Research priorities for control of zoonoses in South Africa

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Abstract

Background: Zoonoses pose major threats to the health of humans, domestic animals and wildlife, as seen in the COVID-19 pandemic. Zoonoses are the commonest source of emerging human infections and inter-species transmission is facilitated by anthropogenic factors such as encroachment and destruction of wilderness areas, wildlife trafficking and climate change. South Africa was selected for a 'One Health' study to identify research priorities for control of zoonoses due to its complex disease burden and an overstretched health system.

Methods: A multidisciplinary group of 18 experts identified priority zoonotic diseases, knowledge gaps and proposed research priorities for the next 5 y. Each priority was scored using predefined criteria by another group of five experts and then weighted by a reference group (n=28) and the 18 experts.

Results: Seventeen diseases were mentioned with the top five being rabies (14/18), TB (13/18), brucellosis (11/18), Rift Valley fever (9/11) and cysticercosis (6/18). In total, 97 specific research priorities were listed, with the majority on basic epidemiological research (n=57), such as measuring the burden of various zoonoses (n=24), followed by 20 on development of new interventions. The highest research priority score was for improving existing interventions (0.77/1.0), followed by health policy and systems research (0.72/1.0).

Conclusion: Future zoonotic research should improve understanding of zoonotic burden and risk factors and new interventions in public health. People with limited rural services,

immunocompromised, in informal settlements and high-risk occupations, should be the highest research priority.

Keywords: disease burden, one health, research priorities, South Africa, zoonoses

Introduction

Zoonoses account for about 60% of all human pathogens and nearly all emerging infectious diseases affecting humans.[1,2] Emerging infections can have major global health, social and economic implications, as demonstrated unequivocally by the current COVID-19 pandemic. The factors that drive increased risk of emerging and re-emerging diseases in humans, domestic animals and wildlife include the rising human population and associated anthropogenic impact on the natural ecosystems, including climate change, land-use change, pollution, wildlife trafficking and overconsumption.[3–5] Disease surveillance at the interfaces between humans, animals and the ecosystem provides the critical information needed to devise and implement strategies of prevention and control.[6] Despite the importance of zoonoses, research on their surveillance and control has been neglected.[7,8] A systematic research prioritisation exercise was undertaken in India by the Public Health Foundation of India/Roadmap to Combat Zoonoses in India to identify knowledge gaps and generate research priorities to control zoonotic disease.[9] Following the Indian exercise, an initiative was created by the Strategic Network on Neglected Diseases and Zoonoses, Institute of Tropical Medicine, Belgium, to repeat this research in other low- and middle-income countries, beginning with South Africa. Two members of the Indian project helped design this South African study.

South Africa has the second largest economy in Africa, with a population of 58 million,[10] yet has one of the highest global inequality indices worldwide. It is also in a region with high human migration and a large HIV epidemic, with about 8 million infected people.[10] Like any other disease that suppresses the immune system, HIV has a direct effect on an individual's susceptibility to infections, including zoonoses.[11]

South Africa is one of the most biologically diverse countries in the world. The country has a sustainable-use wildlife economy and conservation model,[12] which leads to an intimate human–livestock–wildlife interface and opportunities for zoonoses transmission.[3,13,14] Zoonotic diseases may affect many species,[15,16] be transmitted in multiple directions between humans, livestock and wildlife, and cause morbidity and mortality in each group.[2,17] Some diseases, such as brucellosis, have a higher prevalence of infection in livestock in areas where there is an interface with wildlife,[18] although this disease can be controlled in livestock in this setting.[19] To measure the burden of zoonotic diseases, such as brucellosis and TB in sub-Saharan Africa, efficient diagnostic capacity and capability must be present, as well as strong collaboration between veterinary and medical laboratories.[20]

Rural communities and those with a close association with animals are generally at the highest risk of zoonotic infections.[21] A human zoonotic pathogen study in a rural community in Mpumalanga, South Africa, found that almost all those individuals who worked with animals showed evidence of a previous zoonotic infection.[17] Another study of veterinary staff at the South African veterinary faculty found >60% had evidence of a previous zoonotic infection.[22] Despite these risks, medical professionals often have low levels of knowledge about zoonoses, with frequent misdiagnoses or underdiagnoses.[23]

Wildlife is seen as a source of emerging diseases for humans.[24] Yet, wildlife are also victims of zoonotic disease transmission from humans or domestic animals such as sarcoptic mange, respiratory viruses[25] and giardiasis in mountain gorillas, schistosomiasis in chimpanzees from humans[26–28] and *Mycobacterium bovis* in lions and buffalo[29] from cattle.[30] Protection of wildlife health will, in turn, reduce zoonotic risks to human and domestic animals.[4,24]

'One Health' initiatives have been launched in South Africa aiming to assist the National Department of Health by coordinating zoonotic diseases surveillance and identifying gaps and priorities across sectors.[31] Yet, the National Department of Agriculture, Forestry and Fisheries pointed to the sketchy collaboration between animal and human health, which is largely driven by individuals, as opposed to a coordinated national initiative in 2015.[32] By contrast, the more recent WHO Joint External Evaluation mission report in 2017 reported strong national-level collaboration and coordination between human and animal health organisations targeting zoonoses.[33] This is also reflected down to provincial and district level, although often in an unstructured manner and at a more practical level, such as the targeting of zoonotic-specific incidents.[33] Importantly, the report noted staffing gaps in remote areas and some districts, and that further training on zoonoses detection, joint preparedness and response to emergency zoonotic events at local level is needed.[33]

Understanding the strengths and weaknesses in the control of zoonoses could help inform the direction and implementation of national zoonotic control. The goal of this study is to identify the research priorities for zoonoses in South Africa using a systematic framework that has successfully been applied in other fields.[34] The research priority outcomes could facilitate more effective and integrated prevention and control plans for zoonoses by animal and human health organisations.

