etc. For most of these interventions, there are problems of access, affordability or adaptability to local conditions. Many of these technologies were developed for veterinary markets in high income countries. In a few cases there are gaps where no technologies exist. For any particular disease, there is rarely the combination of interventions available to make possible the integrated approach that has characterized success in high income countries. As we have seen in the previous section, there may also be considerable operational and policy barriers to implementing integrated approaches as well.

This makes the selection of interventions for research very challenging. While there are many researcher opportunities to improve the portfolio of diagnostics, drugs, vaccines and management practices for zoonotic diseases in the developing world, investing in interventions is not a guarantee that they will contribute to effective control of zoonoses. In this section, guidance is provided to researchers on how such selection might be made.

Factors influencing zoonotic disease management in the developing world

Social, economic, cultural and biological factors must be understood before effective control technologies and practices can be developed and implemented (Coker et al, 2011). These factors are particularly numerous and significant in low and middle income countries. For instance, the UK Foresight study on Infectious Diseases: Preparing for the Future (Foresight 2006), provided a useful comparison of drivers of human and animal infectious disease risk in UK and Africa. Based on a Delphi process of consultation with local experts, it emerged that factors driving disease emergence, ranging from politics to environment, were much stronger and more diverse in the African setting. It would seem logical that these conclusions would apply as well to zoonotic diseases.

Factors contributing to zoonotic disease emergence can be broadly human-related, pathogen-related, or climate/environment-related (adapted from Cascio et al 2011):

Human-related factors include: living conditions, such as lack of infrastructure (housing, sanitation and water provision (Ehrenberg & Ault, 2005) and occupation, where there is greater direct dependency on wild and domestic animals for food, transport and draft. These occupations increase exposure to pathogens through direct contact. Exposure is also affected by poor capacity for adequate food preparation, transport and preservation, due in part to poor access to energy. Intensification of production and lengthening food value chains creates risks for food safety and disease movement, while expansion of agriculture takes these food chains into natural ecosystems creating increased rural and urban disease transmission routes and opportunities. There is often a lack of capacity and resource to identify and address zoonotic disease problems at the household, community and national level, particularly in areas of conflict, where public health and surveillance infrastructure breaks down, and increased human movement spreads disease. Table 4 illustrates some of the costs of interventions and their outcomes for a few selected zoonoses which show that for the majority public funds are necessary to achieve any level of success.

A human-related factor of growing importance is the integration and diversification of livelihoods between rural and urban communities in poor regions. Increasing and frequent movements of animals and people between rural, peri-urban and urban environments is creating new and different disease ecologies/epidemiology.

Pathogen-related factors include: ecosystem change and biodiversity loss, favouring expansion of disease hosts or vectors, pressure for virulence/resistance selection, and genomic homogeneity in domestic animals (Wilcox & Gubler, 2005; Breithaupt, 2003). Intensification of production systems and genetic homogeneity has improved supply of animal-based foods but also created more favourable environments for pathogen emergence (Slingenbergh et al, 2004), including new channels for RNA virus recombination and re-assortment with ready amplification in domestic animal populations)- (FAO, 2007; Springbet et al, 2003; Kock et al, 2012- in press)

Climate/environment-related factors include: changing rainfall patterns and global warming. These affect host–vector life cycles through various means, including drought and/or flooding, which force animal and human populations closer together as they search for food, facilitating cross infection through breeches in the species barrier (Mills et al, 2010; Singh et al, 2011; Gould & Higgs, 2008).

Although the association of these different factors with zoonosis emergence and persistence is strong, there is a weak evidence base for the relative importance of specific drivers of zoonotic disease emergence (Jones et al 2012 – PNAS paper in prep).

Looking across the 20 diseases selected for this study, a single pattern for the relative importance of factors driving zoonoses do not emerge, as we have already seen in Table 3. The diseases selected exhibit enormous diversity in biology and epidemiology, associated with their diverse taxonomy (Table 1), their main sources of infection (Figure 1) and the drivers of their emergence and persistence (Figure 2).

Therefore, it is necessary to consider the selection of intervention on a disease-by-disease basis, and case studies become valuable for this purpose. Appendix 1 provides case studies for all of our 20 selected diseases. In each instance, we present information on drivers, constraints to management, the status on interventions and opportunities for their improvement. This is intended as an illustrative resource, and we use it as a resource for the general arguments to follow on prioritisation of interventions.

Disease	Intervention costs				
	Routine diagnostics	**Drugs and delivery**	**Animal Vaccines and delivery**	**Other intervention costs (Management practices)**	**Examples of Cost-effectiveness**
Schistosomiasis	Becomes more relevant with vaccination control	$5.15 China to each animal (Dandan *et al*. 2009) – reinfection probable so sustainability in question – need vaccine	Vaccine in phase II clinical trials but no cost effective data yet	Ubiquitous organism difficult to eradicate. Contact avoidance optimal for majority of population whilst occupational risk requires alternates. Integrated management practice yielded strong net cost benefit ratio 1:6.5$ once established (Zhou *et al*. 2005)	Proven synergistic benefits from joint human cattle treatment with Praziquantel and predicted improvements with vaccination (Gray *et al*. 2009)
Cysticercosis	Routine diagnosis not applicable in poor settings – $4 ELISA cost and $60 examination cost.			Education – attributable fraction to this intervention 43% (Ngowi *et al*. 2008)	
Human African Trypanosomiasis (HAT)	n/a	50 US cents per treatment year per animal (Grace 2003)	n/a	8-19$ per DALY averted through treatment of cattle and vector control (WHO, 2006). Reinfection and trypanotolerance to trypanocides - overall costs high per animal in constant exposure environments (cost to sub-Saharan African farmers estimates at $20M per year). 20% of cattle in Africa trypanotolerant – optimal sustainable solution in many areas (Grace, 2003).	Focused WHO (public good policy) investment in HAT has reduced reported incidence by 70%. HAT is a different scale of problem (<10000 human cases reported and smaller range - riverine habitat in savannah and forest – West Central Africa). Livestock disease (~40 million cases treated per annum) (Grace 2003).
Rabies	14-44$ per specimen (US)	n/a	$3.11 per dog (Chad – Kayali 2006)	Sylvatic rabies? PEP (Knobel , 2005) Eradication PAHO (human and dog) costs South America $81M (NTD – WHO, 2011) Cost per DALY averted (Tanzania) $10 (WHO, 2006) Requires policy of public good funding in poor settings	**Diagnostics** – relevant to eradication **Treatments –** ineffective **Vaccines** – cost effective for prevention – application of both dog and PEP can increase cost-effectiveness if sustained for 7+ years (Zinstaag *et al*, 2009) **Management-** eradication possible in certain settings but high relative cost.
RVF	For prevention/ surveillance early warning	n/a	40c to emerging farmers (South Africa - not including delivery and other costs) (Anon, 2010)	Requires policy of public good funding in poor settings	**Diagnostics –** relevant to prevention **Treatments** – ineffective **Vaccines** – only likely to be used in face of outbreak in poor setting
Brucellosis	Not relevant to endemic settings only for eradication and control settings	n/a	Individual vaccination is not appropriate – mass vaccination - ~$1 per head year	If costs are apportioned in proportion to livestock and Public Health sector cost <$25 per DALY averted with integrated animal human control - vaccination (Zinsstag *et al.* 2007; Coelho et al, 2011).	US$0.70 to US$4.5 per cattle and year benefit to traditional livestock keeper (Mangen *et al*. 2002) If compensation applied proportionately much higher cost initially compared to vaccine delivery vaccine <2% compensation 84% human costs <14% (Coelho et al 2011)

Table 4: Examples of intervention costs across a selection of diseases

A protocol for selecting appropriate interventions

This section presents a protocol for selecting interventions through a process that considers the human, disease and environmental factors discussed above. It draws upon some earlier protocols for defining research priorities for zoonotic disease management (Patz et al, 2004; Coker et al, 2011; Wilcox et al, 2005). This protocol is intended to help researchers avoid the tendency to conclude that simply filling technological gaps such as those identified in the framework (supplementary document 1) will reduce the impact of zoonoses in the developing world.

The protocol is illustrated graphically in Figure 4. At the core of all zoonosis management lies an understanding of the drivers of disease in animal and human populations. The box on **key zoonoses drivers** illustrates important relationships, which in turn influence control points in disease prevention and management. A failure to understand these drivers will undermine the value of a seemingly useful intervention. For example, a vaccine-based approach to eliminating zoonotic diseases in ruminants in Europe may fail in tropical situations where alternative wildlife hosts are important epidemiological drivers. A first question, therefore, is "is there an understanding of the **biology and epidemiology** of the disease?" If not, the research priority may not be development of an intervention but improving understanding of the disease system.

The local socio-economic and cultural context will influence the nature of interventions relevant to disease management. For example, control of major milk-borne diseases like bovine TB and brucellosis may be best achieved by central pasteurization in some contexts, but not in others, where milk is obtained untreated from cows at the household or village level. A second question, therefore, is "is there an understanding of the **local context** in which disease is managed?" If not, research will be required.

With this knowledge, it is possible to address the inter-sectoral issue – where should interventions be targeted across animal and human systems? For one zoonosis, for instance, the appropriate strategy might be an overall reduction in the level of disease in animal populations or the environment (by eliminating infected animal hosts). For another this may unfeasible, and the best strategy may be to block transmission of the disease between environment, animals and humans. For yet another disease, the best strategy may be to manage cases of the disease as they emerge in human populations. This prompts the question "what is the appropriate **strategy**, or a set of alternative strategies, for managing the disease in animals and humans?"

Selection of strategies will be influenced by the state of understanding of disease epidemiology and socioeconomic contexts, as indicated in Figure 4, but also now by available technologies. For example, where there is no incentive to livestock producers to control a zoonotic disease that has no effect on herd productivity, technologies which would support a strategy of eliminating the disease from animal populations may be less appropriate then where the disease is a problem for both animal production and human health.

Therefore, it is at this point that the value of different **interventions** can be compared and the question for different appropriate strategies. The question can be asked **"**what interventions exist or are emerging, in the form of diagnostics, drugs, vaccines and

management practices, which are appropriate for particular control strategies?" It may be that by developing new interventions, we can shift our strategy from e.g. transmission blocking to disease eradication. Hence, selection of interventions may influence selection of strategies, and *vice versa*.

This structured approach may help researchers to identify the most appropriate research on specific diagnostics, drugs, vaccines and management practices for zoonotic diseases in a developing world context. It may be that development of a new technology would make possible a new, superior strategy, e.g. a vaccine that might allow eradication, but its promise as an area for research will be informed by an understanding of the disease system, a local situational analysis, and the range of alternative strategies appropriate to that context.

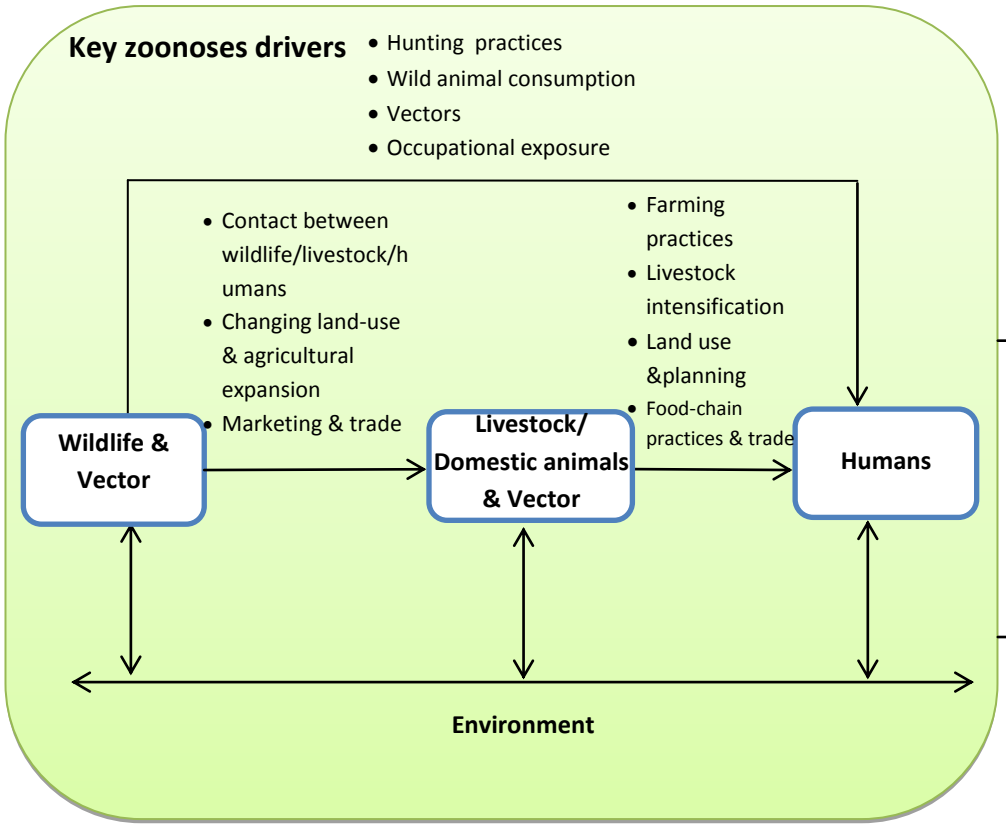
In Table 5, this protocol has been applied, for illustrative purposes, to the diseases selected for this study. This is based on a subjective interpretation of the literature and expert opinion gathered for this study. Each value in a particular cell is based on the evidence found, with red indicating the strongest supportive evidence. Columns are grouped broadly according to the steps illustrated in Figure 4 for biology and epidemiology, context, strategy and interventions:

- biological and epidemiological drivers of zoonotic disease emergence and persistence and the relative importance of environmental, human and animal factors;
- strategies for disease management that relate to the biological and situational context of the disease and indicate control points to be targeted;
- technologies for intervention and their relative value with respect to this strategic context.

Diseases are arranged in taxonomic groups, permitting comparison of these features within and between bacterial, viral and parasitic zoonoses.

While for many of these diseases there is currently in sufficient information at different steps of the protocol, even at this superficial level of analysis some insightful patterns can be seen. For instance, management practices are of consistently high importance across diseases, while other interventions have a more specific distribution. Drugs, for example, appear of greatest value with parasitic infections, while vaccines are of greatest value with management of viruses. Integrated strategic approaches, based on more than one intervention, are identified as preferable for most diseases, but not all. For Ebola, for instance, with its biology of human infection from direct contact with wildlife and few available or promising technological options for reducing pathogen levels, blocking transmission or case management in humans, the optimal strategy may be a single target – human behaviour and blocking transmission by reducing harvesting and consumption of infected wildlife.

In conclusion, Figure 4 provides a procedure that can be applied to specific zoonoses to help identify the most appropriate interventions research. Table 5 shows, in a purely illustrative manner, how doing this may lead to different research priorities for different zoonotic diseases.



Specific Zoonoses

Is there an understanding of disease biology & epidemiology?

NO

RESEARCH:

- Human populations affected
- Prevalence in humans/animals
- Epidemiology (Reservoirs affected and transmission dynamics)
- Biological feasibility

YES

Is there understanding of the local context in which disease is managed?

NO

RESEARCH Context specific factors & barriers implicated by geographic distribution of disease burden:

- Cultural
- Social
- Economic
- Structural (infrastructure & institutional arrangement)

YES

What is the set of alternative strategies, for managing the disease in animals and humans?

NO

RESEARCH
Desired outcome needs to be assessed in context specific setting: e.g. Reduction of disease in environment, transmission blocking at the human-animal-environment interface, management of human cases

YES

What interventions exist or are emerging, in the form of diagnostics, drugs, vaccines & management practices, which are appropriate for particular control strategies?

NO

RESEARCH
Use interventions framework to assess most appropriate/feasible technologies
Consider best management approaches and integrated strategies where needed

FIGURE 4: PROTOCOL TO ASSIST IDENTIFICATION OF APPROPRIATE INTERVENTIONS FOR RESEARCH

Table 5: Zoonotic disease heat map

Zoonoses Heat Map	Biological/epidemiological drivers of disease				Strategies for Disease Management				Interventions for disease management		
Evidence High/medium/low	**Factor**	Human^	Pathogen	Environment*	Integrated (animal +/- human+/- environment)	Human^ Only	Domestic Animal Only	Environment Only	Practice	Drugs (domestic animals +/- vector)	Vaccine (animals)
Disease											
Anthrax		Low	high	high	High	Low	low	medium	medium	low	medium
Brucellosis		high	high	low	Medium	medium	low	Low	high	Low	medium
Bovine Tuberculosis		high	high	High	High	medium	low	Low	high	Low	medium
Leptospirosis		high	low	high	High	medium	low	medium	high	Low	medium
Campylobacteriosis		high	low	medium	High	medium	medium	low	high	Low	Low
Salmonellosis		high	medium	high	High	medium	medium	medium	high	Low	low
JEV		medium	medium	medium	Medium	medium	medium	low	medium	Low	high
Rabies		medium	low	low	High	medium	medium	low	medium	Low	high
Ebola		high	medium	high	Low	high	low	low	high	Low	medium
HPAI H5N1		high	high	medium	high	high	medium	low	high	low	medium
Rift Valley Fever		low	Low	high	high	low	low	medium	medium	low	medium
Lassa Fever		high	low	high	high	high	low	medium	high	low	medium
Zoonotic. Hepatitis E		medium	medium	medium	high	medium	low	medium	medium	low	High
Echinococcosis		high	low	medium	high	low	medium	low	high	high	high
Cryptosporidosis		high	low	high	high	low	low	medium	high	medium	Low
Fascioliasis		high	low	high	high	high	medium	Medium	high	medium	medium
HAT		high	medium	high	high	medium	medium	Medium	high	high	low
Zoonotic Schistosomiasis		medium	medium	high	high	medium	low	Medium	high	high	low
Zoonotic. Leishmaniasis		medium	medium	high	high	medium	High (ZVL)	medium	medium	medium	low

Environment - includes climate, vector, wildlife, water?, soils etc; ^ Human includes human behaviour, food chain, landuse change etc.

Patterns of successful interventions

On the basis of the 20 case studies in Appendix 1 and the Framework for investigating interventions in Supplementary document 1, a set of success stories has been identified and are summarized below. Some successes have been restricted geographically, usually to high income settings, and constraints that have contributed to this are noted.

