A methodological framework for attributing the burden of animal disease to specific causes

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Summary

The Global Burden of Animal Diseases provides an analytical framework to measure the overall health of various farmed animal populations, estimate the farm-level burden of different diseases incorporating production losses due to morbidity and mortality, and health expenditure, and identify the wider economic and human health impacts. Attributing the burden of animal diseases to specific causes or groups of causes, requires methodological choices, including the classification of diseases, and the resulting health states that manifest in the loss of production. The aim of this paper is to address the key challenges of the process including the ambiguity in terminology, data availability and collation, and adjustments for comorbidity. Using infection with zoonotic *Brucella* spp. in small ruminants as an aetiological cause of disease and abortion as a sequela of multiple diseases practical examples are provided. Cause-specific attribution of the burden of animal disease captures temporal and spatial trends, which is essential for planning, monitoring, and evaluating animal health programmes and disease interventions.

Keywords

Animal health loss envelope – Attribution – Burden of animal disease – Cause-specific burden – Economics of animal health – Mortality – Production loss.

Introduction

For animal health systems to provide adequate resources for the health and efficiency of farmed animals under their care, governments and other organisations first need to understand the true nature of the health challenges, and how these challenges are changing over time. This requires high-quality, comparable data based on a comprehensive assessment of the health of each population. The Global Burden of Animal Diseases (GBADs) provides an analytical framework to measure the overall health of various farmed animal populations, estimate the farm-level burden of different diseases incorporating production losses due to morbidity and mortality and health expenditure, and identify the wider economic and human health impacts [1,2]. The underlying theoretical assumption of GBADs is that, in the absence of disease, all farmed animals have a maximum physiological production potential [3]. In this context GBADs programme uses a 'yield gap' approach termed the animal health loss envelope (AHLE) and estimates changes in the production system due to all causes of ill-health using a dynamic population model (DPM) [3,4].

A key component for quantifying the burden is the relationship between the presence of the disease in the population and the impact of that disease on production within a farmed animal production system. Broadly, disease refers to a deviation from a normal phenotype, the observable characteristics of the animal, due to genome and environment [5]. Within the GBADs programme disease in farmed animals is defined as the inability to perform physiologic functions at normal levels [3,6]. The outcome of disease is a decrease in the technical efficiency of the production system due to a decreased volume of output without change in the production inputs (labour, feed and management costs), or an increase in inputs needed to achieve the same volume of outputs [7,8]. The cause of disease is typically referred to as its aetiology from the Greek word meaning study of cause. However, one disease entity can have more than one aetiology, and one aetiology can lead to more than one disease [5]. In this context there are two fundamental challenges associated with burden of disease estimates. First, the ambiguity in the use terminology, which is compounded by the inconsistency in how diseases, their causes and their impacts are defined and measured. Second, the various methods used to account for comorbidity, whereby animals or herds that are affected by two or more diseases concurrently.

Economic analyses such as the cost-effectiveness and cost-benefit analyses measure the value of animal health interventions for a specific disease or management of an animal health problem. Such analyses require baseline data on the current burden of the disease, including production losses measured in monetary terms and expenditure on disease mitigation [9], which require methodological decisions and assumptions to be made. If the basic process of the analysis is not adequately described or differs between studies the comparison of different estimates becomes limited. This is exemplified by Kiiza *et al.* who systematically reviewed economic assessments for brucellosis control in livestock populations [10]. Of the 191 articles screened only 11 included details of production losses due to brucellosis, and all four studies with data on small ruminants used different components of loss (i.e. abortion, milk loss, and liveweight) as well as different values of impact (i.e. the proportion of animals that abort due to infection with *Brucella* spp. ranging from 15% to 50%). This is not unique to brucellosis burden studies in livestock, with Di Bari *et al.* finding burden of disease studies in humans also very widely in their methodology and assumptions [11]. The inconsistency of methods and assumptions limit the interpretation of results and comparability across studies, demonstrating the need for a globally accepted framework.

This paper introduces the GBADs framework for attributing the burden of animal diseases to specific causes or groups of causes, including the classification of diseases, and the resulting health states that manifest in the loss of production. To address the key challenges of ambiguous terminology, it identifies key terms such as morbidity and mortality, proposes definitions, and highlights data needs. Methodological choices and assumptions are discussed, including the adjustment for comorbidity. Using infection with *Brucella* spp. in small ruminants as an aetiological cause of disease and abortion as a sequela of multiple diseases practical examples of the methodological framework is provided.

A framework for attributing the burden of animal disease to specific causes

In this section the underlying principles of, and the methodological approach to, causal attribution of morbidity and mortality that are outlined. The examples use data from Ethiopian small ruminant systems and are mathematically modelled using the GBADs

DPMv1.0. All data and results are available in the GBADs Github repository accessed via https://github.com/GBADsInformatics.