Materials and Methods

Background to study methodology

The approach followed in the current study adapted the methodology used by the Child Health and Nutrition Research Initiative, which was developed by the WHO and the Child Survival Group.[35,36] It allows technical experts to set the research priorities and score competing priorities in a systematic manner, taking into account inputs from stakeholders and the wider public. To limit the influence of peer biases on research topics, the experts submit their inputs to the process independently from each other; the final result is a simple quantitative outcome called the 'research priority score'. The methodology can simultaneously evaluate and score different types of research (e.g. health policy and systems research, implementation research and research on new interventions) using the same set of criteria.

There are other similar methodologies,[37,38] each with particular strengths. In the One Health Zoonotic Disease Prioritization (OHZDP) workshop methodology, a group of experts also chooses the zoonotic diseases of relevance before stakeholders select the criteria to prioritise the zoonoses,[37] while in the study presented here, each expert chooses their own five priority zoonoses and then research priorities for those diseases. The prioritising criteria in this study are selected beforehand and applied to each identified research priority. The One Health Systems Assessments for Priority Zoonoses identifies important zoonoses through literature review, then uses stakeholders to prioritise, map and assess information sharing and coordination systems for priority zoonoses.[39,40] Another methodology is the One Health

Systems Mapping and Analysis Resource Toolkit, which helps countries to analyse their existing health systems and create relevant action plans to improve cross-sectoral collaborations. Although relevant, these toolkits focus on systems, cross-sectoral communications and disease prioritisation,[41] while our study looks more broadly at zoonotic research priorities.

Methodology phases

The steering committee (n=5), consisting of authors GS, FQ, PC, MK and ST, coordinated and oversaw each of the study phases. The committee all have experience in zoonotic disease research. In phase 1, 18 experts were selected for in-depth interviews, based on their zoonoses-related experience, occupation and positions (Figure 1). A wide range of professionals within the One Health framework were considered. Nine were veterinarians (five have experience in wildlife health and three in research, four worked for academic institutions and the others worked for national parks, a national zoo and in private practice). Five experts were medical doctors in the public health sector (three in academia, one in a national institution and one in government clinical service) and the remainder were environmental science academics (n=2), a social science academic and an economist from a non-governmental agency. Three experts worked at a regional level, seven at national and eight at international level. We were not able to interview representatives from the national government. The interviews were conducted from February to March 2016.