In the developed and some parts of the developing world the most common zoonotic infections have become routine public health events: the epidemiology is understood, some diagnostic tests, medicines and or vaccines exist, practices and policies are clear. There is an understanding of the response dictated by these policies by both animal and human health experts, and the response is implemented routinely. These are considered as success stories and some examples are as follows.

a) Zoonotic tryps – 69% reduction in reported deaths in Africa through a free WHO diagnosis and treatment campaign (Simmaro et al, 2008). Constraints include under-reporting of infection (Fevre et al, 2008).

b) Visceral Leishmaniasis – there has been significant progress in control through testing and removal of infected hosts (dogs) in South America but expanding population, lack of control over dog (especially amongst the poor) and incursion into forest ecosystems (edge effect) is increasing the exposure and case load. (Romero & Boelaert, 2010) (Note: in contrast cutaneous leishmaniasis is a poorly understood and neglected disease especially in Africa).(Reithinger et al, 2007)

c) Zoonotic Schistosomiasis – use of praziquantel in humans has significantly reduced the mortality but since its introduction little overall change in prevalence of infection in the environment and amongst the animal population (Zhou et al, 2008). One case study of a One Health intervention show that integrated animal and human health approach could be a major step forward in schistosomiasis control(Gray et al 2009; McManus et al, 2010).

d) JEV – regulation of pig farming, control of rice production (dry cycle) and use of vaccinations shown to be highly effective (but costly) in Japan (Daniels, 2001; Amerasinghe, 2003). Economic and cultural barriers in many SEA countries (Expert opinion).

e) Zoonotic bTB – strict livestock control, test slaughter and meat inspection, and pasteurisation have reduced the zoonotic disease to negligible levels in developed countries (e.g. New Zealand- O'Brien et al, 2011)- barriers to control and eradication include; wildlife reservoirs and poverty, poor infrastructure and sanitation, weak veterinary and meat hygiene services and abscence of pasteurisation (Ayele et al, 2004). Co-infection with HIV AIDS a concern in poor communities exposed to bTB (Amanfu, 2006).

f) Anthrax – regular vaccination of livestock in anthrax prone zones largely controls the disease but this is not possible in poor countries where veterinary services have largely collapsed after structural adjustment policies were implemented (CFSPH, 2007). Wildlife anthrax is a risk for hunting (and scavenging) poor communities in Africa (Hugh-Jones and Vos, 2002) and the barrier to reducing this incidence is remoteness and lack of awareness and education of traditional communities in disease risk .

g) Leptospirosis – success where social infrastructure improves, with better sanitation, water quality and management of agriculture and livestock (Karande et al, 2002; Maciel et al, 2008). The barriers to control are environmental challenges from changing agroecology increasing the habitat for leptospirosis and its carriers (rats, domestic animals- Reis et al, 2008; Perez et al, 2011) in close association with developing agricultural communities in densely population parts of the world. E.g. Increased rice cultivation is increasing exposure and risk. Food security priority with disease trade off.

h) Ebola – some success from education campaigns around protected areas in Central Africa reducing exposure risk to infected wildlife amongst hunters and their families and in markets selling products (LeBreton et al, 2006; Rizkalla et al, 2007). However this is not quantified – difficult to measure with such a sporadic and relatively rare disease with wide potential geographic range of exposure.

i) Lassa Fever – improved housing and rodent control associated with this has largely removed the threat where applied (Senior 2009, Bonner et al 2007). Poverty and widely dispersed, poorly serviced communities, with high exposure to reservoirs through living in proximity to and through catching and eating rodents are barriers to control (Fichet-Calvet & Rogers, 2009).

j) Echinococcosis – strict domestic dog control, host removal and/or treatment leads to much reduced incidence which is difficult to achieve in poor communities with high feral dog populations (New Zealand- Craig & Larrieu, 2006). Cultural barriers exist in many countries to culling feral dogs along with poverty, lack of veterinary services.

k) Rabies – success story for controlling disease where domestic dog population highly regulated through quarantine, transboundary movement controls, vaccination and monitoring. Including eradication of virus from wildlife reservoir in Europe (fox) with control through oral bait applied by aerial drop (Smith et al, 2008). Barrier to these approaches in poor countries with more biodiverse wild carnivore communities. Feral dogs form a considerable barrier to control and in many endemic zones cultural resistance to dog removal (Kaare et al, 2009).

l) Cysticercosis – good pig husbandry, meat inspection and treatment reduces this zoonotic to negligible levels (Flisser et al, 2006; Engels et al, 2003). Barriers to intervention are related to poor settings and services.

m) Brucellosis – strict regulation, good husbandry, movement control practiced in wealthier countries with strong veterinary services, the disease and zoonoses is largely controlled or eradicated (McDermott & Arimi, 2002). In poor settings the nature of the husbandry systems, mixed species and close contact with humans with few veterinary services, little movement control and with lack of pasteurisation it is difficult to achieve any control. (Marcotty et al, 2009; Godfroid et al, 2011).

n) Rift Valley Fever – success stories are few given the sporadic nature of the epidemics, variable outbreak focus, complex epidemiology and difficulties implementing control measures in the face of an outbreak, all this despite improved remote prediction. The last epidemic in Kenya showed signs of improved intervention with more integrated approaches (Rich & Wanyoike, 2010). Barriers are political and at the level of veterinary and human health

services and the lack of integration and coordination especially at the community level (Davies, 2010; Zinstagg et al, 2007).

o) Salmonellosis, campylobacter and cryptosporidosis – increasing incidence is a product of increasing poultry and pig use and more intensive industrialised systems (in the context of low general levels of sanitation) whilst farm to fork control of food safety has reduced to some extent the risk in advanced economies (Ashbolt, 2004; OIE, 2010; Herman et al, 2003; Devane et al, 2005). Here there is a food security vs food safety/health trade off. In developing countries the constraint on control includes the complex markets and marketing systems which includes, wet markets, a more integrated rural and urban system with small producers and large producers much more exposed to pathogen flow. This is set against considerable adaptation amongst local communities to digestive pathogens but diarrhoea and neonatal/perinatal and juvenile statistics show these infections are a considerable burden of poverty and arise from poor sanitation and lack of adequate hygiene generally and poor cooking facilities/lack of fuel (Coker et al, 2002; Vandenberg et al, 2009; Snelling et al, 2007.

p) Zoonotic Avian Influenza H5N1 – success is only seen where the disease has been eradicated - endemic settings (4+ countries in SEA and including Egypt) are proving difficult to manage with barriers largely associated with the social, cultural and agricultural ecology (Hogerwerf et al. 2010).

Gaps and opportunities for research in zoonotic disease policy and management interventions

The analysis of the 20 selected zoonotic diseases permitted some general conclusions regarding research gaps and opportunities that cut across specific diseases. These are presented below, indicating in brackets some of the diseases to which they particularly apply (refer to Appendix 1 for disease specifics). Note that they focus on gaps where research might be applied to provide innovative, integrated approaches, involving a range of disciplinary specialisms.

- **Proof of concept studies for integrated human, animal and environmental management and control of zoonotic diseases (**Btb, anthrax, brucellosis, leptospirosis, salmonellosis, campylobacteriosis, Ebola, JEV, HPAI, Hepatitis E, RVF, lassa fever, schistosomiasis, echinococcosis, cysticercosis, cryptosporidiosis, fascioliasis, leishmaniasis, HAT**).**

- **Targeted surveillance and sociological surveys of poor communities to map where proven intervention solutions could be applied** (bTB, brucellosis, anthrax, leptospirosis, lassa fever, fascioliasis, HAT).

- **Targeted surveillance and sociological surveys of emerging/re-emerging infections, particularly in poor communities growing demographically, occupying new areas, practising new agriculture, and including horizon scanning** (leptospirosis,

cryptosporidiosis, campylobacteriosis, tuberculosis, leishmaniasis and fascioliasis, JEV, influenza, schistosomiasis, hepatitis E).

- **Epidemiological and socioecological studies in identified high prevalence communities , including appropriate tools to monitor the impacts of disease control e.g. post vaccination surveillance** (schistosomiasis, hepatitis E, bovine TB, brucellosis, Ebola virus, leptospirosis, leishmaniasis, RVF, cryptosporidiosis, campylobacteriosis).

- **Education and awareness methods targeting zoonoses, suitable for application in poor often illiterate communities and** (cysticercosis, echinococcosis, Ebola virus, hepatitis E, Ebola virus, leptospirosis, leishmaniasis, RVF, cryptosporidiosis, campylobacteriosis, JEV, fasciola, lassa fever).

- **Targeted surveillance of high risk environments for zoonosis transmission e.g. where inadequate housing, sanitation and water supplies** (lassa fever, leptospirosis, salmonella, campylobacterosis, cysticercosis, hepatitis E, fascioliasis, leishmaniasis, bovine TB).

- **Food safety measures applicable in poor communities to reduce food borne infections** (echinococcosis, salmonellosis, cryptosporidiosis, cysticercosis, Ebola, fasciola, lassa fever (from consuming rats), anthrax, brucellosis, hepatitis E).

- **Role of intensification of livestock production and prioritisation of food security in socioeconomy, impacts on the emergence and incidence of zoonotic disease** (HPAI, JEV, cysticercosis, leptospirosis, echinococcosis, schistosomiasis, fascioliasis, anthrax, brucellosis, bovine TB, salmonellosis, campylobacteriosis, HAT, Cryptosporidiosis).

- **Drivers of zoonoses emergence and persistence e.g. land use change, settlement patterns, agroecology, transportation links** (JEV, Ebola, fasciola, RVF, schistosomiasis, leishmaniasis, HAT).

- **Policy, political and professional governance and communication systems for improved zoonoses control** (All diseases).

- **Socioeconomics of zoonotic disease control and cost/benefits to different sectors** (all diseases).

These gaps suggest a range of general opportunities for improving short and medium term interventions for control of zoonoses, and highlight an opportunity for an integrated approach to research, which should be transdisciplinary.

Gaps and opportunities for specific technologies will be discussed in sections to follow on; diagnostics, drugs and vaccines.

5. Diagnostics

Summary of main messages

- The ability to detect and identify infection and disease is crucial for surveillance and as a prelude to intervention for controlling the disease.
- For all diseases studied, access to accurate diagnostic tests was found to be sub optimal; this was due to the unsuitability of the current technology for developing country and field settings or because accurate tests have yet to be developed.
- The lack of regulation for in vitro diagnostic devices (IVDs) and inadequate evaluation of tests results in the use of tests of uncertain quality and performance.
- Development of high quality rapid 'field friendly' diagnostic tests that improve access should be considered a priority for the zoonoses studied.
- New technology has yet to be explored/exploited/evaluated.

Introduction

Detection of infection and identification of the cause(s) of an infectious disease is fundamental to efforts to manage the condition and control the disease. Early diagnosis improves treatment outcomes and reduces inappropriate medication, thereby reducing the risks of developing drug resistance. For those infectious diseases where there is not an effective vaccine, early detection leading to effective treatment or isolation/culling to remove the affected individual is the only means of interrupting transmission and spread of the disease. Tools for surveillance of zoonoses are mainly aimed at animals. However, there is also **need for knowledge** of the dynamics and scale of transmission to humans. In some cases a simple diagnostic test will not suffice and it is necessary to investigate the strain or serotype of the pathogen. Examples of this are tuberculosis, where is it necessary to differentiate human to human transmission of *Mycobacterium tuberculosis* from that of zoonotic strains such as *M. bovis* or *M. microti*, and influenza, where numerous reservoirs and potential sources of an outbreak may be present.

The **market** for diagnostic tests is smaller and less profitable than that for drugs and consequently commercial investment has been lower, a trend that is amplified for diseases that affect mainly developing countries (Peeling & McNerney, 2011). The choice of test for many zoonotic and tropical diseases is limited by cost considerations and the lack of laboratory infrastructure. **Regulation** of IVD for the human market is weak in developing countries, where tests may be marketed without evidence of their efficacy. In such countries sub-standard tests are openly sold and used, most particularly by private practitioners (Peeling & McNerney, 2011; Jaroskawski & Pai, 2012). **Access** to high quality diagnostic services in developing countries is frequently affected by their cost. An additional factor is the **suitability of technology,** as tests developed for industrialized countries may not be appropriate for use in developing countries, where laboratories are frequently under resourced and where access to basic infrastructure such as electricity or water may be problematic. Availability is also affected by logistical and technical challenges caused by remote location or harsh environment. However, recent technological advances and progress in the development of rapid test platforms designed to be used at 'point of care'

without referral to a laboratory offers opportunities to develop a new generation of tests with the potential to expand access to diagnosis in developing countries greatly (McNerney & Daley, 2011). For some pathogens that are considered potential agents of terror such as anthrax, rapid, 'easy to use' tests have been developed in countries such as the USA (JAMA 2004; Yamey 2001), but these have not so far been applied to disease control in developing countries.

Diagnostic tools may be used for surveillance purposes or as part of animal/patient management and diagnostic tools for zoonotic diseases can be divided into four categories.

i. **Screening tests** for infection and sub clinical disease. Used for surveillance and monitoring of population based interventions.

ii. **Diagnostic tests** used for disease management. Such tests must specific for the condition and readily accessible, with results available in a timely manner.

iii. **Pathogen identification** used for post mortem investigation and in surveillance studies. They range from simple identification of a pathogen to more sophisticated typing methods to identify the particular strain(s) involved in an outbreak.

iv. **Drug susceptibility tests** - the emergence of drug resistance is reducing our ability to treat some conditions and knowledge of which antimicrobials are effective may be important for surveillance purposes as well as to guide treatment.

Findings

This study assessed the role of diagnostic tests in the control of 20 zoonotic diseases. The findings reported below are derived from the combined expertise of the study participants, interviews with disease specific experts and from review of the scientific literature and published reports. It should be noted that there is a paucity of published data on the assessment of diagnostic technology and that quantifiable evidence on the effectiveness of diagnostic technologies in developing county settings is lacking.

The study revealed variation across diseases with regard to the impact of diagnostic tools. For diseases such as anthrax, early detection of the disease in humans is vital to ensure effective treatment, and detection in animals allows safe disposal of corpses to prevent transmission. However, for diseases where individualised treatment or culling is not undertaken, there is less need for rapid or highly specific diagnostic tests. In such populations where the risks associated with a false positive or false negative test result are reduced, less sophisticated screening tools may be adequate. Examples include monitoring the prevalence of bovine tuberculosis or leishmania infection in wild animals where an 'on the spot' diagnosis is not needed. Similarly, there are differences between tools used in academic research, where complex laboratory based tests such as culturing the organism or genome sequencing may be beneficial, and tools that are suitable for routine monitoring activities. Testing for drug resistance was found to be of less concern to those working in

animal health, where drug interventions are more limited, than for human interventions. An example of this is tuberculosis where inadequate treatment in humans has led to multi drug-resistance and the emergence of disease that cannot be cured by standard drug regimens, a phenomenon not seen in animals (Guerrero et al. 1997).

Improving access to diagnostics was a common theme across the diseases studied. Evaluation of current status revealed that for some diseases tests are available but considered unaffordable (e.g. rapid tests for cryptosporidiosis). For other diseases, tests are available but not accessible due to their technical complexity and need for specialist facilities and/or skilled personnel (e.g. isolation of viruses, manual nucleic acid amplification tests)- (Connell et al, 2007). For some conditions, accurate tests have yet to be developed e.g. our current inability to differentiate exposure or past disease from active disease for pathogens such as *Mycobacterium bovis or Brucella spp* (Lyashchenko et al, 2008; Kiel & Khan, 1987). Tests for human diseases were more in evidence than tests for animals; whereas technologies to detect the pathogen (PCR, culture) might be applied across species, serological tests developed for humans are rarely used to test animals. The potential of new technology to improve access was mentioned by most of the experts interviewed but studies on the impact of new technologies are largely absent. A considerable number of innovative prototype, 'in house' or 'home brew' tests have been reported in the scientific literature but they remain unavailable, as relatively few have been thoroughly validated and translated into manufactured products.

Because the need for improved diagnostic tools varies according to the intended use, tools for disease management and tools for surveillance were considered separately. For disease management, a high priority is placed on the ability to predict disease accurately in a timely and affordable manner. For surveillance tools, convenience and cost are primary considerations. Diseases identified as lacking suitable diagnostic tools are listed in table 6. It should be noted that no expert regarded current diagnostic tools as good, and even where experts reported that current tools were efficacious, they frequently suggested that improvements in technology were desirable to improve access and/or reduce costs.

Table 6. Diseases for which appropriate diagnostic tools are lacking

For disease management	Animal testing	Human testing
	Bovine tuberculosis	Bovine tuberculosis
	Campylobacter	Cysticercosis
	Cysticercosis	Fascioliasis
	Ebola	Lassa fever
	Echinococcosis/Hydatidosis	Leishmaniasis
	Fascioliasis	Leptospirosis
	Hepatitis E	Japanese B Encephalitis
	Lassa fever	Rabies Trypanosomiasis
	Leishmaniasis	
	Leptospirosis	
	Japanese B Encephalitis	
	Rabies	
	Trypanosomiasis	

For surveillance	Animal testing	Human testing
	Campylobacter	Bovine tuberculosis
	Cysticercosis	Campylobacter
	Echinococcosis/Hydatidosis	Echinococcosis/Hydatidosis
	Fascioliasis	Fascioliasis
	Hepatitis E,	Lassa fever
	Lassa fever	Leishmaniasis
	Leishmaniasis	Leptospirosis
	Leptospirosis	Japanese B Encephalitis
	Japanese B Encephalitis	Rabies
	Rabies	Trypanosomiasis
	Trypanosomiasis	
	Ebola	

The potential impact of a test is dependent on the uptake of its result, and the significance of any consequent intervention disease control. Thus a test that triggers appropriate drug therapy has a high potential impact on health, whereas a test for a condition for which treatment is either not available or will not be provided has a low potential impact. Similarly, for a condition where syndromic treatment is the norm, a diagnostic test adds little value. There are also differences when testing animal and human populations. If notification of a livestock disease causes changes in herd management, or culling, then the test will have a direct impact on disease control. In contrast, routine surveillance in human populations may result in no direct action on the population tested and thus the impact of the test will be reduced.

Affordability of diagnostic technologies

The affordability of a diagnostic test is governed by who pays for the test, and the mechanism of funding. Surveillance studies are more often funded from public sources or international donors, whereas testing individual animals or persons for disease may fall upon the farmer, patient or their families, who may pay directly or indirectly through insurance or voucher schemes.
Access to diagnostic tests in developing countries is dependent on multiple factors and varies according to the type of technology and the skill and infrastructure requirements. Tests may be classed according to the level of the health care system in which they may be deployed (in addition, example generic costs have been included where possible & further info/examples in Table 4.).

i. Reference laboratory e.g. isolation of viruses and bacteria, manual NAAT
ii. Peripheral laboratory e.g. ELISA
iii. Clinic or farm e.g. microscopy, automated NAAT -(GeneXpert MTB/RIF technology platform which detects *Mycobacterium tuberculosis* & drug resistant isolates- machine currently costs US$17,000–$62,000 and each disposable test-cartridge costs US$17–$120 - Evans, 2011)
iv. Point of care or point of sample collection e.g. dip stick and rapid immunochromatographic devices for use in the field. -(e.g. $4 per ELISA field kit for cysticercosis)

The cost of the diagnostic process comprises the cost of the reagents, the purchase and maintenance costs of equipment used, labour costs and the infrastructure (buildings) and services required (e.g. electricity and water). As the level of the infrastructure and logistical barriers decrease, theoretical access to the technology increases. For tests used within a laboratory, the level of infrastructure is an additional variable as the cost of maintaining buildings and services for specialist procedures such as the culture of infectious agents or molecular genotyping tests may be substantial. Maintenance of equipment at peripheral sites is a major challenge, and even in reference labs in urban conurbations has proved difficult (Howie et al, 2008). The cost effectiveness of diagnostic technologies is dependent on their impact. Point of care tests that trigger an intervention to control the disease may have benefits not provided by less costly high-throughput testing at a distant reference laboratory where results are not provided in a timely manner. However, it should be noted

that an easy to perform rapid test that does not need sophisticated laboratory facilities may be less affordable than the lab based test if the purchase price of the device is high.

Transport is also a significant factor, where there is a need to take the test to the animal or to bring specimens to a laboratory. Such costs are highly dependent on batch size, as the same transport costs may be incurred for testing an individual as when testing an entire herd. Costs of providing cold chain transportation (refrigeration) or air conditioning may be prohibitive and in some laboratory or field settings it may not be possible to use technologies that are not heat stable. Examples of technologies that have experienced stability problems include antibody-antigen dipstick devices (Chiodini et al, 2007) and nucleic acid amplification reactions (Boehme et al, 2010) that lose their specificity at elevated temperatures. Tests that require skilled operators to undertake or interpret the test may be difficult to implement in regions such as Africa where there are shortages of suitably educated personnel. Novel tests that require specialist training and supervision will attract additional costs for the healthcare provider. An additional 'hidden cost' is quality management, particularly with tests that require the implementation of an external quality assessment program.
The purchase cost of a diagnostic device varies according to the raw materials used, the complexity of manufacture, site of manufacture, volume of sales, shipping costs, import charges (official and unofficial) and tax. Producers of commercial tests may be obliged to honour patent protection and pay royalties for components of their device. For 'in house' tests that are assembled locally and used on a not-for-profit basis, royalties are sometimes avoided.

