Cross-disciplinary and participatory livestock and human health research for successful control of zoonoses in the developing world

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Abstract

Conventional disciplinary research approach is losing momentum in the face of dynamic health challenges of the 21st century. There is a need for a new, suitable approach, to tackle these emerging and re-emerging human and animal diseases through integrating livestock and human health research in a cross-disciplinary approach for greater impact. This is particularly important for the developing world owing to the closer contact of humans with animals as well as the consumption of raw animal products, worsened by low levels of literacy. Animals are the major source of today's emerging and re-emerging infectious diseases that threaten both human and animal populations of the world. Among recent examples are SARS (severe acute respiratory syndrome), the Hendra and Nipah virus infections, BSE or mad cow disease (bovine spongiform encephalopathy) and now highly pathogenic avian influenza (HPAI), or bird flu. In addition, bovine tuberculosis and rift valley fever (RVF) are some examples of important re-emerging zoonoses. In recent years, bovine tuberculosis has become increasingly important with the HIV and AIDS pandemic in the developing world. This paper highlights the past and current research portfolio of ILRI and its partners, focusing on diseases that are transmissible between human and animals in the context of developing countries. [*Ethiop.J.Health Dev.* 2008;22(Special Issue): 109-116]

Introduction

Veterinary public health (VPH) is not integrated into the mainstream of public health services in sub-Saharan African countries. There are no formal mechanisms within government public health services through which veterinary skills and resources can be effectively harnessed to bear upon community health. There is no conscious, overt or substantial effort by public authorities to incorporate VPH services in the overall approach to public health. VPH activities cover mainly the control of the major animal diseases transmissible to man (zoonoses), meat inspection and, to a limited degree, the quality control of milk, fish and their products. These services are carried out by the Veterinary Services of the Ministry of Agriculture in each country (1).

Zoonotic diseases, transmitted between humans and animals, are mostly associated with people who have close direct contact with animals or indirect contact via vector or other transmission vehicles. Farmers, pastoralists, veterinarians, butchers and abattoir workers are people with a high risk of zoonotic infections. Zoonoses have important impacts on public health and the economies of the people who depend on animal agriculture. Taylor *et al*. (2) reported the number of zoonotic infections at 868 representing 61% of all infectious organisms identified to be pathogenic to humans. Some of these infections have been recognised early in history (e.g. rabies) while others have recently emerged (e.g. SARS, BSE, HPAI). For example, raw milk consumption was recognised and proved as means of transmission for bovine TB only two decades ago, and pasteurisation drastically reduced the disease occurrence in Europe.

Measures taken to control major diseases in Europe include disease surveys, monitoring, and control through concerted efforts of important key players in the food chain (e.g. slaughterhouses and milk processors); these have reduced the prevalence of many zoonotic diseases. In contrast, many zoonotic infections are still common in the sub-Saharan African countries. The occurrence of zoonotic diseases such as bovine TB, rabies, RVF, HPAI, brucellosis, and anthrax in humans could be reduced or eliminated if the diseases are controlled in livestock. Hence, vaccinating livestock or companion animals against these diseases should also be considered as part of public health measures.

Despite the above challenges that could have acted as a focal point for change, there has not been a cross-disciplinary breakthrough in collaboration among relevant professionals and other key stakeholders in targeting zoonoses. This paper summarises research focus areas at ILRI, areas of collaboration, and a way forward for zoonoses in the context of developing countries.

Concept of cross-disciplinary approach – a need for change

Despite huge international and national efforts towards improving health and livelihoods of people, there has not been substantial progress towards achieving the Millennium Development Goals (MDGs) set for health. In spite of the increasing challenge from emerging and re-emerging zoonotic infections in the world, collaboration among professionals has not achieved momentum. There is a need for a strategic shift in the types of collaborations – from mono-disciplinary to cross-disciplinary and participatory approaches.