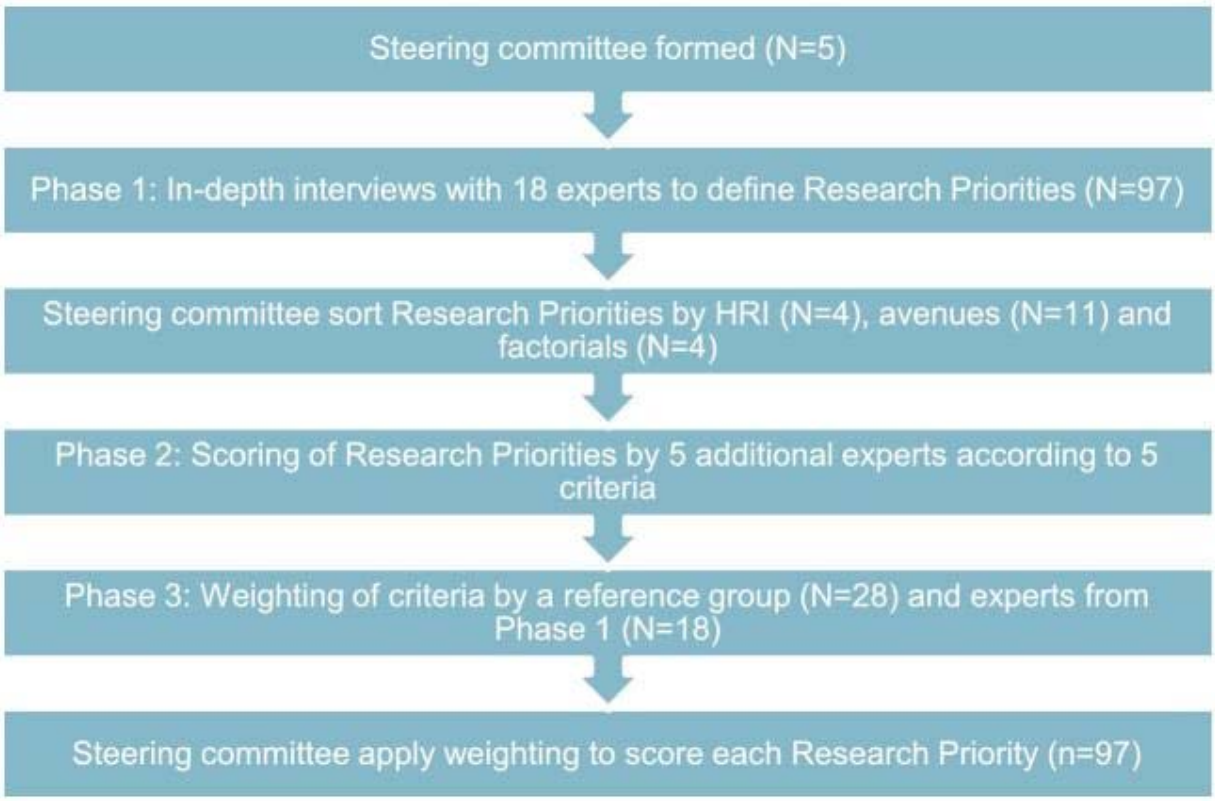

Figure 1. Flowchart of study phases.

The in-depth interviews asked the 18 experts to identify up to five priority zoonotic diseases important in the context of zoonoses in South Africa over the next 5 y and to explain their choices. They were also requested to list up to three priority human populations/groups susceptible to or affected by zoonotic diseases and up to three priority commodities, such as domesticated animals (e.g. cats, dogs and horses), farm animals and products (e.g. poultry, milk and leather), wildlife (e.g. wild birds and primates) and vectors (e.g. soil and water).

The experts were then asked to identify research priorities in four health research instruments (HRIs), each with several subcategories or 'avenues' for each of their priority zoonotic diseases. The first HRI, basic epidemiological research, has three avenues, namely, measuring the burden, understanding risk factors and evaluating existing interventions. The other HRIs are health policy and systems research, research to improve existing interventions and research for the development of new interventions.[36]

The experts were also asked for the priority knowledge gaps for understanding the following four factorials: (1) genetic and biological; (2) physical and environmental; (3) ecological; and (4) social, political and economic factors of each disease. The steering committee then collated the outcomes of the interviews into a list of 97 research priorities and sorted these by HRIs, the avenues within each HRI and factorials.

In phase 2, a second set of zoonotic experts (n=5) scored each of the 97 research priorities based on five scoring criteria: (1) answerability (the likelihood that the research will indeed reach its proposed endpoints) and ethics; (2) efficacy and effectiveness (the likelihood that the results of the research will have an effect against the disease), (3) deliverability, affordability and sustainability (the likelihood that the results of the research will be delivered to those who need them in an affordable fashion); (4) maximum impact for disease burden reduction (the likelihood that the research can influence reduction in a substantial share of disease cases); and (5) equity (the likelihood that the results of the research will improve health inequities in the population). Three questions on each of these criteria were asked to ascertain the likelihood that the research priorities would meet these five criteria. The answers were scored either yes (=1), no (=0), maybe (=0.5) or cannot answer (blank and removed from the analysis). The means of the scores were then calculated.

In the third phase, a large reference group of 28 individuals was constituted, including people within the medical field, but also journalists, business people, activists, social entrepreneurs and consultants. This group and the 18 experts from phase 1 were asked to give weightings to the five scoring criteria listed above, aiming to optimise the relevance of the research to societal needs. To develop the weighting they had to divide R100 (100 South African rand) over the criteria based on their judgement. This was used as a symbolic amount to help prioritise the scoring criteria. Lastly, the steering committee developed final scores by applying the weightings to the raw scores.

Results

Priority zoonoses

Seventeen diseases or classes of diseases were identified as zoonotic priorities by the 18 experts in step 1 (Table 1). The priorities covered viral, bacterial, protozoal, fungal and multidrug-resistant bacterial infections. Rabies, TB, brucellosis and Rift Valley fever were

each rated as priorities by at least 9 of the 18 experts. Rabies was the most frequently mentioned (n=14) and Crimean-Congo haemorrhagic the least mentioned (n=1).