Gaps and opportunities

Significant gaps in the availability and delivery of diagnostic tools are apparent. Identified needs include product development to improve test accuracy and innovation to make tools more accessible.

Lack of capacity

Infrastructure Training needs:

- Laboratory infrastructure is weak in many countries - this includes a lack of suitable skilled and trained technical personnel.
- Quality standards are lacking (Quality assessment, GLP/ISO)
- There is a lack of local capacity for research and development of improved diagnostic tools.
- Few countries have capacity for technology assessment.

Technological gaps

The overriding need is for simple, easy to use technology that may be used in the field without referral to a laboratory or personnel with specialist technical skills. However, there is concern that some of the currently available rapid serological tests lack specificity and sensitivity. For diseases where vaccines may be introduced there is a requirement for tests that can differentiate vaccinated and infected individuals.

Knowledge Gaps

Knowledge gaps may be divided into those that would enable product development and those that address delivery of the intervention.

i. Improved understanding of the biology and pathogenesis of diseases, leading to the discovery of biomarkers that are predictive for the disease.
ii. Improved understanding of delivery mechanisms and the contribution of commercial, non-commercial and government agencies.
iii. Improved understanding of barriers to production of diagnostic for zoonoses.
iv. Improved understanding of the impact of diagnostic tools on disease control/transmission and cost effectiveness of implementation strategies.

Opportunities

New technologies are becoming available that offer improved accuracy with convenience of use. Examples of these are tools to amplify and detect nucleic acids. Traditionally this technology required specialist facilities and skilled personnel to contain cross contamination but automated platforms have been developed that allow tests to be performed in low resource settings (Holland & Kiechle, 2005). These technologies have yet to be exploited for the detection of zoonoses in developing countries.
For some diseases tests have been developed but have not been commercialized are not widely available. Innovative solutions by which to produce, manufacture and distribute these products should be explored

Conclusion

For some diseases, diagnostics are a vital component of disease control, but for others they have more limited impact. Appropriate diagnostic tools are lacking for some diseases. Better understanding of the role of diagnostics in disease control should be sought. Investment is needed in product development and service delivery mechanisms.

6. Drugs

Summary of main messages

- The ability to treat infection prophylactically or therapeutically is desirable and can form an important component in certain integrated intervention strategies.
- For nine of the diseases we consider that there are Gaps with respect to the available drugs.
- For the majority of the diseases studied a drug intervention approach is not considered to be appropriate relative to the alternatives.
- For six parasitic diseases studies, we found evidence for potential opportunities to address existing Gaps, discussed below.
- The risk of antimicrobial resistance and the opportunity to prevent the development of antimicrobial resistance should be considered.

Introduction

Of the four Intervention areas considered – diagnostics, drugs, vaccines and management practices, drugs feature least prominently in our framework (see supplement and Figure 5) as gaps and potential opportunities for intervention. In this report, "drug" refers to a substance that is administered as a therapy to treat or prevent a disease, but does not include vaccines, sanitisers or insecticides. From an animal health perspective, six diseases present opportunities for therapeutic intervention. The six diseases are: Leishmaniasis, Cysticercosis, Schistosomiasis, African trypanosomiasis, Fascioliasis and Cryptosporidiosis. Several of these diseases are very high burden diseases. Therefore, both prophylactic (preventative) and therapeutic interventions with drugs, while often not providing a rational opportunity for intervention on their own, are extremely important overall and in particular disease situations should form a core component of any integrated intervention strategy. From a broader health perspective there are strong arguments for therapeutic intervention within animal health as a way of reducing disease transmission to humans (Curran & MacLehose, 2002). However, there are also concerns that such interventions lead to increased antimicrobial resistance in pathogens in animals and by extension, through zoonoses, to pathogens in humans. Opportunities for improved use of existing and new drugs should be considered within an integrated approach. The risk of antimicrobial resistance was highlighted as an important factor for consideration.

Findings

For many zoonoses, the experts considered that therapeutic intervention is difficult to rationalise as a priority strategy over the other disease control options within a development context. Even for those diseases where prophylactic and therapeutics are applicable or potentially applicable, the current status is highly variable. The difficulties range from: (a) lack of suitable compounds to a lack of agreement on treatment strategies (b) different requirements for prophylactic and therapeutic drugs and formulations, and (c) different approaches to interventions from animal and human health perspectives. Not

surprisingly, cost constraints, toxicity and resistance were also highlighted as problems with current strategies.

Major barriers in the area include economic, social and technical issues. **Economic**: drugs can be expensive and the problem of expense is compounded in developing countries and in the case of animal health. For many zoonoses, the experts highlighted cost as a major barrier to implementation. Particularly for large animals, costs can be prohibitive. **Political:** antimicrobial usage is poorly regulated in many countries and this is particularly the case in developing countries. While lack of regulation does not pose a barrier to implementation, it may pose a barrier to responsible implementation. **Social:** Animal husbandry practices vary greatly between and within countries. Also, development brings further stratification of practices, with a complex mix of low-intensity and high intensity and rural/urban production. Such diversity makes it very difficult to implement standard treatment strategies and an appropriate regulatory framework. **Technical/scientific:** in many cases, the experts rated the available drugs, diagnostics and vaccines as having poor efficacy and suitability. Also, toxicity problems with existing drugs were frequently highlighted. Although it has proved difficult for academia and the Pharma/Biotech/Agrochemical sectors to develop effective tools for control and treatment of infectious diseases, this has been improved through focus, funding and novel partnerships. New partnerships are needed that are able to integrate technical / scientific advances for development of tools and epidemiology studies.

Gaps and Opportunities

The experts highlighted a need for better therapeutics or therapeutic strategies for the several diseases, listed in Table 7. These are the diseases where interventions are most needed and achievable.

Given that it is difficult to develop new therapeutics for any disease and anti-infective drug development efforts have progressed slowly in recent decades, it seems unwise to consider novel drug development alone, although opportunities are available through interactions with PPPs and the Pharma/Agrochemical sectors involved in drug development for parasitic diseases. Nevertheless, as progress is made in human zoonoses, it is important to consider opportunities for extension to animal health (Martinez & Rathbone, 2002). Also, opportunities to develop formulations, including slow release formulations (Winzenburg, Schmidt, Fuchs, & Kissel, 2004) and better insecticide strategies are under development. Within this area, approaches that are more compatible with preventative approaches to animal health in a development context were highlighted by experts. Overall, better management practice appears to provide the best opportunities for short or medium term progress in the developing world. Specific examples are discussed below. Each of the diseases where we find evidence for a Gap is presented in the table below and discussed within the appendix.

Table 7. List of nine diseases with evident gaps. The Six diseases (underlined), present Opportunities for intervention in developing countries.

Disease	Gaps	Opportunities	Potential impact
Bovine TB	Current treatment long and expensive. Not viable for herd or free range.	Difficult to foresee and effective single dose, without leading the AMR	Difficult to foresee
Japanese B Encephalitis virus	No existing specific treatment for human or animal	Difficult to foresee in animals given absence of advocated human treatment	Difficult to foresee
Hepatitis E	No available therapy is capable of altering the course of acute infection.	Difficult to foresee drug approach; in human only ribovarin used and there is a lack of evidence for efficacy; improved sanitation is the most important measure	Difficult to foresee
Leishmaniasis	Difficult to treat feral dogs	Drugs exist (pentavalent antimonials, miltefosine), which are used in humans, but reduced efficiency in dogs (Evans & Kedzierski, 2012). Opportunities where feral dog problem can be controlled. Drug combinations should be considered.	Improved animal health and welfare and reduced transmission to humans.
Cysticercosis	No drug licensed for porcine, where a large problem exists	Oxfendazole used in humans and likely effective. Likely best to combine with other interventions. Requires licensing for pigs (García et al., 2007)	Improved animals health and welfare and reduced transmission to humans
Schistosomiasis	Only praziquantel available and not optimised for use in animals at appropriate doses. Drug cost is a limitation.	Injectable formulation may help deal with dosing issues. May be advisable to use where animals are pastured in snail (*O. hupenensis*) habitats (Lin, Hu, & Zhang, 2005). In the longer term, efforts to develop new drugs should be considered.	Improved animal's health/welfare reduced transmission to humans.
African trypanosomiasis	Existing trypanocides used in humans are toxic or have modest efficiency. e.g. d*iminazene aceturate* and *quinapyramine methylsulfate* used where disease incidence is low. Prophylactic drugs used where the risk is so high that the health of the herds cannot be maintained using curative approach. Concerns about resistance.	Opportunity to limit resistance. Little attention given to combinations or rotational use,	Improved animals health and welfare and reduced transmission to humans through vector control
Fascioliasis	Triclabendazole- expensive and drug resistance emerging reported.	Drugs not yet widely used in developed world, so difficult to plan for use in developing world. Also, need improved diagnostics (Brennan et al., 2007) and standardised protocols to understand true extent of drug resistance	Improved animals health and welfare and reduced transmission to humans
Cryptosporidiosis	No reliable treatment for humans or animals.	New drugs are being developed and may become more available (Smith & Corcoran, 2004). Nitazoxanide used to treat cryptosporidiosis offers a possible strategy; it is not widely used in veterinary medicine, expensive in the developing world and may lead to resistance.	Improved animals health and welfare and reduced transmission to humans

Perspective on drug treatment at the Animal/Human interface

For several zoonoses, effective therapeutic control could offer substantial added value to human health through transmission control. In certain cases the benefits to human health could well justify animal level interventions if the costs and benefits could be accurately accounted and distributed. The opportunity to reduce transmission between animals and humans argues strongly for improved animal level therapy. These opportunities need to be considered within the context of:

(a) The integrated approach of improved diagnostics, drugs/vaccines to prevent or treat, vector control, environmental barriers and education

(b) The specific requirements around intervention for each disease, both in terms of specific disease nidality and the ideal target product profile for tools for intervention

(c) The discovery, development, delivery and access to the new tools that are required to improve control and change policy and practice

Antimicrobial resistance

The risk of increasing antimicrobial resistance must be considered.

The body of literature is overwhelming that supports the theory that resistant bacteria arising in animal populations can transfer to and colonise humans, and that genetic material from bacteria present in farm animals can transfer to bacteria normally present in humans (Mather et al, 2011). There is increasing evidence that the use of antimicrobials in animal health contributes to increasing levels of antimicrobial resistance in pathogens in humans. This can be through the development of resistance in animals followed by spread of the resistant pathogen to humans or by spread of genetic material through horizontal transfer. Naturally, it is difficult to detect such events, but the problem of resistance in human and animal health is clear and there is a growing list of examples where the probable origin of resistance in pathogens in humans can be attributed to antimicrobial treatment in animals. Antibiotic use on farms only contributes to a limited range of resistance problems in humans. However, evidence is building that for some infections the development of antibiotic resistance on farms is a significant part of the problem which makes it more difficult to treat affected patients, with potentially fatal delays in identifying an effective antibiotic when needed (Nunan and Young 2012).

Livestock production in developing countries is changing substantially and rapidly. In many regions production is intensifying and moving into peri-urban centres. The use of antimicrobials tends to increase with intensification and increasing levels of antimicrobial resistance is expected, and has been reported. However, there may not be a parallel modernisation of best practices associated with drug use. Most developing countries suffer from a poor infrastructure of veterinary services and training. Diagnostic services, discussed in the preceding chapter are crucial for effective drug use, particularly with respect to limiting antimicrobial resistance (Okeke et al., 2011). Indeed, a lack of veterinary services

infrastructure leads to a range of problems. Also, in efforts to save money, producers may under-dose or use low quality drugs. For example, drug quality analyses in West Africa have revealed that 69% of veterinary medicinal products failed to comply with requirements in Cameroon and 67% in Senegal (Teko-agbo et al., 2008).

The Gulf between Animal and Human Health Therapeutic Markets

There is an inherent economic gulf between animal and human health markets and this gulf is most striking in the case of therapeutics. Within the drug industry, the animal health market size is only 1-3% of the size of the human market. Furthermore, within the animal health market only about 3% is within the developing countries. Therefore, drug companies have great difficulty making a business case for servicing the animal health in developing countries. Given this large market divide, it is important to seek opportunities to bridge the gulf. Increasingly there are opportunities to construct public/private partnerships. However, it is important to avoid market damage; there are examples where publicly funded interventions have skewed the local market making it more difficult for companies to operate in the region in the longer term (IFAH; International Federation for Animal Health, *Leaders Group, personal communications.).*

There are several examples where the gulf between animal and human health therapeutics markets is being bridged with notable initial success. At the market level, there is a need for growth in sustainable local animal therapeutics markets. For example, Sidai Africa is a social enterprise operating in the livestock sector in Kenya (www.sidai.com). S*idai aims to set up a network of franchises owned and managed by qualified livestock professionals with drug quality and price controls in place.* At the research level, there are opportunities to ensure that drug discovery and development programmes are more effectively integrated, as, for example, those in place with some pharma/tech companies, such as SCYNEXIS, N. Carolina. The cost of screening of focussed compound libraries is relatively low when the potential and pathway is well defined. An example of such collaborative PPP drug discovery activity is on-going efforts to develop new inhibitors of human African trypanosomiasis (HAT) and animal African trypanosomiasis (AAT), involving both pharmaceutical companies and academic drug screening centres. As part of this approach, an “old drug” Fexinidazole has recently emerged as an inhibitor of HAT that is being pursued for use in the developing world (Torreele et al., 2010). Finally, when considering these efforts and further opportunities, it is important to note that animals have a high relative value in the developing world, which may help to motivate or justify investments that have a longer term view for market and health development.

Conclusions

Currently there are limited opportunities for drug interventions in the control of zoonotic infections although there are clear possibilities for drug use that would improve both prevention and treatment. The limitations (potency, toxicity and resistance) associated with the available drugs is a key reason why this intervention is not exploited more effectively. There has also been an absence of strategy to demonstrate the potential of more rigorous drug trials in animal populations, to explore therapeutic switching of drugs registered for

other indications, and to implement studies to identify appropriate drug combinations or novel formulations. Therefore, there are select, but significant, opportunities to improve interventions through drug use, as well as clear strategies that could be deployed to limit antimicrobial resistance.

7. Vaccines

Introduction

The use of vaccination to control infectious disease predates the development of therapeutic options, and it continues to represent the preferred mitigation in both humans and livestock. However, whereas a number of viral and bacterial diseases can be successfully controlled by vaccination, a significant proportion remain for which effective vaccines have yet to be identified. This gap is even more evident for parasitic disease, for which there are only few examples of effective commercially available vaccines (Evans and Kedzierski, 2012).

Deployment of vaccines against zoonotic pathogens presents a number of challenges. First, the desired outcomes in human and animal hosts are likely to be different. Whereas prevention of clinical disease is desirable in the case of human hosts, prevention, or significant reduction, of transmission is required for the animal reservoir. Second, it is often the case that the infection is subclinical in the reservoir host, despite causing disease in humans. This imposes a reliance on effective diagnostics to identify infected animals. Furthermore, where the reservoir is a livestock species, the farmer is unlikely to consider the infection a problem under these circumstances and will be reluctant to invest in vaccination. Third, where the reservoir host is a wildlife species, it must first be reliably identified; this remains to be achieved for a number of emerging virus infections such as Ebola virus and Rift Valley Fever virus. The viability of vaccination strategies for a given wildlife species is likely to depend more on its ecology than on vaccine efficacy. Finally, whereas live attenuated vaccines with reasonable efficacy are available for a number of zoonotic pathogens, these are often unacceptable for human use on the basis of residual pathogenicity.

The 20 priority zoonotic diseases addressed in the current study can roughly be divided into those that manifest as sporadic outbreaks (some of which become epidemic) and those that have established endemicity (Table 8)

Sporadic outbreaks	Endemic
• Avian influenza, • Ebola • Rift valley fever • Anthrax • Campylobacteriosis • Leptospirosis • Salmonellosis • Cryptosporidiosis	• Hepatitis E • Japanese encephalitis • Rabies • Bovine tuberculosis • Brucellosis • Leishmania • Echinococcus • Fasciola • Schistosomiasis

Table 8. Epidemiological manifestation of priority zoonotic diseases

In any of these disease systems, vaccines can be targeted to human or animal hosts, and their utility can be considered in terms of reduction in morbidity and/or capacity to block transmission. Effective vaccination of human or animal hosts in the face of sporadic outbreaks requires accurate predictive capacity, whereas deployment of vaccines in endemic settings is more straightforward.

Findings

The use of, and potential for vaccines is so widespread and so disease specific that we refer the reader to the case studies of the 20 selected zoonotic diseases in Appendix 1 where vaccines and their value are discussed relative to other interventions and knowledge gaps identified.

In terms of vaccine availability, the diseases can be grouped into four major categories:

1. Vaccines are unavailable for both human and animal hosts
    a. Human African Trypanosomiasis
    b. Lassa fever
    c. Cryptosporidiosis
2. Vaccines are available for the animal reservoir but not for humans
    a. Brucellosis
    b. Campylobacteriosis
    c. Cysticercosis
    d. Echinococcus
    e. Fasciola
    f. Rift Valley Fever
3. Vaccines are available for humans but not the animal reservoir
    a. Schistosoma
4. Vaccines are available for both human and animal hosts
    a. Avian influenza
    b. Anthrax

c. Japanese encephalitis
d. Salmonella
e. Hepatitis E
f. Leishmania
g. Leptospirosis
h. Rabies
i. Bovine tuberculosis

Gaps and Opportunities

Intervention gaps emerge from this analysis at a number of levels. Hence, available vaccines are not always adequately efficacious in terms of morbidity or transmission blocking. For example, although cattle vaccines for bovine tuberculosis are considered essential for effective control under circumstances of high prevalence, available formulations have limited efficacy (Waters et al., 2012). Similarly, it is unclear whether available vaccines for leptospirosis block transmission (Adler and de la Pena Moctezuma, 2010).

In respect of the category 1 diseases outlined above, identification of a vaccine strategy for Human African Trypanosomiasis is extremely unlikely in the short to medium term (Radwanska et al., 2008) and will require substantial investment. In contrast, good progress has been made in identifying protective antigens of Lassa fever virus (Ogbu et al., 2007) and there are opportunities for engaging with the pharmaceutical industry to get these into production. The lack of vaccines for cryptosporidiosis is not a significant constraint to control, given its sporadic occurrence and tractability to control by water sanitation and availability of effective therapeutics for humans (Kelly, 2011).

For the category 2 diseases, the lack of human vaccines has greater relevance for those that are endemic - brucellosis, cysticercosis, hydatid disease and fascioliasis. Of these, a compelling case for a human vaccine is apparent only for brucellosis (Perkins et al., 2010). A number of approaches are being pursued towards filling this gap. Vaccines for the sporadic diseases in category 2 – campylobacteriosis and Rift Valley fever - are more appropriately targeted at the animal reservoirs. The gaps in respect of the animal vaccines for the diseases in this category relate to efficacy, attenuation and suitability for field conditions (Boshra et al., 2011, Hermans et al., 2011). In the case of the sporadic diseases, the utility of available vaccines is constrained by predictive capacity (See diagnostics section).

A vaccine against the category 3 pathogen *S. japonicum* in water buffalo would be a compelling adjunct to chemotherapy in reducing transmission of the parasite (Gray et al., 2009). Progression of identified candidate antigens to a commercially available vaccine is an obvious gap in this regard (McManus and Loukas, 2008).

Gaps in respect of the diseases in category 4 relate largely to the efficacy and suitability of the available vaccines. For the sporadically occurring diseases, utility is also constrained by deficiencies in predictive capability. Hence, avian influenza vaccines are vulnerable to antigenic drift in circulating virus populations and therefore require support of epidemiological monitoring (van den Berg et al., 2008). Further, the available vaccine for Japanese encephalitis in pigs is unsuitable for delivery to roaming/feral pigs, highlighting a

need for an oral bait formulation. Gaps in respect of the endemic diseases in this category include the lack of evidence that animal vaccines for leishmaniasis and leptospirosis block transmission (Adler and de la Pena Moctezuma, 2010) and the poor efficacy of available vaccines against bovine tuberculosis (Waters et al., 2012).