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Problems are usually multidimensional and interlinked and the search for solutions calls for application of the combined methodologies as well as mobilisation of new ideas of expertise and application of theoretical frameworks which transcend traditional professional boundaries (3). Cross-disciplinarity is a cover term for different types of collaboration. By definition a discipline is a complex phenomenon with social as well as cognitive aspects, "a community, a network of communication, a particular set of values and beliefs, a domain, a mode of enquiry, and a conceptual structure" (4). Rosenfield (1932, 1951) cited in Aargaard-Hansen *et al*. (3) distinguished three different levels of cross-disciplinary collaboration:

A. Multidisciplinary – researchers work in parallel or sequentially from disciplinary-specific base to address common problem
B. Interdisciplinary – researchers work jointly but still from disciplinary-specific base to address common problem
C. Trans-disciplinary – researchers work jointly using shared conceptual framework drawing together disciplinary-specific theories, concepts, and approaches to address common problem. Cross-disciplinary approach can provide more useful answers to the pertinent problem because it applies more holistic view. Moreover, collaboration between different disciplines increases the possibility of raising new and innovative research questions and provision of cross-fertilisation in terms of methodologies and theories and direct academic benefit per se.

Therefore, it is time for change in addressing zoonoses research to generate viable control options through cross-disciplinary collaboration for all professionals and stakeholders.

Zoonoses research by the ILRI

ILRI conducts research to protect and enhance the physical human capital of the poor by developing strategies to reduce health risks and improve nutritional benefits associated with livestock keeping. Other projects focused on the use of water and feed for livestock also consider human health impacts. ILRI is working to improve understanding of the links between livestock keeping and the health and nutrition of poor people, particularly those engaging in smallholder livestock production and marketing. Activities underway include field studies, literature reviews and explorations of the ways in which livestock keeping might benefit the care of people with HIV/AIDS.

Poor people in developing countries have a high risk of exposure to zoonoses. ILRI is helping to bridge the artificial divide between animal and human health, and helping to bring out more clearly the links between agriculture and health. With over three-quarters of human infections having a zoonotic origin, the need to examine the epidemiological relationships between pathogens and their animal and human hosts is paramount. Poor households that keep livestock often live in close proximity to their animals, with animals and people alike living in poor sanitary conditions (5). The several species of livestock kept by the poor benefit from little if any veterinary care, and medical facilities for the people themselves are also scarce. Poor keepers and non-keepers of livestock alike typically consume livestock products that have not been subject to inspection or improved processing and storage. Furthermore, many developing countries lack the information, awareness and control strategies needed to control zoonotic diseases, often because conventional disease control and food safety strategies are ill-suited or too expensive for smallholder production and marketing systems. Typically, little investment has been made to develop appropriate control strategies and there is a lack of coordination between the relevant veterinary and medical sectors. Through a joint research programme with the Swiss Tropical Institute, ILRI research is addressing the strategic methodological challenge of integrating veterinary-medical assessments of the impacts of the zoonotic disease burden on livelihoods of the poor.

I. Bovine tuberculosis

Due to the global importance of tuberculosis as one of the most prevalent infectious diseases and leading cause of death and because the infection caused by bovine tubercle bacillus, *Mycobacterium bovis*, is clinically indistinguishable from tuberculosis caused by *Mycobacterium tuberculosis*, ILRI has recognized the disease as one of the most important zoonosis for collaborative research. In this connection ILRI has been undertaking research in bovine TB both directly and indirectly in collaboration with partners, examples are highlighted below:

1. *The role of ILRI in contributing to novel vaccination strategies for control of bovine tuberculosis in cattle and understanding the immunological basis of breed differences in susceptibility to the disease*:

The first context in which ILRI became involved in bovine tuberculosis research was in evaluation of heterologous prime-boost vaccination regimes based on priming with plasmid DNA or avian poxvirus antigen constructs and boosting with the same recombinant antigen expressed in replication attenuated poxviruses in cattle. Such strategies had previously been demonstrated to induce immunity, based on CD4 and CD8 T cells, against several diseases in both rodents and primates. The ILRI study demonstrated that conceptually similar prime-boost vaccination strategies using the p85a antigen of *M. tuberculosis*, which is conserved with the *M. bovis* homologue, were highly effective in inducing antigen-specific gamma interferon secreting CD4 and CD8 T cells, detected using a bovine ELISPOT assay, in *Bos indicus* cattle (6). T cell responses

induced by priming with either plasmid DNA or fowlpox p85a recombinant antigen expression constructs were enhanced by boosting with modified vaccinia virus Ankara (MVA) administered intradermally. Intradermal priming was markedly more effective than intramuscular delivery of the priming dose for MVA boosting in cattle. Fowlpox or plasmid DNA priming were both effective and using either fowlpox or DNA priming there was a significant bias toward induction of CD4, rather than CD8 T cell responses. These data illustrated the general applicability of prime-boost vaccination strategies for induction of antigen-specific T-cell responses and suggested that the method may be useful for development of veterinary vaccines. Due to the lack of a BSL3 containment facility at ILRI it was not possible to perform challenge experiments with virulent *M. bovis* to test whether the T cell responses induced might be protective.