Table 1. Priority diseases in South Africa and rationale for prioritisation

Disease and frequency	Rationale for prioritisation in South Africa
Rabies (14/18)	Disease widespread, causing fatalities in humans, domestic carnivores and wildlife
	Is underdiagnosed and misdiagnosed in humans, including in cases of rabies meningitis
	It is a preventable zoonoses. It can be controlled with an economical vaccination in dogs, however discontinuity in government vaccination plans and traditional beliefs in rural areas might be limiting its control
	Is a risk for endangered carnivores like wild dogs (*Lycaon pictus*). Death of whole packs of wild dogs were reported in 2016
	Guidelines are available, but interventions must be implemented effectively
TB (*Mycobacterium* spp.) (13/18)	High prevalence in human populations, especially in HIV-infected people
	Drug resistance of *Mycobacterium tuberculosis*
	Cases of TB in humans and cattle seem to have increased in recent years
	Social, cultural and economic factors play a major role in spread of the disease, making it difficult to diagnose, control and treat
	Humans–livestock–wildlife interface: spill-over into wildlife might affect wild animal populations and make this disease uncontrollable in Africa for both animals and humans
Brucellosis (*Brucella melitensis* and *B. abortus*) (11/18)	Epidemiological status and prevalence in livestock of *Brucella melitensis* and also *B. abortus* is unknown
	Possible increasing prevalence of brucellosis among wildlife populations, where source of infection and transmission mode is unclear
	Neglected and undiagnosed disease in humans
Rift Valley fever (9/18)	Outbreaks are infrequent, but can cause mortality in livestock and animal workers
	Is a risk for animal workers in endemic areas, such as farmers, labourers and veterinarians
	There are still important unknown genetic and biological features of this virus and its reservoir
	Potential effects of climate change on vector distribution
Cysticercosis (*Taenia solium*) (6/18)	Suspected high number of undiagnosed neurocysticercoses cases
	Disease distributed in areas with traditional farming practices and strongly associated with poverty, low hygiene and low meat inspection
Diarrhoeas and enteritis: Salmonellosis, *Campylobacter* spp. (5/18)	Is a major public health problem
	Disease can be severe and even fatal, depending on socioeconomic status and higher in children aged <5 y and immunocompromised people
	Poor water supply and therefore hygiene increases cases in poor communities
	South Africa has a high consumption of poultry, with its informal trade uncontrolled, predisposing humans to salmonellosis
	Unreported potential antimicrobial resistance
Tick bite fever (*Rickettsia* spp.) (4/18)	Neglected and undiagnosed disease
	Disease of concern since wildlife industry is growing. Wildlife workers and tourists are at risk. Foreign medical doctors may lack knowledge of this infection
Anthrax (*Bacillus anthracis*) (4/18)	Outbreaks affect wildlife populations, wildlife workers and livestock handlers
Arboviruses	Too many unknown facts make these diseases undiagnosed in humans and wildlife
	Potential for climate change to shift vector distribution and increase epidemics
Antimicrobial resistance (4/18)	Since several bacteria/helminth species are showing resistance to antibiotics/anthelmintics, what is the way forward?
	This is a very important challenge for both humans and animals. This could have a major public health impact and influence on zoonosis management
Toxoplasmosis (*Toxoplasma gondii*) (3/18)	A disease of concern in pregnant women
	Considered a silent and neglected disease
	Number of infections causing disease is unknown
	More accurate diagnostic needed in HIV-infected people where acute meningitis can cause mortality
Leptospirosis (3/18)	Considered a neglected zoonotic disease in South Africa despite being well known in veterinary practices
	Often undiagnosed and thus medical sector must be trained to diagnose cases and control outbreaks
	High presence of rodents in informal settlement and rural areas might be spreading the disease
Avian influenza (3/18)	The potential risk of becoming a pandemic
Schistosomiasis (*Schistosomiasis* spp.) (2/18)	A neglected disease
	High number of young children affected
	Commonly diagnosed late in infection
Crimean-Congo haemorrhagic fever (1/18)	Cases are unreported in humans and animals, but outbreaks might have a significant effect on public health

Priority areas, occupations and populations

Disadvantaged communities in rural areas with a lack of services such as water, sanitation, education, health clinics and veterinary management were seen as the most vulnerable to zoonoses (Table 2). Immunosuppressed people, such as those with HIV infection, were rated second; groups working with livestock or at abattoirs, such as veterinarians, farmers and animal workers, were rated as the third most vulnerable. Two different areas were highlighted as high priority: people in urban informal settlements where the population density is high and illegal immigration is common; and people involved with wildlife.

Table 2. Frequency of priority areas, occupations and populations mentioned by phase 1 experts

Priority area, occupation or population	Reason for priority
Disadvantaged communities in rural areas with poor water system, education, veterinary management and access to health clinics (13/18)	Greater exposure to and severity of zoonotic disease
HIV-infected and immunosuppressed people (10/18)	Many zoonoses can cause death
Livestock veterinarians, farmers, animal and abattoirs workers (10/18)	Brucellosis, RVF
Wildlife workers: veterinarians, farmers, labourers (6/18)	Anthrax, brucellosis, RVF
Disadvantaged informal urban communities with low hygiene, high human density and immigration (6/18)	Greater spread and case severity of GI diseases and TB. High concentration of HIV-infected people
Endemic areas for arboviruses (5/18)	RVF
Population with strong traditional medicine beliefs and traditional cultural practices (4/18)	These populations and their animals may not be vaccinated. When their animals become ill, they may go to traditional healers rather than to a hospital or clinic
Poorly educated or suppressed women (3/18)	Fewer visits to clinics in rural areas can raise severity of zoonoses
Children aged <5 y living in rural or disadvantaged areas (3/18)	Predisposed to infections from unpasteurised milk Risk of severe-fatal gastrointestinal diseases
Outdoor activities/safaris/poaching (3/18)	Tick bite fever
Young uneducated children in disadvantaged areas (2/18)	Young boys as shepherds: TB, brucellosis, TBF. Greater exposure to rabies bites. More predisposed to getting HIV. Swimming in standing water: bilharzia
Population living at wildlife/livestock interface (1/18)	
Any person in the country (1/18)	Arbovirus

Abbreviations: GI, gastrointestinal; RVF, Rift Valley fever; TBF, tick bite fever.

Research priorities and their scores

A list of 97 research priorities were identified: 57 were classified in the basic epidemiological research category, 15 in the health policy and systems research category, 5 in the research to improve existing interventions category and 20 in the research category for development of new interventions (Table 3).