In terms of research, there are further opportunities to assess cost-benefit/effectiveness for different vaccination strategies (i.e. cost-sharing mechanisms proportionate to impact/benefit across sectors), as previously attempted with rabies (Knobel et al. 2005; Canning, 2006; Molyneux et al. 2011) and brucellosis (Roth et al, 2003).

Conclusions

In light of the foregoing considerations, it is clear that progress in vaccine development, epidemiological and economic considerations, vector dynamics and policy issues vary across the 20 priority zoonotic diseases that have been targeted in this study. In each case, it is impossible to consider deployment of vaccines in isolation. Each imposes distinct demands regarding the outcome of vaccination in host and/or reservoir, and in no case is it apparent that deployment of a vaccine in isolation would achieve control. Indeed, there are several examples where vaccines and therapeutic interventions are complementary, and both depend on reliable diagnostics for effective deployment. In addition, neither option can be effective in the absence of appropriate management measures, which in turn are reliant on sound epidemiological understanding. Control of these zoonoses is therefore dependent on all four interventions, with the relative importance of each varying with disease system.

8. Discussion

An analysis of existing and “in development” diagnostics, drugs, vaccines and management practices for selected diseases shows that many diseases have current interventions, particularly management practices. These are effective but not effectively applied. There are also considerable gaps and opportunities to adapt existing technologies to LMIC contexts and to develop entirely new technologies.

Research is urgently needed to address **key** gaps in knowledge on;

a. Management practices for most diseases in poor settings,

b. Drugs applicable to certain parasitic infections,

c. Vaccines for emerging or persisting viral diseases,

d. Diagnostics for use in poor settings,

With respect to **management** of zoonotic diseases and **best** practices in control, it is a widely held view that better policy, integrated transdisciplinary approaches and a combination of technical interventions are needed but few scientific studies have been done to prove this. The analysis (see zoonoses heat map table.5) shows strong evidence that integrated approaches can potentially bring benefits to disease control. And the very few examples scientifically evaluated, illustrate how important it is to have good science behind future intervention strategies, otherwise investment in intuitively appropriate methods might prove wasteful. **Given a lack of knowledge on integrated approaches, controlled studies are a priority on combined, human, animal and environmental management of zoonotic diseases to prove the concept.**

It has been repeated often that isolated or ad hoc interventions are not a solution and **for best practices, the context and situational analysis of a particular zoonotic disease are priorities for research**. Such an approach requires specific research including; targeted disease surveillance and socioeconomic surveys of poor communities to map where proven or novel intervention solutions could be applied. These can be focused on emerging/re-emerging infections, particularly in communities in high risk environments for zoonosis transmission e.g. where there is inadequate housing, sanitation and water supplies**.** Expert opinion suggests that problems will be most prominent where communities are growing demographically, have complex social and economic networks, are occupying new areas or practising new agriculture, **all these factors are considered drivers of zoonoses emergence and persistence but research is needed to confirm this**. Once these foci are identified **epidemiological and socioecological studies are needed**, including appropriate tools to monitor the impacts of disease control e.g. post vaccination surveillance. **Education and awareness methods targeting zoonoses, suitable for application in poor, often illiterate communities and new political and professional governance and communication systems for zoonoses control will be an essential part of translational research**. **One important area for research, given the high burden of food borne zoonoses in LMIC, is appropriate and applicable food safety measures. Related to this aspect is necessary research on food policy in LMIC and its impact on the emergence and incidence of zoonotic disease.** This requires a better understanding of the likely impacts of intensification of livestock production where there is inadequate biosecurity and food safety measures in place and insufficient understanding of socioeconomic impacts.

Diagnostics are crucial and a prelude to intervention for controlling disease. For some zoonoses, diagnostics are a vital component of disease control, but for others they have more limited impact. For all 20 diseases studied, access to accurate diagnostic tests was found to be sub optimal; and research into suitable technology which can be applied in LMIC and reliably in the field, without specialist technical skills is urgently needed and in some cases more accurate tests are required e.g. current rapid serological tests lack specificity and sensitivity. Research on current levels of quality assurance in testing in LMIC was needed to provide the basis for improving policy and regulation of in vitro diagnostic testing. For diseases where vaccines may be introduced there is a requirement for tests that can differentiate vaccinated and infected individuals.

Research on knowledge gaps in diagnostics may be divided into those that would enable product development and those that address delivery of the intervention. In the first case

improved understanding of the biology and pathogenesis of diseases, leading to the discovery of biomarkers that are predictive for the disease are core. Secondly improved understanding of delivery mechanisms and the contribution of commercial, non commercial and government agencies and barriers to production of diagnostic for zoonoses will be vital to planning intervention strategies. Improved understanding of the impact of diagnostic tools on disease control/transmission and cost effectiveness of implementation strategies is also required. Particular research areas that are relevant include automated platforms and tools to amplify and detect nucleic acids robust enough for field use or use in low grade laboratories. For some diseases tests have been developed but have not been commercialized and are not widely available. Innovative solutions by which to produce, manufacture and distribute these products should be explored.

Drugs are used in zoonosis control in LMIC, whether in animals or people but those that are accessible are not often applied effectively. For the majority of the diseases studied a drug intervention approach is not considered to be appropriate relative to the alternatives. Nevertheless, the ability to treat infection prophylactically or therapeutically is desirable and can form an important component in certain integrated intervention strategies. Of the 20 diseases studied realistic research opportunities exist in improved therapies or therapeutic strategies for; leishmaniasis, cysticercosis, schistosomiasis, human african trypanosomiasis, fascioliasis and cryptosporidiosis.

Research is as much needed in providing novel agents as it is in reducing or mitigating the risk of antimicrobial resistance and the opportunity to prevent the development of antimicrobial resistance should be considered (both in terms of invention and application). Nevertheless, as progress is made in human zoonoses, it is important to consider opportunities for extension to animal health. Also, opportunities to develop formulations, including slow release formulations and better insecticide strategies are appropriate fields of research. Overall, better management practice with drugs appears to provide the best opportunities for short or medium term progress in the developing world.

Vaccines like drugs should not be considered in isolation, and examples exist where vaccines and therapeutic interventions are complementary, and both depend on reliable diagnostics for effective deployment. Appropriate management underpins their use and requires a sound epidemiological and ecological knowledge of the disease. Intervention gaps emerge from this analysis. Available vaccines are not always adequate e.g cattle vaccines for bTB are not efficacious and vaccines for leptospirosis or leishmaniasis may not block transmission. A vaccine strategy for Human African Trypanosomiasis is extremely unlikely in the short to medium term (and will be costly. Candidate vaccines for Lassa fever virus are in the offing with protective antigens identified but translational research is needed. The lack of vaccines for cryptosporidiosis is not a significant constraint to control, given its sporadic occurrence and tractability to control by water sanitation and availability of effective therapeutics for humans. The lack of human vaccines has greater relevance for those that are endemic - brucellosis, cysticercosis, hydatid disease and fascioliasis. Of these, a compelling case for a human vaccine is apparent only for brucellosis. Vaccines for the sporadic diseases, campylobacteriosis and Rift Valley fever - are more appropriately targeted at the animal reservoirs. The gaps in respect of the animal vaccines for the diseases in this category relate

to efficacy, attenuation and suitability for field conditions. In the case of the sporadic diseases, the utility of available vaccines is constrained by predictive capacity.
A vaccine against the category 3 pathogen *S. japonicum* in water buffalo is a compelling adjunct to chemotherapy in reducing transmission of the parasite and first generation vaccines are now available commercially in China.
For other of the sporadically occurring zoonotics, utility is also constrained by deficiencies in predictive capability. Hence, avian influenza vaccines are vulnerable to antigenic drift in circulating virus populations and therefore require support of epidemiological monitoring. Further, the available vaccine for Japanese encephalitis in pigs is unsuitable for delivery to roaming/feral pigs, highlighting a need for an oral bait formulation.

Conclusion

Opportunities for improving short and medium term research for zoonoses in poor settings have been highlighted in the document. A pathway for developing effective research strategies and to ensure it is translated into practice, has been fully explained and 20 diseases have been explored, in some detail, to illustrate the points and give general direction and focus for planned research activities.

Appendices

1. Disease by Disease analysis for intervention opportunities

Bacterial diseases

Anthrax

Management practices: Anthrax is an important bacterial infection causing either sporadic or epidemic disease of animals, which can then zoonotically infect humans through contact or the food chain (Woods et al, 2004). Humans can be infected directly from animals, the environment and from fomites (woolsorter's disease). Infected carcass disposal is essential to reduce contamination of the environment with the highly infective bacillus spore, and thereby reduce epidemic impact and risk in the short and long term (Gombe et al, 2007; Beyer & Turnbull, 2009). Exposure to the air of an infected animal's tissues and blood, *post mortem*, results in spore formation and subsequently, distribution of spores through various vectors (blowflies, scavengers) and ultimately by wind and water (Hugh-Jones & Blackburn, 2009). The longer a carcass of an animal dying from anthrax is left unattended to, the higher the risk of infection to other animals and people at that time or in the future. Incineration in situ is the most effective method of disposal but this requires a lot of fuel (Turnbull- see WHO Guidelines). This is expensive and in a poor setting there is a lack of fuel even wood, which makes this method impractical especially in an epidemic with multiple carcasses. Burial is an alternative (with lime), but this again is not feasible in poor settings and should be widely discouraged- this practice often leads to new outbreaks, sometimes decades later (Nishi et al, 2002). Alternatives that need to be proven to be effective are use of black plastic body bags, which in warm climates provide a sealed "disposal" system for the unopened carcass to be placed in the open and exposed to sunlight (Turnbull, 2006; expert opinion)- this opportunity lends itself to an integrated control approach at the human-animal-environment interface. The theory is that the resultant heat generated in the bag will kill vegetative bacteria in the body and prevent spore formation. After several hours it is presumed there will be no risk of further problems even if the carcass is then opened. This hypothesis needs to be scientifically evaluated, either through its use in an epidemic, with subsequent study of carcass infectivity and in controls or through other experimental methods. Wildlife populations are also affected and in some locations there is endemic anthrax where it is considered an "ecological disease" and important in natural population regulation (Hugh-Jones & Blackburn, 2009; Beyer & Turnbull, 2009). Control is not considered necessary except where the disease is epidemic from livestock sources or species populations are endangered or where there is a risk of spill over to livestock or people (CFSPH, 2007). More coordination of information on incidence and application of preventive measures, across the sectors will help to reduce impacts and risks across all species populations. This collaboration is often lacking (expert opinion).

With all diseases of this nature, which are sporadic and sometimes occurring in locations where such a disease is an event beyond living memory, there is a need for rapid community and professional education. This can focus on; the risks, opportunities to prevent or manage

an anthrax outbreak and about the tools and interventions that can be applied(Turnbull, 2008) .

Diagnostics: Naturally occurring anthrax in an animal is quite easy to diagnose and knowledge of the simple tests needed is as good as 'cutting edge' systems for endemic area poor communities (expert opinion). The definitive test is culture, alternatives are microscopy (gram stain), direct fluorescent antibody (DFA) test, ELISA for antigen detection and PCR (Rao et al, 2010)- although most of these technologies are restricted to highly specialised labs, and are only really accessible within developed countries for human anthrax cases. PCR is becoming available in a few better-equipped central laboratories (human and veterinary) and PCR on specimens without prior culture is becoming possible. But the infrastructure for a quick diagnosis of anthrax by this means when suspect cases arise is not in place in poorest community settings (expert opinion). The bio-aggressive profile attained by Anthrax in recent times has meant that simple bacteriological based diagnostic tests have been restricted (reagents and training reduced), even in developing countries (Turnbull- see WHO guidelines)

Drugs: Antibiotic therapy is effective if administered early enough in the infection. Ideal new treatments which would inhibit the action of the toxin, rather than simply killing the bacterium, and that, therefore, would be effective at a later stage of infection than antibiotics, however in developing countries penicillin antibiotic treatment considered accessible/effective (expert opinion).

Vaccines: are an important component of anthrax control in livestock (and, potentially, wildlife), particularly in the face of epidemic outbreaks, by providing protection while environmental contamination erodes (Turnbull, 2008). In the case of human zoonotic anthrax, control is more a matter of education and appropriate measures towards limiting exposure. Available livestock vaccines are based on living spore preparations of attenuated variants of the organism, in particular the Sterne vaccine, which lacks the immune-protective capsule. These vaccines provide immunity for ~ 1 year (Chitlaru et al, 2011). It is worthy of note that the near eradication of anthrax in the developed world is ascribable to deployment of these vaccines in the livestock sector- it is recommended that in endemic areas in the developing world livestock should be vaccinated yearly with currently available vaccine (Turnbull, 2008). Live vaccines are not regarded as suitable for use in humans and, with the advent of anthrax as a bioterrorism threat, substantial interest has been placed in the identification of alternative vaccine options for the disease in humans- however current vaccine options for humans are only suitable for vaccination of individuals at occupational risk (e.g. lab workers), not for response to sudden outbreaks in developing countries (Turnbull, 2008). These have focused largely on the use of culture supernatants containing the pathogenic toxin, or recombinant forms of PA, its non-pathogenic subunit (Chitlaru et al, 2011).

Brucellosis

Management practices: In humans, brucellosis is an important chronic, debilitating disease, caused by gram negative bacteria of the genus *Brucella* (Franco et al, 2007). Humans can contract disease from a number of (animal) sources involving different brucella species (Fitzpatrick et al, 2010). There are approximately half a million human cases reported globally each year; however it is likely that the true figure is significantly higher due to underreporting (Pappas et al, 2006). Human brucellosis is most commonly associated with drinking infected unpasteurised milk (and milk products) and with occupational exposure risk (individuals with direct and regular contact with infected livestock or rarely wildlife)-(Makita et al, 2008). In animals, brucella species affect a wide range of hosts including swine, cattle, sheep and goats (Corbel et al, 2006- WHO) and wildlife species (e.g. carnivores, hoofed mammals and even cetaceans and pinnepeds, both aquatic species)-(Godfroid, 2002). The main zoonotic species are as follows; *B. melitensis* which infects for example sheep, goats, camels and gazelles and is the most common cause of human brucellosis, with hot spots in North Africa and the Middle East where the highest incidence of zoonotic brucellosis occurs*; B. abortus* which infects for example cattle, domestic and wild African buffalo, wild and farmed elk, yaks, camels and *B. suis*, infecting for example domestic pigs and various wildlife (e.g. boar, reindeer, caribou and rodents). Animal brucellosis occurs globally in all types of production systems and habitats in either endemic or epidemic forms (Pappas, 2010). For example Brucellosis is endemic across much of sub-Saharan Africa, with a varying degree of prevalence between production systems (McDermott, 2002). There are examples where brucellosis control is complicated by wildlife reservoirs (Treanor et al 2011) but the role of wildlife in the evolution of new strains and as a reservoir and source of infection remains poorly understood (Pappas, 2010). In areas where brucellosis is tightly controlled, or eliminated, epidemics can occur with re-introduction of the pathogen into animal populations e.g. periodic outbreaks in China (Deqiu et al, 2002).

There are currently a range of diagnostic tests for animal brucellosis (Godfroid et al, 2010). The problem with them in relatively poor countries with weak health services is they are inappropriately applied (Godfroid et al, 2011; expert opinion). Endemic settings don't require them for detection as simple clinical observation is sufficient but once control measures are desired they become vital. In regions where herd prevalence is low and the disease is cryptic, screening using either milk or serum samples will be the most practical approach (Corbel et al, 2006- WHO).
While there are no treatments for animals and a lack of an 'ideal' vaccine for brucellosis currently, best practice is to use the attenuated strains of *B.melitensus* strain Rev.1 for sheep and goats and *B.abortus* strain 19 for cattle are currently recommended and demonstrate the greatest efficacy (Corbel et al, 2006- WHO). However, unwanted adverse side-effects reduce the suitability of the vaccine in livestock and the relatively high cost of available vaccine hampers the accessibility in developing countries. The complex nature of brucellosis epidemiology means that best disease management practices play an important role in effective control (expert opinion). In highly organised and compartmentalised livestock industry in countries where livestock are no longer part of subsistence the disease

is relatively easily controlled or eradicated by test and slaughter with vaccination as an alternative (McDermott & Arimi, 2002). Control of the disease under certain socioecological conditions, where there is poverty and dependence on multiple livestock for livelihood or food is difficult, partly due to the fact that individuals at risk of exposure are ill-informed about brucellosis (and form emotional attachments to their animals- Marcotty et al, 2009), its multiple hosts and possible transmission routes or have few options available to avoid contact with the bacteria, even if controlled but not eradicated. However control at the animal-human health interface is likely to yield the best results (Godfroid et al, 2011); pasteurization of milk and milk products remains the most effective option for preventing infection (from this source) to the wider community, whereas control of the disease (with accessible cheap effective vaccine applied in the reservoir host population) or preferably eradication in livestock, provides the best long term solution to brucellosis in occupationally exposed communities.

A key issue faced with brucellosis and especially within the developing country context is the lack of epidemiological knowledge of classical brucella species and others including those infecting wildlife species (Godfroid et al, 2012; expert opinion). The relative importance of reservoirs and spill-over hosts in an ecosystem needs to be understood. This knowledge will guide targeted control strategies where resources are limited. The ability to trace back the chain of infection events leading up to human brucellosis through isolation and identification of specific *brucella* spp is vital but largely lacking in endemic settings (Whatmore, 2009; expert opinion) . There is a tendency to assume it is a cattle problem and focus attention there. A molecular epidemiological approach will help determine the transmission routes, drivers and main reservoir hosts (Godfroid et al, 2012; Kabagambe et al, 2001) but this requires good laboratory facility. Failing this the wider utilisation of currently available diagnostics, particularly the ELISA serological tests (suitable for seroprevelance surveys across endemic countries and a wide range of domestic and wild species) would prove a suitable option to examine the epidemiology and from this gain a greater understanding to identify intervention points and improve control efforts (expert opinion). This requires access to the diagnostics kits and sufficient resources for surveillance to establish established patterns prior to developing any control strategy. In most countries this is likely to follow progressive control policy, first in sectors where specific opportunities will arise e.g. in emerging markets and production systems, enabling wider use of e.g. pasteurization practices, an approach that will prove difficult in many traditional nomadic or extensive small scale farming systems where practical (lack of cooking fuels and necessity to move according to pasture availability) and cultural barriers exist to rational disease control best practice. There is a trade-off often in what communities do in this context, preferring to risk disease whilst reducing the risk of starvation. Such approaches could be coupled with innovative approaches involving education/health-promotion campaigns aimed at high risk groups and could provide additional benefits at the community level (Smit, 2011).

Diagnostics: Diagnosis in animals by clinical observation is sufficient in endemic settings but if controls are to be implemented then testing of animals and/or food products is necessary. Due to the low cost and ease of use one of the most widely used tests is the Rose Bengal Plate Test (RBPT) complement fixation test (DISCONTOOLS, 2011; Godforid et al, 2010; CFSPH, 2007; Diaz et al, 2011). However this test has reduced performance in chronically

infected animals. More accurate serological tests include CFT (complement fixation test) and enzyme linked immunosorbent immunoassays (ELISA), but cost, and in the case of CFT- lab and training requirements make these tests both unsuitable and inaccessible for many developing countries(DISCONTOOLS, 2011; Godfroid et al, 2012) . Commercial and non-commercial tests are used.