A growing body of evidence suggests that Zebu cattle (*Bos indicus*) are more resistant to *Mycobacterium bovis* infection than exotic (*Bos taurus*) cattle. As long ago as 1940, Carmichael concluded that the incidence of bovine TB in Uganda, was dramatically lower in Zebu (*Bos indicus*) cattle 0.1–0.7%, compared to Ankole (*Bos taurus*) 12.5–41.4% (7). More recently, a comparison of slaughterhouse examinations in India indicated that *Bos indicus* breeds were less affected by bovine TB than pure European breeds like Jersey, Holstein-Friesians and Brown-Swiss (8). Skin testing results compiled in Ethiopia further support the hypothesis that cattle breeds differ in their relative susceptibility to bovine TB. Tadelle (9) found that in central Ethiopia local *Bos indicus* breeds had much lower prevalence rates (5.6%) than exotic breeds (mainly Holsteins, 86.4%); crosses showed 13.9% prevalence. Similar differences in prevalence rates and severity of pathology have also recently been demonstrated between Holsteins and Zebus north-east of Addis Ababa, by Ameni and co-workers (10).

In view of this evidence for differential susceptibility of breeds to bovine TB derived from field studies, ILRI is currently performing a comparative analysis of the immune responses and pathology of experimentally infected cattle of East African Boran (*Bos indicus*) and Friesian (*Bos taurus*) breeds. This represents one module within a Wellcome Trust-funded Animal Health in the Developing World project, involving an international consortium which seeks to make a systematic survey of the prevalence, genotypes and economic impact of bovine TB in both livestock and humans, focused on Ethiopia. It is envisaged that the results may be synergistic with the definition of genomic regions associated with differences in bovine TB prevalence identified using single nucleotide polymorphisms that differentiate *Bos indicus* and *Bos taurus*. These data may ultimately provide insights into the molecular basis of the resistance/susceptibility phenotype in cattle.

2. *Comparison between comparative tuberculin and gamma-interferon tests for the diagnosis of bovine tuberculosis in Ethiopia (11)*

   Comparative cervical tuberculin (CCT) test as standard test for the detection of bovine tuberculosis (12) has been in use since the last two decades and measuring gamma-interferon release in a whole-blood culture system has been developed (13) as a new diagnostic method for bovine tuberculosis. Diana and Carole (14) found that single caudal-fold skin test as more sensitive than the commercial IFN-γ test. However, the sensitivities and specificities of the IFN- γ and CCT tests have not been compared before. A study aimed at determining and comparing the sensitivities and specificities of the comparative cervical tuberculin (CCT) and gamma-interferon (IFN-γ) tests for the diagnosis of bovine tuberculosis was conducted on 30 Zebu oxen in Ethiopia. The results of the tests were compared with the presence of acid-fast bacilli found by bacteriological culturing and histopathological examinations. The results indicated that the sensitivity of CCT was 90.9% and its specificity was 100%. Those of the commercial IFN-γ test were determined to be 95.5% and 87.7%, respectively. No significant differences were found between the sensitivities or the specificities of the two tests. It was therefore concluded that the choice between the two tests depends on their cost and simplicity and on livestock management and time factors rather than on their respective diagnostic value.

3. *Kinetics of interferon-γ (IFN-γ) release in the peripheral blood of calves vaccinated with BCG*

   Buddle *et al*. (15), studying on the efficacy of BCG, have shown that a low dose of BCG will protect calves from experimental infection with *M. bovis*. One of the mechanisms by which BCG protected calves from experimental infection is by inducing the release of IFN-γ. We conducted a study (16) on 13 Friesian-Zebu crossbred calves, the ages of which lie between 6 and 18 months, to investigate the kinetics of IFN-γ release in the peripheral blood following Bacille Calmette Guerin (BCG) vaccination. After being screened for bovine tuberculosis (BTB), the calves were vaccinated with 1ml inoculums containing 6×10^6 CFU of BCG. The level of IFN-γ in the peripheral blood was measured two times before vaccination and seven times after vaccination, using a sandwich ELISA. The kinetics of IFN-γ post vaccination presented itself in three phases: rising, falling and steady phases. The concentration of IFN-γ, before and after vaccination, both in stimulated and non-stimulated samples, was statistically significant ($P<0.01$). Strong positive correlation ($r=0.86$) was recorded between the levels of IFN-γ release in avian