Table 3. Research priorities grouped by health research instruments, their avenues and factorials, with weighted research priority scores

	Frequency of research priority	Average research priority score	Minimum research priority score	Maximum research priority score
Health research instruments and associated avenues of research				
1: Basic epidemiological research	57	0.67	0.36	0.91
A. Measuring the burden	24	0.66	0.37	0.88
B. Understanding risk factors	22	0.64	0.38	0.88
C. Evaluating existing interventions	11	0.73	0.36	0.93
2: Health policy and systems research	15	0.72	0.41	0.90
D. Studying system capacity to reduce exposure to proven health risks	6	0.74	0.62	0.88
E. Studying system capacity to deliver efficacious interventions	9	0.70	0.41	0.90
3: Research to improve existing interventions	5	0.77	0.72	0.84
F. Research to improve deliverability of existing interventions	4	0.75	0.72	0.81
G. Research to improve affordability of existing interventions	1	0.84	0.84	0.84
H. Research to improve sustainability of existing interventions	0	0	0	0
4: Research for development of new interventions	20	0.70	0.40	0.88
I. Basic research into new interventions	5	0.75	0.51	0.88
J. Clinical research in new interventions	6	0.64	0.47	0.88
K. Public health research in new interventions	9	0.71	0.40	0.88
Factorials				
1 Social, Political, Economic	41	0.72	0.36	0.91
2. Genetic and Biological	49	0.66	0.34	0.88
3. Physical and Environmental	3	0.66	0.55	0.78
4. Ecological	4	0.63	0.36	0.75

In the basic epidemiological research category, 24 research priorities pertained to measuring the burden of disease followed by 22 for understanding risk factors and 11 for evaluating existing interventions. In the priorities on health policy and systems research, six were for studying system capacity to reduce exposure to proven health risk and nine for studying system capacity to deliver efficacious interventions. In research to improve existing interventions, four priorities were for improving deliverability, one for improving affordability, but none for improving sustainability. In the development of new interventions, five were for basic research, six for clinical research and nine for public health research.

Weighting of scoring criteria and final weighted scores

In the second phase, a second set of experts (n=5) developed average raw scores for each of the scoring criteria for each of the 97 research priorities, marking each as 0, 0.5, 1 or removed from analysis. The mean was 0.68, ranging from 0.34 to 0.92. In the third step, the initial group of experts (n=18), along with the 28 people in the reference group, weighted the five scoring criteria for the study out of 100. Deliverability, affordability and sustainability were deemed the most important with 24, followed by effectiveness with 22, equity with 21, answerability with 17 and maximum impact for disease burden reduction with 16, totalling 100. The weighted scores were similar to the raw scores, with a mean of 0.69, ranging from 0.34 to 0.93.

The top 25 of the 97 questions are shown in Table 4 and the remainder in Supplementary Table 1. Optimal rabies vaccination strategies are seen as key priorities. For brucellosis the largest concern is what strains are circulating, having a strain-specific test and what is the best way to control the disease in a non-commercial setting: ‘Will a test and slaughter policy for brucellosis control brucellosis in a non-commercial setting?’ Understanding how to apply the brucellosis control strategies that have worked in high-income countries to the priority

Table 4. Highest scored priorities for zoonoses research by weighted score

HRI	Avenues	Factorial	Research option	Answerability	Effectiveness	Deliverability	Maximum potential for disease burden reduction	Effect on Equity	Raw Score	Weighted score
1	C	1	Herd immunity factors: What proportion of the dog population need to be vaccinated to control the diseases?	1.00	0.93	0.93	0.73	1.00	0.92	0.93
1	C	4	Are Brucella control mechanisms effective in non-commercial farms?	1.00	0.93	0.93	0.62	1.00	0.89	0.91
2	E	4	How best to ensure the diagnosis and treatment availability of human TB in rural clinics?	0.92	0.93	0.93	0.67	1.00	0.89	0.90
1	A	1	What is the true prevalence and geographic distribution of brucellosis in livestock and humans in RSA?	1.00	0.82	0.92	0.71	0.93	0.88	0.88
1	C	4	How can pathogen detection and traceability be improved in small abattoirs?	1.00	0.85	0.92	0.60	1.00	0.87	0.88
4	K	4	How to increase education and public awareness on zoonotic diseases?	1.00	0.88	0.92	0.69	0.87	0.87	0.88
4	I	1	Developing a more accurate and strain specific test for Brucella in humans and animals?	0.92	1.00	0.92	0.69	0.80	0.87	0.88
1	B	4	What are the risk factors and prevention measures for anthrax outbreaks in humans and animals?	0.91	0.91	0.92	0.57	1.00	0.86	0.88
2	E	4	Why do hospitals not follow rabies PEP guidelines?	1.00	0.80	1.00	0.50	1.00	0.86	0.88
2	D	4	Why is there a lack of communication between doctors and vets in areas when an outbreak occurs?	1.00	0.86	0.93	0.60	0.93	0.86	0.88
1	C	4	Vaccinations plans: optimal vaccination strategies adapted to demography and culture. Assess the effectiveness of education and chemoprophylaxis in poor areas in preventing rabies and considering traditional beliefs?	0.92	0.86	0.80	0.73	1.00	0.86	0.86