For human diagnosis diagnostic tests are important where the clinical signs are often difficult to interpret unless there are strong indicators of prior exposure. The definitive test for brucellosis is isolation and culture of the organism, usually from blood or bone marrow; however, this is a slow process (weeks) that requires specialist laboratory facilities not often available in developing countries (Franco et al, 2007). Serological tests are more commonly used, either agglutination tests or enzyme linked immunosorbent immunoassays (ELISAs). Rapid POC tests have been developed but are not well validated. Due to the cross-reactivity between species diagnosis by serology is not reliable (Cutler et al, 2005). Tests may also cross-react with other gram-negative bacteria (Schoerner et al, 2000) increasing the rate of false positive tests and in endemic areas subclinical infection may affect test interpretation. Serological tests remain positive for a period following treatment and so are of limited value for diagnosing relapse or reinfection. RBPT are used to screen human sera in some countries, but confirmatory testing should be performed (Corbel, 2006-WHO). Nucleic acid amplification tests such as PCR have been reported to have high sensitivity and specificity. However, methods are not standardised and the technology is not widely used (Yu & Nielsen, 2010).

Drugs: No treatments for animals currently. Human diseases are treated with antibiotics. The tetracyclines, streptomycin and gentamicin and the anti-tuberculosis drug rifampicin are effective against Brucella bacteria. Two drugs are used concurrently, with some treatment regimens lasting six weeks. A triple therapy of doxycycline, with rifampin and cotrimoxazole, has been used successfully. Even with optimal therapy, relapses may occur in 5–10 percent of patients (Franco et al, 2007; Corbel, 2006-WHO)

Vaccines: The most prevalent of the bacterial zoonoses, Brucellosis is probably one of the least understood in terms of pathogen population structure, host immunity and pathogenesis. With the exception of *B. ovis*, effective livestock vaccines are available based on live attenuated organisms, although it is questionable whether these apply sufficient pressure for eradication (Godfroid et al, 2011). However in developed country situations Rev1 vaccine has been vital wherever eradication has been achieved and the use of this vaccine makes a strong economic case for effectiveness (Zinsstag et al, 2007). Within the developing country context, the vaccines are priced highly and cannot be used in pregnant animals or breeding sires- clear negatives (DISCONTOOLS, 2011). In addition, inability to distinguish vaccinates from naturally infected animals constrains the utility of these vaccines for eradication Furthermore, these formulations are not acceptable for use in humans on the basis of residual pathogenicity and substantial gaps exist in respect of the identification of improved human vaccine for brucellosis. Current avenues for research include evaluation of sub-cellular fractions and LPS-protein conjugates and generation of attenuated mutants with defined mutations (DISCONTOOLS, 2011).

Bovine tuberculosis

Management practices: The zoonotic risk of bovine TB in extensive livestock systems in dryland ecosystems (rangeland) and associated poor communities has been of interest in recent years (Ayele et al, 2004) especially with rising levels of HIV/AIDS in many communities and association of infection with mostly rural environments. A few studies are available from extensive traditional pastoral systems and these show that, although endemic, the prevalence of BTB in cattle in extensive settings is low at <1% of the herd, although between herd prevalence can be higher (Tschopp et al, 2009; Cleaveland et al, 2007). Here at least the risk would appear quite low. The risk of infection increases for people with close daily contact with infected livestock and where poorly cooked meat and unpasteurised milk is consumed. With stall managed, sedentary, higher density and intensive systems the prevalence and risk increases, especially for families keeping livestock in their homes and for livestock farmers or workers, slaughterers and meat processors in endemic areas, where there is poor biosecurity on farms and lack of movement controls (Boukary et al, 2012). Data on the relative importance of Bovine TB in cases of human e.g. extrapulmonary tuberculosis is limited but it was estimated at 3.1% of tuberculosis cases globally at the turn of the century (Byarugaba et al, 2009). Sputum positive cases can range from 0.1 – 10% in African surveys, despite it being mostly an extrapulmonary disease and data varies according to region and country (Michel, 2010). Cattle are owned by the richer families in communities whilst goats and sheep are vital food security if in poverty. The risk from small stock is largely undetermined but infection in these species is not uncommon (Tschopp et al, 2011).

Evidence is strong that control measures against zoonotic BTB, where applied rigorously, work well even if the disease in livestock persists, e.g. where there is a wildlife reservoir in the environment and re-infection. Best management practices are largely focused on reducing the incidence in livestock (preferably eradication)- (Renwick et al, 2007; Cousins, 2001; Ayele et al, 2004) -), through test and slaughter policies, movement controls and on improving hygiene, through meat inspection at slaughter and control of the food chain to ensure meat and milk are safe. There have also been great successes with btB control in New Zealand where culling of wildlife coupled with control in livestock has proved largely effective (O'Brien et al, 2011). These are not all possible in poor settings. The current best practices for poor communities (and directed at the associated health professionals and governments) include (Ayele et al, 2004; Amanfu, 2006; Cosivi et al, 1999):

a) Education and awareness about; health risks of contact with and eating, uncooked meat and unpasteurised milk from infected livestock (and bush meat), and an appreciation of the density dependent nature of the disease and its association with poor nutrition and/or co-infection e.g. HIV/AIDS. (WHO, 2007)

b) Retaining traditional extensive systems in dry rangeland ecosystems (where there is low prevalence and risk),

c) Improved biosecurity of sedentary herds (reduced infection) in rural areas and where possible testing and BCG vaccination to reduce spread

d) A one health approach to researching knowledge gaps in the epidemiology of BTB in mixed species systems, will increase understanding of the contribution of BTB to

the tuberculosis burden in poor communities and from where it originates and where interventions are best applied.

Diagnostics: Screening animals and food products for bovine TB is not common practice in developing countries. Skin tests where an immune reaction indicates exposure of the animal to the bacteria are the most commonly used test (Amanfu, 2006; Engers et al, 2008; CFSPH, 2009). More sophisticated tests that assess gamma interferon production following incubation of blood samples with TB antigens (IGRAs- Neill et al, 1994) have been developed but their high cost and technical complexity restrict their use (Schiller et al, 2010). Test kits have also been developed for humans but the inability to differentiate active disease from latent infection has restricted their usefulness and WHO have recommended that they not be used in TB endemic countries (McNerney & Daley, 2011; WHO, 2011). Smear microscopy to identify acid fast bacteria is the most frequently used tool to diagnose TB, however the low sensitivity of the method means it is of limited value. The test is most usually applied to sputum samples for the detection of pulmonary disease; detection of extra pulmonary forms of the disease (frequently encountered with bovine Tb) is problematic (WHO, 2007). Definitive diagnosis requires isolation and culture of the bacteria, a slow and often difficult process that requires stringent safety precautions. An easy to use molecular test was recently endorsed by WHO for use with sputum for human diagnosis. The test is expensive and requires a computer and electricity. More portable and cheaper technologies are currently being evaluated. A number of rapid serological tests are sold in developing countries for human use but all tests so far evaluated have been found to be substandard and their use is not recommended.

Drugs: Current treatment is long and expensive- not viable for herd or free range (expert opinion). Opportunities are difficult to foresee regarding an effective single dose- opportunities regarding slow release formulations/delivery strategies potentially problematic due to perceived antimicrobial resistance risk- with potential for antimicrobial resistance emergence in humans (expert opinion; Rivero, 2001; Michel et al, 2010).

Vaccine: Significant gaps remain in progress towards an effective vaccine against *Mycobacterium bovis* in cattle (Waters et al, 2012). This has limited impact in the developed world, where the disease is controlled largely through diagnosis and eradication. However, given the absence of practical therapeutic options, there is demand for an effective vaccine for bovine TB in developing countries (Amanfu, 2004). Our expert consultation suggests that this is the only feasible option under circumstances of high prevalence. The BCG format, which has been highly successful in the control of human TB, is expensive, has limited efficacy in the bovine system, high response variability, and shows low adoption rates (Waters et al, 2012; expert opinion). Interestingly, efficacy appears to vary regionally, suggesting possible influences of environmental mycobacteria (Buddle et al, 2002). Control of the spread on infection to humans, as evidenced by the case of the developed world in the middle 20th century, can be accomplished through best management practice (such as pasteurization of milk and dairy products). Control of this zoonosis in developing countries will best be accomplished through development of effective vaccines and implementation of appropriate food chain controls (Cosivi et al, 1998). Research opportunities are evident in

the former area, with a range of options from antigen-specific boosting of BCG vaccines to evaluation of recombinant subunit formulations (Waters et al, 2012).

Leptospirosis

Management practice: Leptospirosis is an emerging problem globally especially in per-urban and urban slums with an estimated 500,000 cases annually (Hartskeerl et al, 2011; Hartskeerl, 2005). Livestock incidence is unknown. Its increasing prominence has been linked to increased global temperatures and rainfall (climate change)- (Luber & Purdent, 2009). It is different to other livestock zoonotic bacterial diseases in that the primary source for spill over infection, most probably, is rodents (WHO, 2011). Humans are an accidental host. There has always been a background rate of leptospirosis associated with livestock keepers and others with occupational risks dealing with animals but this is not where the current focus of attention is needed. The evidence base for almost all aspects of the science relating to leptospira are weak. Knowledge gaps are key and better understanding of the epidemiology of the disease would help identify key intervention points (expert opinion). It is truly a disease derived from the environment as pathogenic leptospira can survive long periods outside the host depending on humidity and warmth (Bharti et al, 2003). Monitoring of chancing ecological conditions, socioeconomic and political influences on demographics urban expansion and slums will allow better prediction of future events and risk (Hartskeer et al., 2011). Best practices are largely undetermined but epidemiological studies identifying risk factors/ determinants e.g. open sewers vs. good drainage- improved sanitation as part of multi-level interventions including rodent control (but chemical pesticides are not advocated) are providing some useful indicators for investment in urban planning for disease prevention (Sugunan et al, 2009; Vijayachari et al, 2008; Sakar et al, 2002). The spread of agricultural systems, especially those involving flooding, are also increasing risks especially where natural flows are reduced and high levels of pollution with organic matter provide a suitable substrate for survival of the spirochaete (Kawaguchi et al, 2008).

Since this is an example of a disease sensitive to ecological change, management and prevention will need to be tackled throughout the global, environmental and landscape level. Particularly those actions focused on reducing the uncontrolled development of slums with poor drainage and sanitation (Karande et al, 2002; Maciel et al, 2008). If planning takes into account rodent ecology (Perez et al, 2011; Holt et al, 2006) and reduces the optimising of habitat for these species in urban housing slum development and surroundings (Reis et al, 2008), this will reduce the risk substantially. Rodent control without doing this is likely to fail and have other unintended consequences. Attention to hydraulics and improved water quality and flow in agricultural systems and reduction in exposure of people and animals to these environments in the farming system (Gamage et al, 2011) will all help. Since many of these interventions require strong social and political governance and cooperation poor settings they also require the highest investment in planning and support. The reality is that demographic trends and politics often prevent governments from acting and limiting expansion in these environments. They are picking up the cost of the disease and trying to treat the problem. Best practice with effective chemoprophylaxis requires sound spatio-temporal epidemiological knowledge (Robertson et al, 2012) to target treatment in the right place and time. Tools for early warning on leptospirosis epidemics need to be developed.

Controlling animal disease (including in humans) through vaccination suffers from a lack of supporting evidence for efficacy in many species and it does not prevent persistence in carrier hosts.

Diagnostics:
Diagnosis is by detection of bacteria in blood or urine or by finding increasing levels of antibodies to Leptospira over time (Adler & de la Peña, 2010). Serological testing, the MAT (microscopic agglutination test), is considered the gold standard but preparation of the reagents is laborious and expensive and the tests is less used in developing countries. Diagnosis may confirmed with enzyme-linked immunosorbent assay (ELISA) and polymerase chain reaction (PCR). For human disease there are a number of tests available, including point of care tests devices; however, the efficacy of the rapid tests is variable and often less than satisfactory (Effler et al, 2002).

Drugs: Tetracycline can be used to treat acute leptospirosis in livestock, and injectable, long-lasting oxytetracycline has been shown to effectively reduce shedding in cattle(Bolin, 2003; Vijayachari et al, 2008) . These are suitable approaches in developed country situations but unlikely to be widely used in developing countries. On human side penicillin and doxycycline can be used but not effective in later stages of disease (Brett-Major & Coldren, 2012)- these pharmaceuticals are likely to be more accessible for human use to treat leptospirosis in the developing world.

Vaccine: This severe zoonotic infection is generally associated with livestock production or with exposure to contamination with rodent urine. Bacterin vaccines are available for humans and animals, but these tend to be restricted in their specificity across the serovars, which results in variable levels of protection (Wang et al, 2007). In addition, it is not clear that animal vaccines prevent establishment of the carrier state and hence block transmission (Adler et al, 2010) . Efforts towards improvement of human formulations have focused on reducing adverse reactions through the use of subunit components and, in the absence of conserved molecules with proven efficacy, are unlikely to address issues of specificity (Cullen et al, 2004; Silva et al, 2007).

Salmonellosis

Management practice: Zoonotic salmonellosis or more specifically, non-typhoid salmonellosis (NTS) occurs globally, but appears to be most prevalent in areas of intensive animal husbandry, especially in pigs and calves and some types of poultry reared in confinement (OIE, 2010) and is not specifically a problem of poor settings or rural subsistence livestock and rarely a problem of extensive pastoral systems. This said, poorly managed industrialised agricultural systems are increasing in sub-Saharan Africa and hospital-based studies reported blood stream Salmonella spp. infections more frequently associated to NTS, particularly S. Enteritidis and S. Typhimurium, than S. Typhi or S. Paratyphi (enteric fevers)- (Gordon & Graham, 2004). In this region, invasive NTS is endemic and has elevated morbidity and mortality in children less 3 years and adults with human immunodeficiency virus (HIV) infection (Gordon, 2008; Vandenberg et al, 2009).

In poor communities, measures to limit infections from food products include; a) proper cooking of food likely to be contaminated with *salmonella*. The best preventive practices include; a) improving fuel provision and access and effective cooking systems, b) education about the risks and the taking of simple preventive measures (Graham, 2002; Expert opinion) such as avoidance of animal faecal material, use of soap and washing before eating, c) improved water and sanitation and, d) better nutrition (Sanchez-Vargas et al 2011). There is nothing remarkable or novel in this but the problem lies in the conditions that exist or are being created by rapid population growth, poor housing and infrastructure in rural communities and in uncontrolled slum development with increasing stress on limited resources especially fuel and water. In the context of farming, there is a need for the development of knowledge base and mechanisms for dissemination of information to farm owners/workers in developing countries to improve biosecurity and increased use of symbiotics (Collins & Gibson, 1999; Tellez et al, 2012; Mani-lopez et al, 2012) (i.e. ration formulation procedures and inclusion of colostrum and natural plant based products). Also consider 'all-in all-out" production cycles (Meroz & Samber, 1995; FAO, 2010) and related biosecurity practices (Berg & Wierup, 2012) to reduce disease transmission across trade networks following the food to fork food safety practices now commonly advocated in industrialised countries. This is easier said than done in poor countries where food security and not safety is the issue and slum dwellers harvest even condemned slaughter house products.

Diagnostics: Detection of Salmonella in animals or foods is by culture, however newer methods such as immunoassay and PCR are available (OIE, 2011; CFSPH, 2005). Where laboratory facilities are available microbiological examination of stool is the most common means of diagnosis in humans (Baker et al, 2010). A number of more rapid tests are now available including nucleic acid amplification and POC devices (expert opinion).

Drugs: Livestock feed containing antibiotics is main route to controlling salmonella in animals- this has however been linked to increasing drug/multi-drug resistant variants in livestock and humans (Archambault et al 2006; Lauderdale et al., 2006; Foley et al, 2008; Molbak, 2004). This pattern has been clearly observed in developed country situations; however the extent of the issue in developing country where antibiotic feed is widely used is yet to be fully assessed.

Vaccine: Zoonotic or Non Typhoid Salmonella infections in humans are associated largely with food animal products or contact with animals (Morpeth et al, 2009). Available Salmonella vaccines for humans target the anthroponotic S. Typhi serovar and can provide some protection against S. Paratyphi (Marathe et al 2012; Paterson and Maskell, 2010; Crump and Mintz, 2010). Because immunity is serovar-specific, little protection can be expected against zoonotic challenge. Vaccines for these infections therefore focus on the target animal. Live attenuated formulations are favoured (Penha Filo et al, 2010) and can provide good protection against homologous challenge. However, efficacy can vary with the quality of production and although transmission is generally reduced (Dorea et al, 2010), it may not be abrogated. Improvements in the attenuation process for vaccine development have arisen through the use of targeted mutation using genetic manipulation. Although this technology can give rise to more stable defined attenuated mutants, uptake of these has

been limited because of public concerns regarding genetically modified organisms (GMO)-(expert opinion).

Campylobacteriosis

Management practice : There are many features of *campylobacter* and best management practice (i.e. improved biosecurity and use of sympbiotics/pre-biotics- Newell et al, 2011; Ganan et al, 2012; expert opinion) for disease that are in common with *salmonella* infection, but this disease in developing countries is primarily paediatric especially for <2 year olds (Coker et al, 2002). It is hyperendemic and mostly associated with poultry sources although other domestic animal sources are involved (Pattison, 2001). It is primarily acquired from environmental contamination or food chain but also occurs from direct contact where there is occupational risk or close proximity with animals (Herman et al, 2003; Devane et al, 2005). Intensification of livestock systems even in rural subsistence production can increase incidence and there is some correlation with human density suggestive of human-human transmission (Coker 2002). An intervention-control study where measures were instigated to reduce contact between children and animals (chickens) through conventional approaches, in this case penning, proved to have a negative effect- in a high childhood diarrhoea incidence, poor community context in South America (Oberhelman et al 2006). The reasons were not determined but suggestive of the impact of intensification of production systems on this disease. Other features in common with e.g. TB and brucellosis is the tendency for increased incidence in high HIV/AIDS communities. Best practices in poor settings are similar to those described for other food borne and environmentally derived infections (White & Baker, 1997), relating largely to food hygiene and cooking but there is evidence of the possible benefits of more traditional, low intensity (village) poultry and livestock systems, rather than intensification, amongst the rural poor (Graham et al, 2008; Oberhelman et al, 2006).

Diagnostics: Detection in animals or foods is by culture, however other methods such as agglutination, immunoassay and PCR are also available (DISCONTOOL, 2011; OIE 2008). Where laboratory facilities are accessible microbiological examination of stool is the most common means of diagnosis in humans (CFSPH, 2005). A number of serological tests have been developed.

Drugs: Antibiotics are not directly applied for treatment/control in livestock animals because asymptomatic infection in animals- however addition of antimicrobial feed to control other bacterial pathogens in livestock has resulted in isolation of campylobacter resistant strains (Rahimi & Ameri, 2011; Alfredson & Korolik, 2007).

Vaccines: Current vaccines against this burgeoning zoonosis are ineffective (DISCONTOOLS, 2011). Efficacious and practical immunization of poultry against Campylobacter will require an orally delivered formulation capable of inducing lifelong protection (Noor et al, 1995; Hermans et al, 2011). Our expert consultation revealed that, even in the face of such a vaccine, control would be difficult because a) immunity does not clear infection and b) Campylobacter strains are diverse. This suggests that an effective vaccine would of necessity

incorporate multiple strains and, as a result, would be too expensive for deployment in developing countries. A more appropriate strategy might therefore be to target breeding flocks (expert opinion), which would involve fewer birds, with a view to providing enduring immunity in chicks and ensure a delay in the onset of infection. Research opportunities exist in the modelling of this system and in clearer definition of Campylobacter strain structure and endemic distribution.

Viral diseases

Japanese Encephalitis

Management practice: Japanese Encephalitis (JE) is a mosquito borne flavivirus infecting animals and causing tens to hundreds of thousands of cases in humans and many thousands of deaths in mostly South East Asia and Western Pacific (Erlanger et al, 2009). Its geographic range is expanding and now extends from Pakistan in the West, Australia in the South, Maritime Siberia in the North and, Philippines and China to the East (Keiser et al 2005; Misra & Kalita, 2010). Effective control depends on adequate investment and implementation of vaccination and has been achieved in many economically advanced countries of East Asia and South-East Asia (i.e. Japan, Republic of Korea and Taiwan) and the burden of JE has been substantially reduced in many other endemic countries (Halstead and Jacobson, 2003). This is in contrast to its range expansion and intensified transmission observed from anthropogenic causes in other parts, most likely due to climate change, expansion of water retention systems and irrigated agriculture and increasing pig husbandry (Amerasinghe and Ariyasena, 1991; Akiba et al., 2001).