PPD- and bovine PPD-stimulated samples. Of the total 13 calves, 11 (84.6%) reacted positively to tuberculin inoculation 15 weeks post vaccination. We concluded that the IFN-γ rises immediately after BCG vaccination, reaching its peak two weeks post vaccination, and then declines gradually in the following weeks. The strong positive reaction of calves to tuberculin inoculation 15 weeks post vaccination showed the capability of BCG in causing the release of IFN-γ in the peripheral blood, indicating its role in protection against infection with *M. bovis* in calves.

4. *Cross-sectional studies of bovine tuberculosis in selected dairy farms and smallholder farms in Ethiopia*

Zoonotic tuberculosis is prevalent in animals of many developing countries where surveillance and control activities are often inadequate or unavailable; Ethiopia is one of these countries where many epidemiologic and public health aspects of the infection remain largely unknown. We conducted a cross-sectional study (17) to generate baseline information on the prevalence of bovine TB and related risk factors in selected dairy farms in Ethiopia using 1171 dairy cattle in 12 randomly selected state-owned, private or research dairy farms. Comparative intra-dermal tuberculin (CIT) test and bacteriologic study through milk culturing were employed. An overall individual animal prevalence of 46.8% and a herd prevalence of 91.7% were recorded. There were significant differences in individual prevalence between farms and breeds (pure Holstein and their crosses with Zebu). It was also found out that herd size and management (sanitation levels) affect the prevalence of bovine tuberculosis. Particularly, breed and management affected the prevalence of bovine TB as confounding variables. *M. bovis* was isolated in the milk of 4 cows out of the 13 reactor cows. The widespread occurrence of bovine TB in the study farms and isolation of *M. bovis* from the milk of reactor cows signified its economic importance and potential risk to public health. Generalization and improved use of milk pasteurization within all dairy sub-sectors is recommended, and this would affect the competitiveness of the dairy sector in Ethiopia.

With the rationale that the introduction of exotic and crossbred cattle into Ethiopia has created favourable condition for the spread of bovine TB, leaving cattle, cattle owners, and consumers of raw cattle products at risk for infection from *M. bovis*, we considered the Wuchale-Jida district, which is one of the 12 districts in the North Shewa Zone (Ethiopia) where dairying is commonly practiced using small herd size. The extent of bovine TB in the district in both cattle and humans, however, was not known. We conducted a cross-sectional study (10) on 94 households and 763 (575 crossbred and 188 indigenous) cattle to determine the prevalence of bovine TB and assess its public health implications in these smallholder farms. Cluster sampling, CCT test, a questionnaire, and mycobacteriology were used. Based on the CCT test, herd prevalence was 42.6% and individual animal prevalence was 7.9%. The individual animal prevalence was significantly affected by herd size, age and body condition of the animal. Among the interviewed households, 24.5% had experienced at least one human tuberculosis case in the family. Of these families, 43.5% had reactor cattle. Nevertheless, no statistically significant association was observed between reactor cattle and human tuberculosis cases in households. The habit of milk and meat consumption was affected by occupation and location of household residence. Although the level of education influenced the habit of milk consumption, it did not impact the habit of meat consumption. Less than half (38.3%) of the respondents knew about bovine TB, and only 30.8% of the respondents were conscious of its transmission from cattle to humans. Secondary data analysis from Muka-Turri human clinic indicated that 85.6% of the human tuberculosis cases were from rural parts of the district. Although the bovine TB prevalence seems low, its potential risk to public health was important based on food consumption, poor sanitary measures, and the lack of understanding about its zoonosis. Presently there are two projects on bovine TB at ILRI (one on-going and one planned):

- Bovine tuberculosis in the developing world: WP5 (the on-going Wellcome Trust funded project)
- Bovine tuberculosis in Ethiopia: molecular epidemiology and recombinant vaccine development using DNA and attenuated poxviruses constructs (a planned PhD research proposal for Fufa Dawo)