Table 4. Continued

HRI	Avenues	Factorial	Research option	Answerability	Effectiveness	Deliverability	Maximum potential for disease burden reduction	Effect on Equity	Raw Score	Weighted score
1	A	1	What proportion of human TB diseases is caused by human TB, bovine TB, avian TB?	1.00	0.92	0.93	0.57	0.80	0.84	0.86
4	k	4	How to improve education to prevent or reduce cases of toxoplasma infections in HIV and pregnant woman	1.00	0.92	0.93	0.64	0.73	0.84	0.85
1	A	1	Identifying the exact cause of zoonotic febrile illness in humans	1.00	1.00	0.83	0.60	0.75	0.84	0.84
2	E	1	How to improve the RVF early warning systems and availability of RVF vaccination?	0.92	0.92	0.80	0.79	0.80	0.85	0.84
4	I	1	Quick, reliable, accurate, specific and affordable diagnostic test for TB in humans, livestock and wildlife	0.92	1.00	0.69	0.57	1.00	0.84	0.84
3	G	1	Develop cost-effective laboratory testing for arbovirus diagnosis in order to establish the risk of infection	0.92	0.93	0.92	0.50	0.83	0.82	0.84
1	A	1	What are the Brucella serotypes circulating in RSA and what are the rates and mechanics of transmission between different species?	1.00	0.92	0.71	0.63	0.87	0.83	0.83
2	E	4	Rabies vaccination programmes in RSA have not been systematically implemented: How is it best to guarantee government vaccination plans are systematically implemented over the years?	0.58	0.88	0.77	0.80	1.00	0.81	0.82
4	K	4	What are the necessary skills and resources of workers in rural clinics and public hospitals to diagnose zoonoses?	1.00	0.86	0.73	0.53	0.93	0.81	0.82
1	A	1	What is the bilharzia burden of disease in human population in the different provinces and can an intervention be put on place?	0.92	0.92	0.77	0.50	0.89	0.80	0.81

Table 4. Continued

HRI	Avenues	Factorial	Research option	Answerability	Effectiveness	Deliverability	Maximum potential for disease burden reduction	Effect on Equity	Raw Score	Weighted score
3	F	4	Why is there a lack of availability of rabies immunoglobulin in South Africa?	0.92	0.82	0.57	0.80	1.00	0.82	0.81
4	J	1	Helminth control and snails control: Would regular human deworming treatment prevent internal parasites diseases such as cysticercosis and bilharzia. What drugs are reliable and do not have resistance?	0.92	0.91	0.67	0.67	0.89	0.81	0.81
1	C	4	What is the efficacy of the zoonotic disease control programmes in non-commercial farms?	1.00	0.85	0.71	0.50	0.93	0.80	0.80
1	A	1	Accurate mapping of zoonotic disease to develop more effective and affordable control plans	0.85	0.93	0.71	0.60	0.87	0.79	0.80

Abbreviations: HRI, health research instruments; PEP, post exposure prophylaxis; RSA, Republic of South Africa; RVF, Rift Valley fever.

populations and settings in South Africa was also prioritised. The key research questions for TB concerned improved diagnostics and treatment, especially in the priority populations.

Diagnosis and detection of zoonoses in general are top research priorities, highlighting the fact that misdiagnosis and underdiagnosis of zoonoses are still seen as significant problems in South Africa. The inclusion of bilharzia, cysticercosis, Rift Valley fever and anthrax in the top 25 research priorities indicates that these are still seen as priority conditions (Table 4).

The lowest scoring average priority score of the health research instruments category was basic epidemiological (0.67), followed by development of new interventions (0.7), health policy and systems (0.72) and the highest scoring was research to improve existing interventions (0.77) (Table 3 and Figure 2).