The classification of disease

There are multiple ways of classifying a disease entity such as: i) anatomical – the organ or organ system primarily affected; ii) clinical manifestations – known patterns of signs and related findings; iii) aetiology – an underlying explanatory mechanism such as infection by a virus, nutritional deficiency or traumatic injury; iv) severity – degree of resultant ill-health; and v) course and outcome – development of the disease over time with sequelae including death or recovery. Within the GBADs framework diseases are classified in two ways, by aetiologic cause and disease syndrome (termed sequela). Aetiologic causes are further classified into a hierarchy of three to four levels, Level 1 causes are aggregates of infectious, non-infectious, and external causes (Figure 1) [12], Level 2 disaggregates Level 1 by body system (i.e. musculoskeletal) or group (i.e. nutritional disorders), and Level 3 includes specific causes such as *B. melitensis*, pregnancy hypocalcaemia, and predation. For most aetiologies these Level 3 are the most detailed classification, while others may be further disaggregated into Level 4, for example animals infested with specific strains of anthelmintic resistant endoparasites will have reduced production efficiency such as carcase weight and fleece value compared to non-resistant strains even in the presence of health expenditure [13]. The cause list is mutually exclusive and collectively exhaustive at every level of aggregation and causes on this list are mapped to concepts within the United Medical Language System wherever possible [14]. Rather than developing an extensive list of causes, GBADs v1.0 took a pragmatic approach to attribution, where only causes with available data are considered and causes not individually specified are captured in residual causes are classified as 'other'. For example, in Ethiopian small ruminants the burden of infectious diseases (Level 1) is further divided at Level 3 due to zoonotic brucellosis, peste des petits ruminants, and 'other infectious' diseases (Figure 2). The aggregation of diseases at Level 3 for Level 2 will only be possible with the addition of more diseases. As more data become available, granularity is increased with attribution due to more diseases at Level 1 such as gastrointestinal parasites, predation, armed conflict, and nutritional deficiencies incorporated into updated GBADs estimates.

GBADs also makes estimates for disease syndromes, conditions such as abortion that occur as a sequela to a range of aetiologies from all three Level 1 categories (Figure 3). Attribution of the AHLE to a syndrome is useful for two reasons. First, there is likely more data and more confidence of the total number of pregnancies that end in abortion (which is referred to as the abortion ‘envelope’) than data on the proportion of animals affected by a particular aetiology that as a consequence suffer an abortion. In the absence of detailed data on morbidity and impact of specific causes, a large burden attributed to a specific syndrome will identify areas of priority for data collection. Secondly, estimating the prevalence of a syndrome will enable the cause-specific estimates to be constrained within the abortion envelope, that is to sum to the total prevalence of abortion. This approach ensures the combined cause-specific estimates of abortion are not larger than the total, thereby reducing the risk of overestimating the total burden of disease [15].

Morbidity and mortality

The term morbidity has different definitions within the health literature but most simply ‘the condition of being diseased’ [16,17]. In veterinary literature, typically morbidity is the ‘..amount of disease…’ pg 62 [18] expressed as a measure of disease frequency, such a prevalence, incidence risk (or attack rate), or incidence rate, without considering duration, severity, or effect on production. As described in *A Dictionary of Epidemiology*, morbidity is a function of three components: i) persons who were ill, ii) the illnesses that these persons experienced; and iii) the duration of these illnesses [19]. All three components are required to calculate the burden of animal disease, thus the GBADs framework uses the broader definition of morbidity (Table I), incorporating a measure of disease frequency, disease sequelae, and resulting health states measured as changes in the value of production parameters.

Mortality refers to death, and within GBADs it is incorporates deaths directly caused by disease but does not include emergency slaughter or salvage slaughter. It is measured as a mortality rate, the probability of death within a specified period of time. Whilst a seemingly simple concept, absolute mortality rates due to a specific cause will have marked spatiotemporal variation, which then changes proportional mortality ratios for the list of causes in the analysis. This is exemplified by the Tigray war in Ethiopia, which broke out in November 2020 and continued to November 2022. It was estimated that 1.7 million sheep and 3.8 million goats were lost over a two-year period [20]. Assuming constant rate of death during the war, and deaths due to other causes were equivalent to the reported deaths in the 2019 census (200,699 sheep and 648,517 goats), the excess number of deaths per year in sheep was 0.6 million and 1.3 million in goats [21]. The absolute mortality loss for infectious and non-infectious causes remains the same, however these become proportionally smaller compared to mortality loss due to external causes, specifically armed conflict, with an excess annual mortality rate of 30.7% in sheep and 25.5% in goats, additional to the average annual mortality rate for a year without conflict.