II. Sleeping Sickness (African Trypanosomosis) and Cysticercosis

ILRI has been working on sleeping sickness (18-25) and cysticercosis (26-28), which are among the major neglected zoonoses. Building on its long research history in trypanosomosis research, ILRI has collaborated with local partners, the University of Edinburgh, and FAO in understanding better the potential role of veterinary interventions to control Sleeping sickness in Uganda. The use of mouse model in the design of control of trypanosomosis and malaria (29-32) is significant. Cysticercosis is a highly complex disease affecting both people and pigs. ILRI has been participating in a Cysticercosis Working Group of Eastern and Southern Africa (CWGESA), which promotes effective communication, collaboration and coordination of

integrated research and control activities aimed at combating cysticercosis.

III. Rift Valley fever (RVF)

Rift Valley fever (RVF) is an acute viral disease, affecting mainly livestock but also humans. The virus is transmitted to humans through mosquito bites or by exposure to blood and bodily fluids. Drinking raw, unpasteurized milk from infected animals can also transmit RVF. Routine vaccination of livestock in Africa has been prohibitively expensive, leading to endemicity of RVF in most African countries. Reports in September 2000 first documented RVF occurring outside of Africa in the Kingdom of Saudi Arabia and Yemen. Prior to this outbreak, the potential for RVF spread into the Arabian Peninsula had already been exemplified by a 1977 Egyptian epidemic. This appearance of RVF outside the African Continent might be related to importation of infected animals from Africa.

IV. Avian influenza or bird flu

World concern over the devastation the pandemic has wrought on the poultry business and the deaths, and risk of death, of people whose livelihoods depend on poultry in some affected countries is overshadowed by the risk that this lethal avian influenza virus will mutate and cross over to humans, where it would be transmitted from person to person and could cause a human pandemic. The danger is real: flu pandemics in the 20th century killed 20 million people in 1918, 2 million people in 1957 and 1 million people in 1968.

In Africa, national task forces are being assembled in countries threatened by the introduction of avian influenza through wild bird migrations. South Africa has strong technical capacity and recent experience in successfully eradicating a type of pathogenic avian influenza not caused by H5N1 from its ostrich population. The African Union's Inter-African Bureau of Animal Resources is the coordinating body for combating trans-boundary diseases in Africa. As the implementing agency of the Pan-African Rinderpest Campaign and the Pan-African Control of Epizootics program, AU-IBAR has supported national programs in epidemio-surveillance and provided technical support to national veterinary services.

The Consultative Group on International Agricultural Research (CGIAR) and its partners can support developing countries in their efforts to prevent and control avian influenza in two main ways.

(1) Provide empirical research results and approaches to determine the following:

- The sector-wide impacts of avian influenza and the predicted distributional impacts of options for its control. Studies by the ILRI and its partners of the impacts of disease and disease control options on poor people in Asia and Africa provide relevant approaches and methodologies. ILRI's operating project on animal health and food safety for trade is a partner in a proposal recently submitted for such a study in Southeast Asia. The International Food Policy Research Institute (IFPRI) has investigated the impacts of human health issues such as HIV-AIDS on the poor and analysed risks to the poor related to food safety and biosecurity issues.
- Alternative institutional and market chain arrangements, norms and standards for poultry products, the feasibility of implementing different control plans, and alternative veterinary service delivery options to meet the needs of poor poultry producers and consumers. This research should be linked to ILRI, IFPRI and FAO's Pro-Poor Livestock Policy Initiative (PPLPI) projects on livestock markets in Southeast Asia.
- The benefits and risks of employing alternative methods of preventing and controlling avian influenza outbreaks for poor people and the world at large to guide equitable decision-making on the choice of disease control methods and the incentives needed to ensure compliance with them. The CGIAR has a comparative advantage in conducting studies that assess the impacts, risks and trade-offs of disease control on different groups of poor people.
- The impacts of avian influenza control options on developing countries in terms of their national, regional and international markets and trade in poultry and poultry products as well as other livestock products. This would require research by ILRI and IFPRI to integrate field-level information to enhance the precision of more aggregate macro-economic models, the latter of which are already in existence.