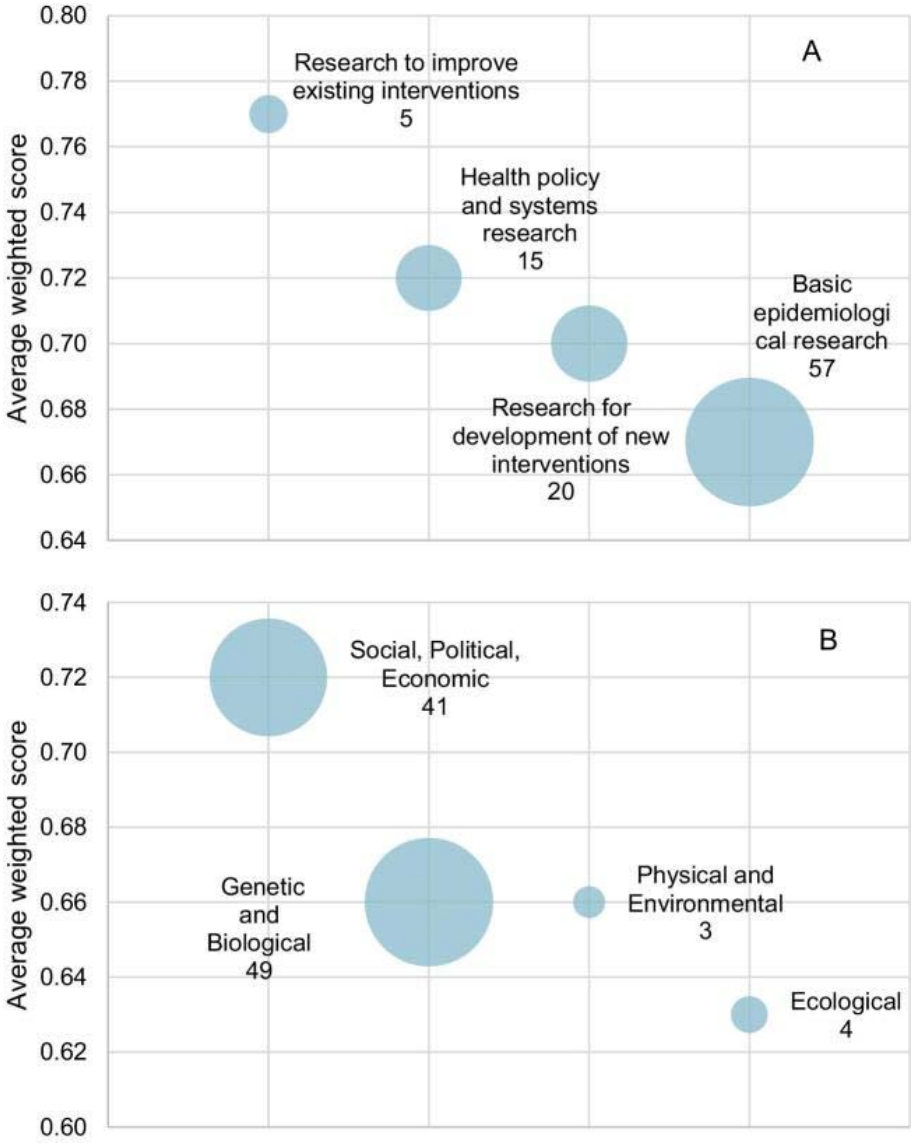

Figure 2. Average weighted score graph with size of circle dependent on frequency of research priorities in each category (frequency indicated with number) by (A) instrument of health research (HRI); and (B) factorial. The x-axis has no significance.

Discussion

This is the first study to systematically identify zoonoses research priorities in South Africa, drawing on interviewees from diverse sectors, educational backgrounds and management levels. This information is of major importance given that there is marked variation in South Africa in socioeconomics, climate, biomes and access to healthcare, which predisposes the country to a high zoonotic disease burden and wide range of conditions. There are scarce resources available for research and these need to be carefully prioritised.

Diversity of the diseases, areas, populations and occupations of interest

A large number of priority diseases were identified from viruses, bacteria and rickettsia to antimicrobial resistance and protozoa. The top three priority diseases were endemic rabies, TB and brucellosis, all of which are found in humans, livestock and wildlife and have considerable mortality and morbidity risks. These diseases have been successfully controlled in many countries, but are unlikely to be controlled in South Africa in the near future. The top diseases in this study overlap to some extent with the OHZDP workshop conducted in 2016 that identified *M. bovis*, salmonellosis, *Brucella abortus, Brucella melitensis* and zoonotic avian influenza as the priority diseases in South Africa.[42] This overlap helps to validate the results of our study. Although there are some similarities in the two study methodologies, our study primarily addresses the research needs within priority zoonoses, while the OH-ZDP workshop identifies zoonotic disease priorities from a health security perspective, with the focus on policy. Our identification of TB as a priority and not just *M. bovis* allows for a broader application of 'One Health' with regards to control of *Mycobacterium* spp. Given that the burden of TB in South Africa is amongst the highest worldwide, there is a concern that the TB control programme in the country may not view animal–human interactions as a priority and concerted efforts may be needed to engage with leaders of the programme.

The priorities overlap only partially with similar studies in other parts of the continent. For example, a study using the OHZDP methodology in Uganda found seven zoonotic diseases as priorities: anthrax, zoonotic influenza viruses, viral haemorrhagic fevers, brucellosis, African trypanosomiasis, plague and rabies.[43] Meanwhile, a health systems study for prevention and control of zoonoses in Guinea found rabies, anthrax, brucellosis, viral haemorrhagic fevers, trypanosomiasis and highly pathogenic avian influenza as the country's top priority zoonoses and used these zoonoses as case studies to evaluate existing processes for prevention and control.[44] In Ethiopia, rabies, anthrax, brucellosis, leptospirosis and echinococcosis were considered the top priorities, and that additional public health and veterinary laboratory enhancement, along with intersectoral (human and animal health) linkages, were needed.[38] A network mapping study in Jordan found that while there is informal communication and effective coordination across the Ministry of Health and Ministry of Agriculture in the event of the emergence of one of the priority zoonoses studied, routine formal coordination is lacking.[40]

Diseases given a low ranking in general had a lower mortality or are very uncommon. The diseases chosen were felt to be important as they are frequently misdiagnosed and are under-reported, preventable and occupational risks, strongly influenced by socioeconomics and affecting endangered animals. Many experts mentioned that additional data on the disease burden of neglected diseases are important as these conditions may actually be of greater public heath significance and are more widespread than is currently appreciated.

The priority areas, occupations and populations chosen by the experts are a clear reflection of the South African reality. Disadvantaged rural communities in areas with poor service delivery and informal urban areas with high densities and numbers of migrants were seen as being at the highest risk. A common concern was the effect of zoonoses on people with HIV infection, and antibiotic and antiparasitic resistance. Children are also seen as a priority population, especially for gastrointestinal diseases. Livestock workers, veterinary staff, abattoir and wildlife workers were considered to be the people in the most at-risk occupations.