Best practices remain to be determined but in poor rural settings with inadequate finance for sustained vaccination in humans and livestock probably should focus on introducing specific agricultural practice (e.g. use of alternate wet and dry (Van der Hoek et al, 2001) – or intermittent irrigation approaches) along with a reduction in human (Amerasinghe, 2003; Rajendran et al, 1995;) – pig spatial co-existence, or encouragement of greater livestock diversity particularly with cattle which are preferred host to the mosquito vector *Culex tritaeniorhynchus* (Arunachalam et al 2005). This would require considerable governance and compliance as the benefit is only likely if the close pig-human agricultural system is reduced, amplification of the virus can be dampened and/or the life cycles of the vector can be disrupted across a wide area. Methods of integrated vector management along with biological controls (Van den Berg & Taken, 2007), in particular the use of larvivorous fish are a potential control measure, but the challenges are frequently site and use in the rice field farming settings may not be effective (Angelon & Petranka, 2002). Reduction in extensive pig husbandry is unlikely to be achieved for sociocultural reasons; it is currently an acceptable trade-off against disease risk (Keiser et al 2005).

Diagnostics: Antigen detection or screening for antibodies are the most common detection methodologies. Nucleic acid amplification is also used.(Daniels, 2001; expert opinion)

Drugs: No existing specific treatment advocated for human or animal use. Opportunities for drug development not likely to be forthcoming in animals given absence of advocated human treatment.

Vaccine: Although human vaccines are widely available for this disease (Saxena & Dhole, 2008), based on live attenuated or killed viruses, and various vaccines are available for pigs, although there has been limited current use of the pig vaccine (vaccination programmes across Japan, Nepal and Taipei China- Daniels, 2001). These act as amplifying hosts for the zoonotic infection and are considered to be the most important reservoir in endemic areas- pig vaccination has not been shown to directly contribute to JE human case reduction in countries where it has been carried out (PATH, 2012) . It is further argued that control in the human populations through vaccination is the most effective approach (Beasley et al, 2008)- however for the poorest communities this approach may just not be feasible. Our expert consultation highlighted inadequate vaccine coverage in human populations as an issue (Singh & Argawal, 2005), such that not all children receive the vaccine (can be used to control JE epidemics i.e. India- Sabesan et al, 2008). In addition the current pig vaccine is inappropriate for delivery to roaming/feral pigs, highlighting the need for an oral bait formulation (expert opinion). Diagnostic support for vaccine programmes is in addition constrained by cross-reactivity of available serological tests with other flaiviruses.

Rabies

Management practices: Rabies is one of the most studied and debated zoonotics with a uniquely tragic and horrifying disease pathogenesis that captures the public imagination. It is another example where relatively high investment by both public and private entities (possible in wealthier economies), has led to the control of disease in domesticated animals and reduced zoonotic risks to negligible levels (usually mostly associated with persistent wildlife hosts), if not eradicated- (Smith et al, 2008). Management best practices where host diversity is limited, and given the tools and resources, is not in question (Lembo et al, 2008). This requires ownership, restriction and vaccination of domestic dogs and removal of feral populations and/or oral bait vaccination of wild hosts (Kaare et al, 2009;). In large parts of the world the disease ecology - including dog ecology (Davlin & Vonville, 2012; Kitala et al, 2001), social, cultural and economic circumstances are a significant constraint although improved epidemiological understanding, indicates immunosterilisation (Carroll et al, 2010) of domestic dogs across the entire area of a contiguous population (not just in urban areas), can reduce infection incidence and therefore zoonotic risk, substantially and reduce the overall environmental burden of virus, even in wild hosts as a loss of the spill-over effect (Lembo et al, 2010; Beyer et al, 2012; Woodroffe et al, 2012). Further to this improved human vaccines and their increasing accessibility (lower cost) and post exposure vaccination has led to considerable reduction in human cases where virus persists, especially in South East Asia (Wilde et al, 2005; Chulasugandha et al, 2006). A combination of strategic human and dog vaccination in developing countries, suffering high incidence of rabies is the best management option but requires considerable public (and probably international) investment, in prophylaxis, education and awareness with implementation by combination of NGO and government entities with community participation (Abbas et al, 2011; Fooks,

2007). Attempts to control domestic dogs through culling, sterilisation campaigns appear not to be helpful and/or are equivocal in their benefits (Kaare et al, 2006; WHO, 2004). A combined vaccination sterilisation package if deemed acceptable in the community might provide additive benefits but this is unproven (WHO, 2006).

Diagnostics: Post-mortem testing of brain tissues by direct fluorescent antibody test (dFA test) is the current gold-standard (Durr et al, 2007). In living humans, several tests are required to diagnose rabies. Samples of saliva may be tested by rtPCR; serum and spinal fluid are tested for antibodies. Tests for antigen have also been developed (Kasempimolporn, et al, 2011; Wang et al, 2011; Fooks et al, 2009). There are a number of rapid tests marketed in developing countries where regulation of diagnostic tests is weak and evidence their efficacy is lacking (Lembo et al, 2006).

Drugs: There is no treatment for animals with prevention centred on vaccine prophylaxis. For humans post-exposure prophylaxis constitutes the use of immunoglobulin with vaccine (Nagarajan et al, 2008).

Vaccine: Highly effective inactivated rabies vaccines are available for humans, dogs and wildlife reservoirs (Sugiyama & Ito, 2007;). The latter are widely available and not constrained by production costs, although they do require a cold chain (Expert opinion). Recombinant poxvirus-vectored vaccines have also been successfully deployed in oral bait form to immunize wild animal reservoirs, such as European foxes (Weyer et al, 2009)- however in the developing country context wildlife vaccination will likely not be an immediate priority (Lembo et al, 2010) given the widespread canine rabies needs (although in some specific geographic location, control in wildlife may need to be considered- Zulu et al, 2009; Randall et al, 2006) Human vaccines are normally administered in the context of post-exposure prophylaxis (PEP), which requires several inoculations and is therefore costly. Issues in respect of rabies vaccination therefore pertain to how vaccines are most effectively applied in conjunction with other measures, such as dog population control by culling or sterilization. It is perceived that the most appropriate control will focus on dog vaccination campaign using current vaccine technologies and ensuring that required coverage levels are achieved (Cleaveland et al, 2006; Durr et al, 2009; Coleman et al, 1996; Kitala et al, 2002).

Highly Pathogenic Avian Influenza Viruses- H5N1 and other zoonotic threats (e.g. H9)

Management practice: Avian influenza viruses are rare zoonotic pathogens. Even H5N1 has an extremely low incidence, globally, with a total of 602 cases and 352 fatalities over 10 years in 16 countries (WHO, 2012b) with over 86% of cases occurring in only 4 countries – China, Vietnam, Egypt and Indonesia, all with a common agroecological systems, conducive to the evolution and spread of these viruses (Ahmed et al, 2012; Martin et al, 2011; Gilbert et al, 2008). The epidemiology of avian influenza and the pathogenic strains in particular has been well documented (Alexander, 2007). Trends in disease emergence are not positive (increasing), mostly for reasons of the importance of poultry in food security, demographic changes, emerging agriculture and market systems and other factors (Vandegrift et al, 2010). This includes the importance of extensive irrigated agriculture, large populations of

intensive and semi-intensive domesticated and semi-domesticated carrier waterfowl (in contact with wild waterfowl), and in close proximity to large populations of highly susceptible chickens in both industrial and backyard husbandry systems (Vankerkhove, 2009; Prins et al, 2010;). This serves to enable a free flow of genetic material from the natural reservoir of avian influenza viruses (non-pathogenic) in free-ranging wild birds of the order anseriformes and Charadriformes to domesticated waterfowl (Dugan et al, 2011) and poultry via shared husbandry and complex extensive trade systems, where evolution of the virus is accelerated to pathogenic forms, amplified in chickens due to the virulence expressed and high environmental viral loads produced (Vijaykrishna et al 2008). This process is reinforced by the highly genetically homogeneous nature of the domestic poultry population (Shinya et al, 2010). The industrial sector in particular has a very narrow genetic origin which tends to promote evolution of homogeneous populations of highly virulent virus (Hogerwerf et al, 2010; Emsley, 2006). Vaccination is also influencing the evolutionary direction taken by virus population, helping to shift the virus from clade to clade in small unpredictable leaps, similar to that seen with human influenza, without necessarily reducing virulence but requiring reconstruction of vaccine virus (Lee et al, 2004; Escorcia et al, 2008; Abdel-Moneim et al, 2011). In some poultry diseases e.g. Marek's disease there is evidence that the application of vaccination is even selecting for more virulence (Maclea and Cheng 2007).The main zoonotic risk with avian influenza virus is in the possibility of reassortment and recombination with other influenza viruses of poultry, humans and pigs in particular (Chen et al, 2006). In South East Asia the close proximity of all three makes this a very real possibility (Nidom et al, 2010; Gilbert et al, 2008). This can lead to genetically distinct strains of human influenza virus and pandemic disease threat.

In poultry epidemics and endemic situations pathogenic virus occasionally spills-back to wild bird populations causing disease and death but the evidence is that this is relatively short lived (the 2006 H5N1 wild bird epidemic being exceptional)- (Capua & Alexander, 2009). The highly heterogeneous nature of the natural bird and natural virus population in wildlife and the constantly evolving immunity therein appears to eradicate the pathogen naturally (Krauss et al, 2007). ***There is no evidence for wild bird reservoirs of human zoonotic or highly pathogenic strains of avian influenza and even in cases of exposure of infected wild birds to humans has not demonstrated its transmissibility (Wallenstein, 2009).*** Zoonotic risk is therefore mainly within the domestic animal sector and further increased by a high turnover of poultry, legal and illegal live and wet market systems, open slaughterhouses with poor ventilation and poor farm, market, abattoir and domestic hygiene, especially in poorer communities (Exposure pathways to humans for H5N1 see- Kerkhove et al, 2011). Backyard poultry in these endemic settings is considered a risk for zoonotic transmission (Walker et al, 2012; Sultana et al, 2009; Hafez et al, 2010) but the evidence for this is weak. In endemic settings, reluctance to change the agroecology, including; use of integrated open rice paddy cultivation and domesticated waterfowl husbandry, market and open slaughter systems, and along with a resistance to culling are likely to be the most important factors in the continued circulation of virulent strains of virus (Capua & Marangon, 2007; Capua & Alexander, 2009; Soares Magalhães et al, 2010). Management best practices in reducing zoonotic risk fall into a number of different categories.

a) First and most important approach, given the fact there is no practical means to reduce the potential of new strains of avian influenza virus entering the poultry sector, from wild birds, it is vital to carefully plan management practices around the

agroecological situation (Hogerwerf et al 2010) with more attention given to the social and economic dimensions (including compensation mechanisms for culling). Given the relatively different susceptibilities of anseriformes and galliformes, it is logical to seek change to the husbandry systems and maintain separation of domesticated waterfowl from chickens. This is possible in the commercial sector but problematic in backyard and rural systems (Cristalli & Capua, 2007; Muzaffar,et al, 2006). The risk of the latter might not be significant in the emergence of HPAI but evidence needs to be gathered on this aspect. Biosecurity and all-in all-out policies in the industrialised sector is a relatively straightforward way to reduce virus transmission, at least in theory but poorly controlled and managed large poultry units are an epidemic time-bomb and when there are breakdowns, these are likely to have more profound impacts on virus population evolution and environmental load than backyard infections (Peiris et al, 2007). Improvements in biosecurity along with more rigorous control of marketing of poultry, hygiene of slaughterhouses, attention to market structure particularly with respect to mixing species will improve the agroecology in favour of a reduction in transmission events, and most important prevent opportunity for virus evolution through recombination with other species influenza strains (FAO, 2009).

b) Another approach is to mimic the natural bird and virus ecology through selection of genetically diverse poultry stock and or selection of birds for natural resistance to avian influenza viruses (Pinard et al, 2008; Chen et al, 2009; Berthouly et al, 2009). There is some progress on this in the industry but much more needs to be done. The presence of wild birds is not a risk factor other than being the source of natural virus and there is no evidence to suggest any measures are necessary in wild bird control (). Conclusive evidence of the role of migratory species in the transmission of virus to poultry or people is absent.

c) Although vaccination is an appropriate emergency measure and as a preventive measure in the face of an outbreak, in epidemic regions (and is used in the industrial sector widely), its use long term and for eradication is equivocal unless the approach can be internationally applied and standardised (Webster et al 2007; Pongcharoensuk et al, 2011). There are also questions about its role in reducing focus on; biosecurity and improved hygiene (water is a costly commodity) and, in reducing the necessity to make fundamental changes in the husbandry systems and genetic management of the poultry sector and as a result this is leading to an endemic situation (Perez, 2012; Cattoli et al, 2011). Huge investment amounting to hundreds of billions of dollars in the disease (Hinrichs et al, 2006; McLeod et al, 2007) has not improved the situation. This is particularly relevant in developing countries and poor settings. One possible improvement recommended by OIE is in the development of DIVA vaccines, proposed to enable more accurate surveillance and identification of endemic infection (Capua and Marangon, 2006; expert opinon—may prove too costly in certain developing country settings).

Diagnostics: Virus Isolation is the gold standard, however the speed for which a Reverse transcriptase polymerase chain reaction can be performed means that this technique is normally adopted- costs may be a barrier to access in developing countries, especially for routine use (Peiris et al, 2007). A large number of serological diagnostic techniques have been developed for human use (WHO, 2007b). Viral antigen may be detected by immunofluorescence or enzyme immunoassay but tests may not differentiate human virus

subtypes H3N2 or H1N1 from avian influenza H5N1- it has also been documented that commercially available enzyme immune assay test kits are <1000 x sensitive than virus isolation techniques (Chen et al, 2007). Antibody detection tests may lack sensitivity and serological tests currently have limited utility for diagnosis of A(H5N1) disease in humans.

Drugs: Not applicable for animal populations- antivirals used for both treatment and prophylaxis in humans (seasonal influenza) and currently used antivirals oseltamivir and zanamivir have shown to be effective against isolated H5N1 in vitro (Govorkova et al, 2001; Leneva et al, 2000)

Vaccine: A number of vaccines are available for the H5N1 avian influenza virus, which is considered the major pandemic threat in this group. China is a major producer and it is a matter of concern that the evidence for the efficacy of these products is not readily available (expert opinion). Influenza vaccines do reduce virus shedding, but their utility is compromised by the rates of evolution that characterize these viruses. Vaccination of poultry flocks must therefore be accompanied by stringent monitoring to ensure that field strains do not emerge that escape the vaccine response and establish endemicity, and formulated as part of an integrated strategy (Lee et al, 2004; Savill et al, 2006; Peiris et al, 2007)

Lassa Fever

Management practice: Lassa fever, a viral haemorrhagic fever transmitted by rodents (*Mastomys natalensis*) is endemic in west Africa with between 300,000 to 500,000 cases of Lassa fever and 5000 deaths occur (Ogbu et al 2007). Emerging arenaviruses are also a concern as well as its potential as a biological weapon (Nakamura et al 2007). Considerable epidemiological knowledge gaps remain (expert opinion), it can be sub-clinical, and potentially transmitted from human to human sexually. Although indigeneous knowledge is present the importance of the rat as a food source (linked to season variability between dry/rain y season- Fichet-Calvet & Rogers, 2009), poverty (Bonner et al, 2007) and lack of access to diagnostic facilities and hospitals, lack of good diagnostic tests and vaccines mean few cases are presented, diagnosed or treated (Ogbu et al, 2007- underreporting issue because lassa fever misdiagnosed due to non-specific symptoms common to other diseases) . There is no vaccine although this is proposed using the yellow fever virus as a vehicle (Richmond and Baglole 2003). The current best practice is to concentrate on education and rodent control around housing in affected regions, until technologies are reached which enable more specific management options (Senior 2009, Bonner et al 2007). Helping these affected communities and those which have poor housing into better accommodation is fundamental to control.

Diagnostics: Diagnosed in humans by enzyme-linked immunosorbent serologic assays (ELISA), which detect IgM and IgG antibodies and Lassa antigen (Inegbenebor et al, 2010; Emmerich et al, 2006). Immunohistochemistry can be used to make a post-mortem diagnosis. Reverse transcription-polymerase chain reaction (RT-PCR) may also be used

(Vieth et al, 2007) but is rarely available in developing countries. The virus can be cultured in 7 to 10 days but requires a sophisticated laboratory infrastructure.

Drugs: Not appropriate on the animal side- ribavirin (broad spectrum antiviral) used with perceived high efficacy in humans (Khan et al, 2008), although major issue around availability and access (Bausch et al, 2010).

Vaccine: Prevention of contact between humans and the rat reservoir is currently the mainstay of control measures for this zoonosis. There is, however, strong demand for a vaccine to complement these efforts- there is also the drive to develop a vaccine to counter spread of the virus into developed countries following tourism and for response to perceived bioterror threats (Geisbert et al, 2005). There is good evidence that protection is engendered by immunization with the virus surface glycoprotein, which raises the prospect of a recombinant vaccine (Geisbert et al, 2005; Schlereth et al, 2000). Progress towards this end has been constrained by poor engagement from the pharmaceutical industry. A dual formulation incorporating Lassa and Yellow Fever components is a potential opportunity in this regard (expert opinion).

Ebola viruses

Management practice: Ebola viruses are members of the Filoviridae family. They are among the most virulent pathogens for humans and great apes, causing acute haemorrhagic fever and death within a matter of days and are potential bioweapons (Mohamadzadeh et al, 2007; Leroy et al, 2011). Since their discovery, filoviruses have caused only a few outbreaks, with 2317 clinical cases and 1671 confirmed deaths, which is negligible compared with the devastation caused by malnutrition and other infectious diseases prevalent in Africa (malaria, cholera, AIDS, dengue, tuberculosis). Yet considerable human and financial resources have been devoted to research on these viruses during the past two decades. As a result, our understanding of the ecology, host interactions, and control of these viruses has improved considerably (Groseth et al, 2007). Bats have been identified as a major filovirus reservoir, and many human outbreaks have been shown to have arisen through the handling of infected chimpanzee and gorilla carcasses (Daszak et al, 2006; Leroy et al, 2005). The 2007 ZEBOV outbreak was linked to fruit bats, although the precise mechanism of transmission to humans was not identified (Leroy et al 2011). The evidence that does exist suggests very low prevalence in bats and this is supported by the fact that millions of bats are consumed in Africa as food (Biek et al, 2006; Pourrut et al, 2007), and there is no evidence to suggest that this is a common route for infection.

Current best practices for Ebola lie in the human domain (expert opinion; Lamunu et al, 2004), through education in endemic areas and measures applied to reduce the cultural use of bush meat and primates in particular, with provision of alternate sources of protein and poverty reduction to enable access to alternate food (LeBreton et al, 2006; Rizkalla et al, 2007). The continued settlement and expansion of human activities in forested zones with Ebola (most likely in bat reservoirs but the full ecology is not known) increases the risk of emergence and should be prevented where possible (ICUN, n.d.). Meanwhile vaccine

development is in process and epidemic control measures such as strict isolation are sufficient to control the sporadic and relatively rare occurrence of this disease (Shears, 2007; Casillas et al, 2003). There is no scientific evidence for any benefits from the control of potential or known reservoirs.