(2) Provide immediate support to help strengthen the capacity of national and regional organizations in developing countries (33), particularly in Africa, in epidemio-surveillance, risk assessment, field study design, analysis of options for new approaches to veterinary service delivery, and decision-support methods and tools. This support can be provided to AU-IBAR and national task forces by ILRI along with FAO, CIRAD, South Africa's Onderstepoort Veterinary Institute, and others. The CGIAR is unlikely to engage in technical research on vaccines and diagnostics for avian influenza, given the comparative advantage of alternative suppliers world-wide. The Group has important roles to play nonetheless. Beyond making immediate responses to help control today's outbreaks of avian influenza, the CGIAR is well-positioned to play a strategic role in accelerating the capacity of developing countries to understand emerging diseases and to design appropriate strategies to deal with them effectively.

One of the important aspects of the work on livestock vaccines involves host functional genomics as it relates to livestock diseases that can be transmitted to humans. A project investigating resistance to trypanosomosis in cattle is shedding light on some of the basic questions of disease resistance, which may have implications for human medical treatment. ILRI researchers first identified several regions of the cattle genome in which genes contributing to resistance or susceptibility must lie. They then identified genes within a part of the bovine genome that affects anaemia, a characteristic of the disease. Remarkably, significant differences between cattle breeds that are susceptible and resistant to the disease were found in one of the candidate genes. Such a result makes it possible that the gene in question is responsible for the difference in susceptibility to anaemia in the two breeds. This is now being further investigated. More recent results of this trypanosomosis genomics research appear to have implications for medical research on cholesterol.

VI. Livestock, water quality, and human health

ILRI has recently initiated limited research on water-mediated impacts on human health and on INRM approaches to reducing health risks. Most of this research falls within ILRI's collaboration with the CGIAR Challenge Program on Water and Food and the CGIAR Comprehensive Assessment of Water Management and Agriculture. Key issues include the transmission of water-borne pathogens such as coliform bacteria, cryptosporidium, and Fasciola that result from animal manure contaminating domestic water supplies and where simple remedial interventions are feasible. One recent MSc thesis demonstrated, for example, that expansion of irrigation into dryland areas may increase the prevalence of sheep Fasciolosis. Livestock keeping may also affect the ecology of water-dependent disease vectors such as mosquitoes. In collaboration with the CGIAR System Wide initiative on Malaria and Agriculture (SIMA), an effort is being made to assess the potential for using cattle management options that can reduce malaria transmission.

VII. Livestock feed quality and human health

Aflatoxin in milk – a possible hazard to human health: ILRI in collaboration with ICRISAT is investigating aflatoxin contamination of fodder (mainly crop residues) as a source of aflatoxin content in milk. In selected sites in Andhra Pradesh, India, close to 50% of the milk samples contained non-permissible levels of aflatoxin. At the same time, only one of the collected fodder samples (groundnut cake) contained non-permissible levels of alflatoxin. Aflatoxin in milk can clearly present a health hazard to the consumer. There appears to be a mismatch between non-permissible levels of aflatoxin in fodder (30µg/kg) and milk (0.5µg/kg) which needs further investigation.

VIII. Food safety associated with livestock and livestock products

This research program has focused on identifying the public health risks associated with the marketing of unpasteurized milk (34-37), with an emphasis on developing policies and technologies for improved quality and safety without jeopardizing market access for the poor. An outcome of this work has been changes in government policies towards more acceptance of raw milk marketing in several East African countries, based on the identified low risks and high dependence of resource poor people on these markets. This work is being expanded, in cooperation with IFPRI, to examine the marketing of other livestock and livestock products, particularly in South Asia. Studies provide policy-relevant analyses of the risks and economic benefits to poor farmers, market agents, and resource-poor consumers (38). ILRI in collaboration with Cornell University (USA) is also analysing the risks faced by the poor of contracting zoonotic and food-borne diseases and modelling the dynamics of these complex, under-reported diseases.

Demand for better quality and safe food is increasing among urban consumers, especially among affluent ones. This poses threats to the market opportunities of smallholder producers who often are unable to access technology, inputs and services to produce high quality products demanded by the market chains serving high-end consumers. ILRI research is trying to understand the nature of quality and safety attributes demanded by consumers, their willingness to pay for such attributes and how smallholders may respond to these through participation in market chains.

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