The potential for new arboviruses associated with climate change is also viewed as an important threat. Decreasing wilderness land, intensification of farming, changing land use and growing human populations are all increasing the spill-over of disease in all three directions at the wildlife–livestock–human interface.

Poverty, and limited sanitation and education in several areas of the country, constrain or complicate the control of zoonoses. Additionally, traditional beliefs and indigenous medical practices are common in many parts of the country and need to be carefully considered when establishing control plans.

Research themes

The priorities seen by the experts were predominately in understanding basic epidemiological research (59%). For example: 'What is the burden of disease, the risk factors and are our current interventions working?' The need for better detection of disease was frequently mentioned, along with the importance of a better understanding of the ecology of zoonoses. This may be due to the concern that zoonoses are underdetected. The need for a better description and recognition of zoonoses by veterinary and medical staff appears to underlie these concerns, together with improved communication between veterinary and public health sectors.

Research to develop new interventions, especially in public health research, was given the second highest priority rating. By contrast, research to improve existing interventions was not frequently mentioned although it was seen as a top priority. This suggests that the experts are confident in the basic scientific underpinnings of current interventions and their potential efficacy, but are perhaps uncertain of the capacity of the health system to implement these and the policy environment. This is supported by the fact that only 5 of the 97 research priorities focused on improving existing interventions.

The Guinea study found that coordination, training, infrastructure, public awareness and research were the main gaps and challenges.[44] Although the methodology is similar that study was more systems focused; broadly speaking it shows an overlap with our research themes.

Weighting of scoring criteria

Deliverability, affordability and sustainability had the highest weightings, yet the lowest priority for research in existing interventions. Maximum potential for disease burden reduction and answerability and ethics had the lowest weightings, indicating that these criteria are seen as being of lesser importance. This is possibly due to the fact that in the context of South Africa, having an intervention that is deliverable, affordable and sustainable is more important than having maximum potential or research answerability.

Strengths and limitations

The study brought together a large group of experts and key stakeholders and followed a rigorous prioritisation method. The method, however, may be limited as it was originally designed for childhood illnesses and not zoonoses. While the methodology aims to minimise the subjectivity of respondents, this bias is likely to remain, at least to some extent. The large diversity of interviewees is a strength of the study and may counteract this bias. Almost 100 research priority questions were devised, which likely reflects the breadth of expertise of the group.

Comparison with an equivalent Indian study

This study used the same methodology as an Indian study,[9] so it is of interest to compare the outcomes. The experts had similar backgrounds, with a ratio of two veterinarians to one medical doctor. However, the Indian study had twice as many experts (n=6) in national research institutes than universities, while in South Africa the largest proportion were based in a university (n=4) and three were at a national research institute. Rabies, brucellosis and TB were in the top five priority diseases in both the Indian study and the current study. There was also overlap in the populations of greatest concerns, which consisted of farmers and tribal communities in the Indian study, and disadvantaged rural communities in areas with poor service delivery and informal urban areas in the current study. Similar risk areas were highlighted, namely, remote villages, urban slums and forest fringes (human–wildlife interface). Both studies had the scoring criteria of deliverability, affordability and sustainability as being the most important. The South African study, however, rated the maximum potential for the burden of disease reduction as least important while it was seen as one of the most important concerns in the Indian study.

The Indian raw priority scores were comparable with the South African ones, with the average raw score being 0.78 (0.68), the lowest 0.35 (0.34) and the highest 0.96 (0.92) (the scores in brackets are from South Africa). The Indian study found that basic epidemiological research had the highest research priority (46%), which was the same as our study (58%). Understanding risk factors was the most frequently cited option, while in our study it was the second most frequent. The social, political and economic factorial was accorded the highest priority score in both sites.

Some research priorities were rated highly in both sites, namely: ‘What are the risk factors and their differences for anthrax transmission?’; ‘What are rabies vaccination and post-exposure prophylaxis policies at clinics and why they are not followed?’; ‘What is the human TB prevalence and proportion of different *Mycobacterium* species’; and ‘Why is there lack of communication between sectors and models to improve collaboration for zoonoses prevention and control?’

Conclusions

This study was able to successfully apply rigorous research prioritisation methods in a middle-income African country. Experts indicated that future zoonoses research in South Africa should cover a wide variety of diseases, although focus primarily on rabies, TB, brucellosis and Rift Valley fever. The highest perceived need is for research evaluating existing interventions (e.g. to improve vaccination programmes), understanding risk factors and measuring burden for the priority zoonoses. Experts see rural populations without

essential services, immunocompromised people, children, informal settlements and those in high-risk occupations (farmers, abattoir workers and wildlife workers) as the highest priority.

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Authors' contributions

GS and FQ are joint first authors. Study design: PC, MK, ST, GS and FQ; data collection: FQ and GS; data analysis: FQ and GS; writing: GS, FQ and MC; supervision: MK, PC and ST.

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Competing interests

The authors declare they have no competing interests.

Ethical approval

Not required.

Data availability

The data underlying this article will be shared on reasonable request to the corresponding author.

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