Diagnostics: ELISA techniques have been developed for detection of the viral antigen on inactivated specimens, such as blood, serum, or tissue suspensions (Saijo et al, 2006). Nucleic acid detection (RT-PCR) is more sensitive, but not often available in developing countries (Leroy et al, 2000). Post mortem detection of viral antigen is possible by immunohistochemical staining and histopathology. Tests for pigs are being developed that measure the quantity and type of antibodies (immunoglobulin M or G, or IgM and IgG) present in blood or serum (Ksiazek et al, 1999) but it is unlikely that the necessary reagents will be made available in developing countries.

Drugs: Not applicable on the animal side because wildlife reservoirs and no specific drugs on the human side (Bausch et al, 2008). Currently best approach is supportive treatment-perceived opportunity on the human side to consider best strategies (using existing tools) for intensive supportive care (i.e. monitoring oxygen levels, gas in the blood etc.). Expert opinion suggested that it would be highly beneficial to design protocols to pass ethical reviews fast to implement/assess new care strategies to prevent delay in future outbreak scenarios (Borchert et al, 2011).

Vaccine: Vaccine research on Ebola virus and other filoviruses has been conducted largely in the context of the bioterrorism threat. A number of candidate vaccines have been described, some of which are being assessed for safety in humans (Richardson et al, 2010; Bausch et al, 2008; Oswald et al, 2007; Swenson et al, 2008) although these are 5-10 years away from commercial availability (Expert opinion). However, Ebola infections in the field are sporadic and unpredictable and the properties of a vaccine for deployment in response to an outbreak may differ from those required for protection of large populations against a terrorist threat. It is unclear whether existing candidates will engender 100% protection in human populations, and how they would perform in ring vaccination strategies, where rapid and effective protection would be necessary. Furthermore, inclusion/exclusion criteria for ring vaccination programmes are likely to be challenging, given the panic that prevails when outbreaks occur.

Rift Valley Fever

Management practice: Rift Valley fever is caused by a bunyavirus transmitted by vectors including the Aedes mosquitoes which are capable of transovarial transmission and can act as a reservoir (Rostal et al, 2010). The disease has been known for some 80 years affecting wildlife, livestock and people, most commonly in Kenya. It has a specific disease ecology which has restricted its range to much of sub-Saharan Africa and associated islands (Davies et al, 2010). Recently this extended into the Middle East probably from importation but there is a general opinion that climate change will or has affected its distribution (Balkhy et al, 2003). The disease can be both mild and severe in all of its hosts and many factors

contribute to virulence but the worst epizootics are recorded in the semi-arid rangelands bushed and wooded savannah and flood plains and associated forest (coastal and riverine) and forest edge (Davies, 2010). The disease occurs when there is occasional heavy rainfall and flooding with man-made water systems contributing to its spread and persistence (Anayamba et al, 2007; Hightower et al, 2012). Flooding of these breeding areas for mosquitoes triggers massive emergence and a rapid spread and amplification of virus (and vectors) causing epizootics (Porphyre et al, 2005; Heinrich et al, 2012). The communities occupying these areas are relatively poor, suffer other health challenges including HIV/AIDs, schistosomiasis and malaria and these co-factors might contribute to the more severe and fatal outcomes reported (Davies, 2010). Best management practices revolve around early warning, now based on satellite weather monitoring and models predicting heavy rainfall and flooding events in high risk zones (Vignolles et al, 2009; Britch et al, 2007), sometimes sentinel herds (Hassan et al, 2007; Soumare et al, 2007) have been used and where there is a high risk of disease this is followed up by mobilisation of health services to intervene, including through vaccination, vector control, restrictions on animal movement and awareness campaigns. The theory is rarely if ever practiced and in almost all instances over the last 30 or 40 years the interventions have been too late and either unhelpful or even contributory. For example, where vaccination is applied on livestock already infected with virus, multiple use of needles on animals has simply spread the disease more effectively (Metras et al, 2010; Davies, 2010). One reason for the recorded delay in taking action is the flooding itself, which creates considerable practical constraints on health services delivery in these often remote areas with poor roads and infrastructure this is further compounded by the poor coordination and integration of human and animal health services. The former are usually better resourced, arriving sooner but the main source of infection for humans relates to the animals infected so this is counterproductive. Sentinel herds (goats and sheep) if well positioned have been helpful (Chevalier et al, 2005) but this is relatively costly and has not been able to provide range wide early warning. Vector control has also been used (Diallo et al, 2008) but usually too late and during epidemics. Vector control focused on treating dambos (wet circular depressions across flat range (Pope et al, 1992; Logan et al, 1990; Anayamba et al, 2009). This approach is rarely practical on a wide scale or ecologically acceptable when poorly targeted.

Surprisingly the one reliable indicator never exploited in these high risk zones for RVF are the livestock keepers themselves who are uniquely positioned to provide necessary early warning of an epidemic (ILRI/FAO, 2008). At a local scale studies have shown herders are aware of the increasing risk and early stages of an epidemic some weeks before the health services. With mobile phones now reaching most affected zones there is a need to integrate community based animal health workers into the surveillance systems of veterinary and human health services (Breiman et al, 2010). This, along with the more general awareness provided by the weather predictions (Linthicum, 1999), which enable governments to mobilise human, material and financial resources ahead of an epidemic, should reduce the time from index cases to interventions. A further recommendation is to further study populations of hosts in the inter-epidemic periods when some circulation appears to occur (Rostal et al, 2010; Hay, 2000;) and through spatial and temporal mapping of these foci predictive maps can be constructed to further refine hot spots and likely emergence zones for the disease (Caminade et al, 2011; Bicout & Sabatier, 2004). Here vaccination can be done using available products more effectively and efficiently ahead of epidemics or in the

face of epidemics to dampen their effect. Animal movement restrictions are largely unhelpful or not adhered to under the prevailing conditions but some effort at restricting movement (Rich & Wanyoike, 2010) at least to the affected zones can reduce spread to other areas with competent vectors.

Diagnostics: The diagnostic tests currently available must be performed in a laboratory. Serological tests such as enzyme-linked immunoassay (the "ELISA" or "EIA" methods) test for the presence of specific IgM antibodies. The virus may be detected in blood during the early phase of illness or in post-mortem tissue by antigen detection tests and RT-PCR (CFSPH, 2007; expert opinion)).

Drugs: There are no approved antivirals for animals and ribavirin is no longer recommended (expert opinion).

Vaccine: Several options are available for vaccination of both humans and livestock against this sporadic epidemic disease (Boshra et al, 2011; Ikegami & Makino, 2009). These comprise live attenuated, inactivated and subunit vaccines, which include those based on virus-like particles, recombinant virus and DNA plasmids. Live RVF vaccines are hampered by adverse effects such as abortion in vaccinated livestock and, although less virulent clones have been identified, these are not yet widely available. Killed formulations address the issue of virulence but require boosting, which reduces their utility in the face of an outbreak. Despite the apparent plethora of available vaccine options, the question of “when to vaccinate?” remains a difficulty in effective deployment of these products to control the disease. Prediction of outbreaks is difficult, not least because the mechanisms for viral persistence between outbreaks are incompletely understood (Kotekass et al, 2011). In addition, the range of relevant mosquito vectors can be large, which extends the potential catchment area for ring-vaccination strategies.

Zoonotic Hepatitis E

Management practice: This zoonosis is recognised as a problem in developed countries (Dalton et al, 2008; Meng, 2010), however there is a growing concern particularly for this disease in tropical and subtropical zones (Indian sub-continent, Southeast and Central Asia, the Middle East, parts of Africa, and Mexico) and where there is poor sanitation. Surveillance has identified an emerging problem (Goens & Perdue, 2004) with respect to the genotypes 3 and 4 associated with rodent populations (studies in Norway- Kanai et al, 2012), pigs (in China potential transmission between pigs-humans- Fu et al, 2010; Zhu et al, 2011; swine faecal contamination of water sources in India- Vasickova et al, 2007)and wild artiodactyls and is food borne (Aggarwal 2011; Sika deer- Tei et al, 2003). Its prevalence in low income countries is poorly known but an association is emerging with immunosuppressed people or those with pre-existing liver disease and particularly elderly men who associate occupationally or through food with the animal source.

Best management practice is through improved hygiene, food and water safety and education about the zoonotic risks from association with certain species (Wellenberg et al,

2008) and their food products (Pavio et al, 2010). More research and surveillance on the latter is needed to better define the role of wild and domestic animals in zoonotically derived infection. The role of rodents in the disease in poor settings needs further research (Kanai et al 2012). The disease is otherwise self-limiting and where there are unavoidable risks then the potential sub-unit vaccine under development provides a means of prevention (Pavio et al 2010, Dalton et al 2008) in high risk groups.

Diagnostics: Hepatitis E is not clinically distinguishable from other types of acute viral hepatitis and diagnosis can be confirmed only by testing for the presence of antibody to Hepatitis E or HEV RNA. (Vasickova et al, 2007) In pigs, there is no demand for diagnostics because it is avirulent, and endemic where present- however if the zoonotic potential is confirmed this may change (Goens & Perdue, 2004). RT-PCR and real-time RT-PCR have emerged as the main type of test for detection of RNA viruses such as heptatitis E (Inoue et al, 2006) and could play a key role in helping to elucidate the zoonotic transmission potential in developing country settings. Antigen detection kits are also available for humans.

Drugs: No available therapy is capable of altering the course of acute infection. It is difficult to foresee a near-future drug approach; currently only option for treatment in human utilises Ribavirin (in severe acute cases- Gerolami et al, 2011), however there is a lack of evidence for efficacy.

Vaccine: An efficacious vaccine for humans has been previously taken to commercial production (expert opinion)- it was however withdrawn on the basis of poor market uptake. This technology has been further developed in China (Zhu et al, 2010; Dalton et al, 2008) and is now available with the hope that this technology will now be more accessible across the developing world if zoonotic hep E is confirmed as a major problem. It is possible that the zoonotic infection will emerge in developing countries with intensification of pig production.

Parasitic diseases (*Protozoan & Helminthic*)

Fascioliasis

Management practice: This ancient zoonotic infection (*F.hepatica*) is on the rise, primarily due to increasing demographics of humans and domestic animals and intensification of the infection interface, the latter through invasion of snail host habitat, climate change is also considered a driver (Fairweather, 2011). The parasite has both a wide host and geographic range (Mas-Coma et al, 2005). There has been a dramatic rise in fascioliasis cases in recent times, prior to 1992 there were estimated to be less than 3000 cases but that figure has increased to between 2.4 and 17 million (Keiser & Utzinger, 2005).

The disease is well controlled, where there is managed separation between people and livestock and, livestock and snails, including prevention of food contamination when grown in these habitats (expert opinion; Robinson & Dalton, 2009). This provides a guide to best

practices but this depends on investment and considerate development of settling communities, education (although required- Ortiz et al, 2000; Rojas et al, 2010) alone is unlikely to prevent this occurring where lack of resources exist. Separation of livestock and people is fine but if the faeces of the animal are used for agriculture (Slifko et al, 2000) then a transmission route for infection will persist. It remains a problem where poverty persists and best practices will include improved surveillance, diagnostics and treatment. Care is needed in application of the single therapeutic triclabendazole since resistance exists (at least in Europe) if overall the incidence is ill defined (Brennan et al, 2007). There is also a need to improve epidemiological and ecological knowledge (Hurtrez-Boussè et al, 2007) about the disease in differing social, economic and ecological contexts. *F. hepatica* affects the immune system of the host to an extent that it may impact on other conditions. For example, there is evidence that skin tests for bovine TB are compromised in coinfected animals (Claridge et al, 2012). There is also a trend of increasing hybridisation between *F. gigantica* and *F. hepatica* species (Le et al, 2008; Mas-Come & Bargues, 1997) and the impacts of this are not well understood in zoonotic terms. More research on this aspect is needed.

Diagnostics: For animals, intravital diagnosis is based predominantly on faeces examinations and immunological methods (e.g. ELISA test to detect antibodies in milk- Reichel et al, 2005; Mezo et al, 2007). For humans ELISA or Western blot to detect species-specific antibodies from sera are the most important diagnostic methods. Examination of stool for fluke eggs in stool can be used but lacks sensitivity (Mas-Coma et al, 2005), and it may difficult to differentiate eggs of F. hepatica, F. gigantica and Fasciolopsis buski (expert opinion)- it may be more appropriate to use Restriction Fragment Length Polymorphism (RFLP) assay to distinguish in areas of endemic sympatry (Marcilla et al, 2002). Methods based on antigen detection (circulating in serum or in faeces) are less frequent. Ultrasonography and RTG[disambiguation needed] of the abdominal cavity, biopsy of liver, and gallbladder punctuate can also be used (Esteban et al, 1998). It will be utilise existing technologies on a wider scale to help determine fasciola populations and risk of infection for farmers at both herd and regional level (Fairweather, 2011)

Drugs: Triclabendazole for human use (applicable for animals but not widely used)- however this option is expensive and drug resistance emergence has been reported in developed countries on the human side. There is a further need for improved diagnostics (Brennan et al., 2007) and standardised protocols (expert opinion; Fairweather, 2011) to understand true extent of drug resistance. Currently the coproantigen test has been used to assess drug resistance across a number of studies (Flanagan et al, 2011). Multiple drug combination therapies may also be a way of reducing the emergence of resistance (Devine et al, 2011)

Vaccine: A number of candidate antigens have been evaluated for protection of livestock against challenge with *Fasciola hepatica*, which is emerging as a zoonotic pathogen (Vaccines in testing through the PARAVAC Consortium; see http://ec.europa.eu/research/bioeconomy /agriculture/projects/paravacen.htm. Such levels (~ 70%) of protection might be compelling in the developed world, where the disease can also be moderated by management practices to reduce contact between livestock and the snail intermediate host, and zoonotic infections are rare because of the separation of livestock and their owners (McManus & Dalton, 2006). It is unclear however whether they

would significantly impact on the incidence of zoonotic infections in the absence of other control measures.

Cryptosporidiosis

Management practices: Cryptosporidiosis is a worldwide cause of morbidity and mortality in animals and humans, resulting primarily in diarrhoea, and resulting in the most severe infections in immune-compromised individuals (Fayer, 2004; Ayuo, 2009). With the control of other common causes of diarrhoea the importance of this infection has become more apparent (contributing significantly to the under-5 mortality/morbidity- expert opinion; Snelling et al, 2007). Its incidence is closely associated with hygiene and sanitation, the infection is mostly water borne (Ashbolt, 2004). Along with the other common causes of water or food borne enteric disease, similar practices are advisable and equally problematic in implementing in a poor community, where basic conditions are conducive to persistence (poor sanitation and water supply) and especially in cool temperate conditions (Studies conducted to examine impact of household hygiene and animal control- Morse et al, 2007). Artiodactyls, rodents, lagomorphs and primates are species affected but little is known about the relative importance of different hosts in the epidemiology of infection (Das et al, 2011; Leav et al, 2003). This aspect can be highly contextual and in most LMIC it is unlikely that data on the specific disease ecology are available. The epidemiology might be very complex and there are no simple solutions. Diarrhoea is common in poor communities (Bogaerts et al, 1984; Fischer et al, 2010) and a common cause of particularly childhood disease but response to education is likely to be poor, there is not much they can do about this given their living conditions and there are possibly many more critical issues to be concerned about. Best practices relate to improved policy and efforts to the public good, external investment to raise communities out of risk of infection, through better urban and rural land use planning and development (Lake et al, 2007; Kandalu, 2009) , centralised control over water and its fair distribution, attention to water quality and where possible introduce reticulation to individual households, as well as, raising levels of nutrition (Lima & Guerrant, 1992) and general health to improve resistance to infection and disease.

Diagnostics: Identification of oocysts in fecal matter by staining and microscopy or by using antibodies. Polymerase chain reaction (PCR) can be used for diagnosis and to identify the species of Cryptosporidium (Feyer et al, 2000). Molecular diagnostic techniques will help to determine transmission dynamics, importance of different animal reservoirs and links to zoonoses emergence and cryptosporidium population structures (expert opinion; Widmer et al, 2002; Xiao & Feng, 2008)

Drugs: For animals, *halofuginone lactate* can be used for treating livestock (Giadinis et al, 2008; Jarvie et al, 2005)- currently however this is only applied within farming setting in developed countries. The key *issue being that toxic dose is only twice the recommended dose*, with *diarrhoea* proving a *contraindication so needs to be given prophylactically*. The expert opinion suggests that if a farm has a history of infection and there are initial cases it could be given to control illness and shedding- more research is needed to confirm the

benefit of such an approach (Trotz-Williams et al, 2011). Again however the applicability and access for such a drug in poor farming communities is likely to be low and not a high priority for farmers (expert opinion). The thiolazide drug nitazoxanide has efficacy against the parasite in humans (Fox & Saravolatz, 2005)- this combined with water sanitation measures are likely to form the basis of any control measures.

Vaccine: The greater proportion of cryptosporidiosis infections in man are anthroponotic, involving *C. hominis.* Zoonotic infections arise largely through contamination of water with parasites of cattle or sheep origin, although those from dogs, cats, poultry and even gekkos have been implicated. Because of the nature of cryptosporidiosis infection, sporadic disease outbreaks are often seen, vaccination of humans against zoonotic cryptosporidiosis is not a rational strategy towards control (expert opinion). Furthermore, as discussed in the introductory section above, cryptosporidiosis is not perceived to be a problem in livestock species, especially in developing country situations. Only young animals are susceptible and infection is often subclinical in spite of high levels of shedding (Innes et al, 2011)- approaches to reduce environmental contamination with Cryptosporidium oocysts through immunise dams a few weeks prior to parturition (Innes et al, 2011; Jenkins, 2004) may prove a promising vaccination approach in the future. Farmer compliance in livestock vaccination efforts would therefore be expected to be low. No vaccines against human or animal cryptosporidium species are in any case available (Fayer et al, 2004).

Human African Trypanosomiasis (HAT)

Management Practice: Tsetse flies (vector) and trypanosomes are present in more or less the same places and at the same intensity in Africa when compared to over a century ago. This is despite considerable investment in disease control, environmental change and demographic shift in hosts and in their diversity and distribution (Brun et al, 2010). Despite this, the case load of HAT remains significant and high amongst zoonoses in relative impact (on average 20000-30000 cases a year and over a million DALYs over much of the last decades of the 20th Century) caused by *Trypanosoma.brucei rhodesiense* and *T.b. gambiense* (Fevre et al, 2008; Simarro et al, 2008). Although these figures have not increased proportionate to the demographic increases in humans and livestock it is probably underreported in many regions of Africa (Mumba et al, 2011; Odiit et al, 2005). The situation for HAT is no worse primarily due to improved treatments of humans (e.g. WHO case detection and free treatment programme with cases dropping to <10000 in 2009) and better access to drugs for animal disease and its vector control and through better awareness in the communities of the causation over the last decades (WHO, 2006). Animal veterinary medicines are used prophylactically by communities which have learned to offset their high cost with strategic use for limited periods of the year, benefiting economically from improved nutrition and production, whilst accessing forage in tsetse areas (Roderick et al, 2000). Similarly trypanocides used strategically show similar benefits (Liebenehm et al, 2011) - a process related to improving understanding amongst farmers for tstse control (Pokou et al, 2010). Due to their widespread and common use, counterfeit drugs are becoming an increasing problem (Shaw, 2004; Schofield & Kabayo, 2008). Despite improvements in management HAT remains a persistent problem in Africa, especially in the

more underdeveloped parts and those vulnerable to war and poverty (Simarro et al, 2011; Berrang Ford, 2007). More generally trypanosomiasis is a cause of loss of (mostly) the economic potential in livestock and where communities take risky strategies for reasons of poverty, actual disease losses can be high, rendering them vulnerable to food insecurity (Nok, 2005; Ovbagbedia & Abdullahi, 2010; Lawani, 2008; Thuranira, 2005). HAT is physically debilitating to affected communities causing considerable DALYs. For this reason there is a focus by the African Union on total eradication and not just HAT control.
On the other hand, there are significant increases in the value of the wildlife economy in many countries and with valuing of ecosystems services, the economic justification for tsetse eradication for disease control, at any cost, is no longer viable (Chardonnet et al,, 1988; 2002). To a large extent tsetse have protected wildlife and environment in Africa (restricting livestock and human access to natural habitats and reducing concomitant environmental degradation) and influenced the development of agriculture and from this perspective can be seen as a positive ecosystem service (Wilson et al 1997). A goal of eradication of HAT if not all animal African trypanosomiasis is nevertheless a less environmentally contentious case and perhaps feasible objective in 90% of the range with more subtle targeted control measures applied (Simarro et al 2008).

With appropriate epidemiological knowledge people are better able to avoid disease through reducing exposure, or using prophylaxis on their livestock or seeking early treatment for sleeping sickness (Fevre et al, 2006). HAT is persistent in dense mostly riverine forest, forest edges and some bushed and wooded savannahs (Simarro et al, 2010) affecting livestock communities both settled and nomadic (Salim et al, 2001) and is common in wildlife protected areas throughout Africa (Anderson et al, 2011). There is better management of the disease in some countries (e.g. Ivory Coast and Angola) and increasing absence from highly degraded habitats, where tsetse are no longer able to survive (Burkina Faso- Bouyer et al, 2011) but the associated costs of degradation, agricultural losses, desertification and famine far outweigh the opportunity costs of trypanosome infection. Some countries have managed to control the disease on terrestrial or marine islands (Kenya, Lambwe Valley; Tanzania, Zanzibar) through strict vector control (targets and sterile fly techniques) and in some open grassland habitats highly accessible to targeted vector eradication through aerial spraying (e.g. Botswana, Angola)- (Schofield & Maudlin, 2001).

There have been various and massive investments in tsetse and trypanosome control in Africa, and there is currently an African initiative (PATTEC) globally supported with ambitious goals. History suggests that this global, international agency coordinated high cost approach is not likely to succeed (everywhere) and the results might in the end not justify the financial cost, and yet it is widely subscribed to by African Governments (Alilo et al, 2004; Simarro et al, 2008). This will certainly be the case if it does not achieve widespread eradication and control efforts are not sustained, re-invasion of flies and re-infection of hosts will take place rapidly. Community based approaches have shown significant benefits and more resilience than large scale initiatives and provide examples of some of the best practices available (Catley et al, 2002; Seed, 2001). Where these are scaled up to cover epidemiological units the better the results in long term control. Efforts to this end have shown significant benefits in countries like Uganda, where simple application of trypanocides on preferred domestic animal hosts, at particular body points, dramatically reduced HAT infection rates (Bourn et al, 2005, Welburn & Obitt, 2002). Recognition of

dilution benefits of mixed species host communities has also proved beneficial, a fact paradoxical to the early ideas of tsetse control which involved eradication of wildlife in whole geographic zones (albeit unsuccessfully) (Wacher et al, 1993). Attention to simple, cost effective, robust tsetse control methods show the most promise and in this respect the "walkaway" target vector control method is high on the list. Here small targets, heavily impregnated with long life tsetse killing effectiveness, made of tough materials resistant to sunlight and rain are showing good results, if applied at sufficient densities to effect eradication of the fly (Esterhuizen et al, 2011; Omolo et al, 2009; Peter et al, 2005). For HAT this is an ideal approach given its more focal nature than more generalised animal trypanosomiasis (Kuzoe & Schofield, 2004). More research to inform decision making and project management, with attention to the best scale and focus of investment (global approaches versus focal, community versus government) is required. HAT provides this opportunity for proof of concept, there is no question as to the justification for eradication, which still remains equivocal for livestock trypanosomes when viewed from outside of the livestock sector. There are still many unanswered questions on burden, true economic impact, and epidemiology even if there are now a number of tools that can be applied with positive benefit (Corbel & Henry, 2011). Beyond the more developed and wealthy African nations, and depending on the relative state of the economy, measures should be applied judiciously and at the appropriate time, taking into account alternate land use and economic opportunities, that are less vulnerable to the presence of tsetse and trypanosomes and provide sustained economic services of a more general nature (Wint et al, 2010). A more holistic and one health approach to tsetse and trypanosome management will ensure benefits are reached without undue costs and unintended consequences from control measures taken.

Diagnostics: It will be important to use available diagnostics to determine the extent of the animal reservoir in Human African Trypanosomiasis endemic regions (achieved by identify the main zoonotic circulating parasite, *Trypanosoma brucei rhodesiense* in animals, using PCR - Simmaro et al, 2008). This will help to design control programmes if it appropriate to attempt control in the animal reservoir (i.e. Cattle in villages- Enyaru et al, 2006). Early diagnosis in humans before neurological involvement is important to maximise treatment outcomes. The definitive test is identification of trypanosomes in a sample by microscopic examination. Samples to be tested may include chancre fluid, lymph node aspirates, blood, bone marrow, and, during the neurological stage, cerebrospinal fluid. Detection of trypanosome-specific antibodies can be used to assist diagnosis, but the sensitivity and specificity of these methods vary and caution should be used in their interpretation. Serologic testing is available for *Trypanosoma brucei gambiense* but normally is used for screening purposes. Serological tests are available for detection of the parasite: the micro-CATT, wb-CATT, and wb-LATEX. The first uses dried blood while the other two use whole blood samples. (Chappuis et al, 2005)

Drugs: In livestock, a range of trypanocides are administered by farmers (often as prophylaxis) across the African tstse fly belt (Barrett, 2001; Geerts & Holmes, 1998). Existing trypanocides used in humans are toxic have modest efficiency (Kennedy, 2005). E.g. d*iminazene aceturate* and *quinapyramine methylsulfate* used where disease incidence is low prophylactic drugs where the risk is so high that the health of the herds cannot be maintained using curative approach. Concern about resistance parasite for human

treatments are increasing (Barrett et al, 2011)- Opportunity to limit resistance; however, different drugs may enter cells through common mechanism (Brun et al, 2011).

Vaccine: Despite substantial effort and considerable investment over many years, a vaccine for human trypanosomiasis remains aspirational and is not currently an option for the control of infections of zoonotic origin (La Greca & Magez, 2011; DISCONTOOLS, 2011).

Zoonotic Schistosomiasis

Management practice: Three species of this ubiquitous globally prevalent trematode platyhelminth are significant in public health terms Schistosoma mansoni (Africa, Middle East and South America), S. haematobium (Africa, Middle East) and S. Japonicum (Asia) (Chitsulo et al, 2004; Modena et al, 2008) and there are a number of natural definitive hosts including; domestic animals; cattle, sheep, horses and wild animals; apes (only *S.mansoni*), non-human primates e.g. baboons, artiodactyls e.g. buffalo, rodents and other taxa. The infection cycle requires a common snail and slow moving water, both abundant in the infected zones. Transmission takes place when the host enters the water and the *cercariae* burrow into the skin. The water is contaminated by eggs from human and animal host excretions into the environment (Mitreva, 2012). The zoonotic form is believed to be a particularly significant problem in South East Asia e.g. in China and the Philippines (Robinson and Dalton 2009) but overall Africa is considered most prevalent for disease. In Africa the majority of cases are thought to be a human to human cycle through the intermediate host but this needs re-examination as well as the role of hybrids in zoonotic infection cycles (Standley et al, 2009; Standley et al, 2012). Human DALYs from this disease are estimated at >1 million amongst the near billion people potentially exposed (Hotez & Kamath, 2009). Far too little is known about the disease ecology and epidemiology with respect to different species hosts and how this affects risk of infection in humans and disease persistence. Focus has been on treatment of humans and risk reduction but despite the excellent benefits from praziquantel treatment re-infection is common especially in the younger age groups, prone to exposure (Standley et al 2011; Zhou et al 2010). A one health approach in China has already shown considerable promise and one of the few scientifically defensible studies in One Health approaches shows this (Gray et al 2009; McManus et al, 2010), where both cattle and people were treated simultaneously with positive synergistic affects not seen with single species interventions. If important reservoir species can be identified then in addition to treatments, vaccine development targeting these species might significantly reduce human disease risk, especially with evidence if limited of praziquantel resistant strains in humans appearing (Gray et al, 2010). Efforts to this end are currently ongoing. Other interventions that are not novel but are beneficial especially in a poor setting is improved housing, sanitation and reticulation as with many other zoonoses of the poor (Wang et al, 2009; Steinman et al, 2006). Other measures are not highly efficacious or culturally resisted including culling of bovines and use of toxic, expensive molluscicides (Lin, 2005). More progress in specific reservoir control might be possible in some settings once their role is proven (Wu et al, 2010; Gray et al, 2008). Dogs for example can shed large numbers of eggs into the environment and control of feral populations might reduce both rabies risk and their contribution to schistosomiasis in the environment (Rudge

et al, 2008). Equally rodent control might be efficacious in some situations (Lu et al, 2011). Finally the risk of this disease as an anthroponoses especially for endangered primates and apes is of conservation concern.

Diagnostics: Microscopic examination of stool for eggs is the most common method for diagnosis. Stool examination is be performed when infection with S. mansoni or S. japonicum is suspected, and urine examination when S. haematobium is suspected. Antibody detection can be useful for diagnosis in non-endemic settings but otherwise may be used for clinical management and epidemiologic surveys. (Zhou et al, 2011; McManus et al, 2010; expert opinion)

Drugs: Only praziquantel available and not optimised for use in animals at appropriate doses (Doenhoff et al, 2008; Wang et al, 2009). Drug cost is a limitation. Injectable formulation may help deal with dosing issues. May be advisable to use where animals are pastured in snail (*O. hupenensis*) habitats (Lin et al, 2005). In the longer term, efforts to develop new drugs should be considered.

Vaccine: The introduction of praziquantel in the 1970s an effective control option for human schistomiasis through mass drug administration. Demands for a human vaccine are therefore limited, although sub-unit vaccine candidates have emerged for the *S. mansoni* (in Phase I clinical trials) and *S. haematobium* (in phase II clinical trials) and *S. japonicum*. The major zoonotic schistosome worldwide is *S. japonicum*, which occurs in Asia, S.E. Asia, Indonesia and the Philippines. Water buffalo are the predominant livestock hosts for the parasite and, because chemotherapy is not cost effective in these species, and fails to prevent transmission. It has been proposed that that a veterinary vaccine might complement chemotherapy by reducing transmission (Bregquist et al, 2008) and a number of promising candidates exist (McManus & Loukis, 2008).

Echinococcosis

Management Practices: Four species of echinococcus, a taeniid cestode parasite of canids (definitive host) and ungulates (intermediate), are of public health concern: *Echinococcus granulosus* (which causes cystic echinococcosis), *E.multilocularis* (which causes alveolar echinococcosis), and *E.vogeli* and *E. oligarthrus* (which cause polycystic echinococcosis) (Moro & Schantz, 2009). Cystic hydatidosis has been controlled historically in many countries through rigorous education and legislation to reduce exposure of dogs and subsequent infection of intermediate hosts and humans (Craig & Larrieu, 2006). More recent work has shown where there is persistence that sheep vaccination and dog antihelmintic treatment can have highly cost efficient impacts at reducing disease incidence (Budke et al, 2005; Torgerson, 2005; Torgerson & Health, 2003). In poor settings the problems are directly proportional to the hygiene and slaughter practices, presence of feral dogs, and livestock (Larrieu et al, 2000; Moro et al, 2008). Weakened health under structural adjustment programmes and failed attempts to privatise veterinary services are a reason that, in many developing countries, the disease is re-emerging (Eckert et al, 2000). Alveolar echinococcosis incidence is related to wildlife reservoirs and hosts, the fox and rodents, with

dogs providing an overlap at the interface with humans (Salb et al, 2008; Danson et al, 2008). Best practices include similar efforts as with hydatidosis including education, improved hygiene, sanitation and treatment of domestic dogs and cats that have access to wild animals and their environment (Konno et al, 2003). Polycystic echinococcosis is a disease of the Americas (D'Alessandro et al, 1997)and canids (bush and or feral dogs) are the critical host element for control, requiring similar interventions as with Alveolar disease. The path to management best practices is clear but needs substantial investment in countries to target the affected communities.

Diagnostics: Diagnosis of the infection with *Echinococcus* spp. in definitive hosts is difficult, because the eggs of *Echinococcus* and *Taenia* species are morphologically indistinguishable and egg secretion is irregular. In dogs purging by administration of Arecoline hydrobromide may be used where the worms are excreted (Varcasia et al, 2004). Alternatively antigen in faeces may be detected by ELISA. Serum antibody detection is a highly sensitive test but correlation with worm burden is poor (Torgerson & Deplazes, 2009). For human infections imaging (ultrasonography) is a useful diagnostic tool. Serological tests are also employed (e.g indirect hemogglutination, enzyme linked immunosorbent assay, immunoblots or latex agglutination)- (Barnes et al, 2012).

Drugs: Gold standard for treatment in dogs is through praziquantel administration every 4 weeks- however this is very difficult to achieve in the field (Barnes et al, 2012). A perceived opportunity may be through the development of an implant which will release PZQ over a period of 12 months, and approach especially effective for wild dog populations (Cheng et al, 2010) however no such platform currently exists or is in development.

Vaccine: Vaccine research in respect of this zoonosis has targeted both the definitive canine host, which carries the adult tapeworm, and the sheep intermediate with a view to breaking the transmission cycle (Health et al, 2003). A dog vaccine is in development and, although a vaccine against hydatid cysts for sheep has shown some promise, it is not yet generally available (Zhang et al, 2006; Lightowler & Health, 2004). Further, it requires two initial immunisations followed by a boost, and vaccinates must be on a high plane of nutrition for favorable results. It has no effect on extant cysts. In spite of these developments, the utility of vaccines against this parasite is likely to be constrained by dog owner compliance and deficiencies of available vaccines in the face of field conditions.

Cysticercosis

Management practices: This is another cestode infection of animals of zoonotic importance primarily food borne, with from 10-50% of pigs in endemic settings infected via the faecal-oral route. The high incidence in poor settings is ascribed to inadequate hygiene, husbandry and slaughter practices, which support the life cycle of the parasite and ingestion of the cysts by humans through inadequate cooking of pig meat (Montresor & Palmer, 2006; Praet et al, 2009). This is another example where it is a cost of poverty, where the survival benefits of holding pigs in terms of food security outweigh the health risks in the mind of the poor farmer. The increase in keeping pigs even in periurban systems is leading to an

overall increase in the problem in many countries (Secka et al, 2010; Pondja et al, 2010) with the desakota affect prominent. Solutions are technically available but the environment for application of these requiring strict policy and health services intervention are not conducive to control. This is another case where a combination of treatment and vaccination could be highly effective (Flisser et al, 2006; Engels et al, 2003) but to apply this in the public setting will be costly to any government and there is unlikely to be much uptake amongst poor communities for reasons of cost. Here a One health approach will be particularly beneficial and could reduce costs somewhat. For establishing management best practice there is need to design and test integrative packages with public private partnerships and community engagement (Willingham et al, 2010).

Diagnostics:
Post mortem detection is by examination of tissues for cysts. Lingual Palpation can be used to identify infection in live animals (Githigia et al, 2007). Serological detection can be used for surveillance purposes. Stool studies are not effective for diagnosis in humans and multiple samples collected over a period of time should be examined. Immunodetection of antigen is possible but has remained primarily a research tool (Dorny et al, 2003). Diagnosis of neurocysticercosis in humans is by MRI or CT brain scans. (OIE, 2008)

Drugs: No drug licensed for porcine, where a large problem exists however oxfendazole used in humans shown to be effective for use in pigs. Likely best to combine with other interventions- for example use oxfendazole to clear active infection from pigs (Gonzalez et al, 2001)before administration of vaccine for longer term immunity (vaccine wont remove active infection). Requires licensing for pigs (García et al., 2007)- a process that GALVmed is currently undertaking.

Vaccine: The epidemiology of cysticercosis associated with the *Taenia solium* tapeworm is well understood, and control strategies focus on reducing transmission between humans and pigs and improving sanitary practices in households associated with pig production (Lightoweler, 2010). A vaccine (TSOL18) based on recombinant *T. solium* antigens has recently become available and has completed phase I, II and III trials in pigs. Immunisation does not eliminate existing cysticerci, although these are susceptible to treatment with oxfendazole (Craig et al, 2007). A combined strategy of oxfendazole treatment followed by vaccination therefore seems appealing (Assana thesis) and has shown some success in limited field trials in Camaroon. Further evaluation of this strategy is clearly warranted.

Leishmaniasis- *Visceral (VL) and Cutaneous (CL)*

Management practice: The life cycle involves the amastigote form in the vertebrate host and the promastigote form in the gut of the sandfly vector (Sharma & Singh, 2008). More than 90% of human cases of VL occur in South Asia (Joshi et al, 2008), Sudan and Brazil with >500000 reported annually. Several species of vertebrate mammals may be infected naturally with Leishmania. Canids are the main reservoirs for VL in the Mediterranean, Asia,

North Africa and South America. Zoonotic (ZVL) and anthroponotic (AVL) cycles occur (Palatnik-de-Sousa 2001)
With increased transportation links spreading of VL and CL is occurring outside its normal range and with climate change this trend is likely to increase with changing ecology and natural spread and establishment of vectors outside of historic range (Kaye & Scott, 2011). Current best practice includes; integrated vector management approach (e.g. for anthroponotic cycle swift diagnosis and treatment, the use of insecticide treated bednets- Ostyn et al, 2008) and focus on modifying environmental risk factors in high population densities exposed (Palatnik-de-Sousa & Day, 2011). Avoid settlement of naive people in zoonotic foci. Increase capacity of entomologists, mammalogists and environmentalists in affected regions- use of vector insecticide treatment on dogs and in the environment (Gramiccia & Gradoni, 2005; Dantas-Torres, 2007), Control of ZVL is directed at removal of the candid host after identifying infected dogs (Palatnik-de-Sousa and Day 2011; Quinnell & Courtenay, 2009) In CL, similarly anthroponotic and zoonotic cycle with sandly, rodents (Quaresma et al, 2011)and humans require similar targeted approaches but CL is highly neglected especially in Africa (Reithinger et al, 2007; Lemma et al, 2009).

Diagnostics: Leishmaniasis may be diagnosed by microscopic visualization of the amastigotes (Leishman-Donovan bodies) in marrow, spleen, lymph nodes or skin lesions (Sundar & Rai, 2002). Enzyme-linked immunosorbent assay (ELISA), antigen coated dipsticks, and the direct agglutination test (DAT) are available but have variable sensitivity and specificity (Boelaert et al, 2007). DAT has been found to be a sensitive inexpensive test but requires careful manipulation and eight hours of incubation which limits its application. Nucleic acid amplification methods have been developed but are not readily available in developing countries.

Drugs: A fundamental issue is the difficulty to capture and treat stray dogs- Drugs currently exist (pentavalent antimonials, miltefosine), which are used in humans, but there is reduced efficiency in dogs (Evans & Kedzierski, 2012) leading to the need for standardisation of treatment protocols for dog treatment. There are also perceived opportunities where the stray dog problem can be controlled (Reithinger & Davies, 2002). Drug combinations should be considered.

Vaccine: WHO-recommended mitigation strategies include treatment of infected humans, culling of seropositive dogs and use of insecticides to reduce household sand fly burdens. Two vaccines are available in Brazil for immunization of dogs and available data suggest that one of these delivers an additive effect, in conjunction with dog culling, on the incidence of disease in children (Costa et al, 2011; Palatnik-de-Sousa et al, 2009). However, culling is an unpopular intervention and it is unclear how this conflict with existing policy affects vaccine uptake. A promising human vaccine is in phase II/III clinical trials, which raises the prospect of a vaccine strategy targeting both humans and the reservoir host (Evans & Kedzierski, 2012; Naigill & Kaur, 2011). However, the parasite has complex sylvatic cycles in wildlife in South America, which raises concerns over increasing habitat encroachment. In addition, it is not clear if available dog vaccines block transmission, and there is disturbing evidence that vertical transmission of the parasite occurs in dogs.

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