To measure morbidity and mortality losses, data are required on the proportion of the population that is affected by the aetiological event, the proportion of those that are symptomatic, the various disease sequelae, their severity and duration, and subsequent health states including death and recovery. This process is defined as a conceptual disease model and is completed for every aetiological cause within the Level 3 cause hierarchy.

Conceptual disease model and epidemiological data

Fundamental to the estimation of the cause-specific burden of disease, are epidemiological models that describe the evolution of disease including onset, severity, duration, sequelae, remission, and case fatality for different age and sex classes of animals within a production system. The GBADs approach models the impact of disease as changes in production, schematically represented as an outcome tree. The significant outcomes (termed sequelae) of each aetiological cause are described, followed by the various health states that best represent the health loss from each sequela, as well as the time spent in each health state [22]. Using a similar approach to Devleesschauwer *et al.* [22] disease models are defined as computational models, which reflect both the pathophysiology (the natural history of disease) along with the input parameters needed to calculate prevalence of disease and production loss associated with each health state. A conceptual disease model is illustrated using zoonotic brucellosis in sheep (Figure 2), with detailed cause-specific modelling descriptions available on the GBADs knowledge engine.

Brucellosis is the generic name used for the animal and human infections caused by several species of the genus *Brucella*. Sheep can be infected by two zoonotic species *B. melitensis* and *B. abortus*, as well as *B. ovis* which infects sheep only and is modelled separately. Common diagnostic serological tests rely on the presence of antibodies, indicating exposure to or vaccination against the bacteria but do not differentiate between the two zoonotic species, hence the term zoonotic brucellosis at Level 3, with bacterial species data further divided at Level 4 if available. Sheep are assumed not to recover from zoonotic brucellosis, which results in one or more sequelae which is dependent upon the age and sex of the affected animal. Hence there are three categories, asymptomatic, acute and chronic (Figure 3). For six age-sex categories, zoonotic brucellosis results one or more sequelae. Data on the prevalence, sequelae, and resultant health state including mortality, are collated for six age-sex groups – female and male juvenile (< 6 months of age), sub-adult (6 to 12 months) and adult (> 1 year), in two production systems – crop-livestock mixed and pastoral, for sheep and goats from systematic reviews and national census data. These data together with national population data were then used to estimate the burden of zoonotic brucellosis in small ruminant systems, which was US$0.16 billion in 2021 equivalent to 0.5% of the total burden (data and visualisation available at https://www.gbadske.org/dashboards).

The role of disease on the reproductive capacity of small ruminants

The reproductive capacity of farmed animals serve two essential functions in small ruminant production systems: i) production of young animals which are sold and slaughtered for meat; and ii) production of young animals to enter the breeding flock to maintain flock size as older animals die or are culled [23]. Within the adult female small ruminant population, this capacity is determined by the individual's age at puberty, the age at first parturition, litter size and parturition interval [24]. For Ethiopian small ruminants age at puberty for females is assumed to occur between 6 to 12 months of age, with first parturition occurring after 12 months of age when individuals move from sub-adult to adult age category within the GBADs DPM.v1.0 [25]. Litter size, variously termed prolificacy rate [25] or birth type [26,27], is defined as the number of offspring per parturition and is largely determined by genetics [28]. Parturition interval is the time interval between successive parturitions in the same female animal. Breeding in Ethiopian sheep flocks predominantly uncontrolled, with adult males and females typically grazing together throughout the year [29,30]. In general, the shorter the parturition interval, the more live births per adult female per year, noting however poor survival of neonates from multiple births reduces the economic benefits [26]. Given gestation length and post-partum anoestrus, the shortest parturition interval could be 6 months for sheep and goats in perfect health living in optimal environmental conditions.

There are many aetiological causes that reduce the reproductive capacity of the population. Diseases such as nutritional deficiencies or heat stress delay puberty and increase the age at first parturition. Other diseases result infertility, abortion or stillbirth which increase the parturition interval in affected animals. It is assumed that within a given year, the genetic composition of the national flock does not vary, therefore the distribution of litter size remains constant. In the GBADs DPM.v1.0 reproduction is modelled using the annual parturition rate (the inverse of the parturition interval) multiplied by the litter size. An increase in age at first parturition is modelled as a decrease in the parturition rate in the first year of adulthood whilst infertility and abortion decrease the parturition rate in all adult females. The probability of parturition is thus bounded by the biological minimum, zero, and the theoretical maximum (0.167 per month), which can then be attributed to specific causes.

Accounting for comorbidity

Comorbidity occurs when an animal experiences several diseases or injuries simultaneously. A comprehensive burden of disease study in which multiple aetiological causes are included, a simple sum of production loss from individual diseases would attribute too much impact to specific causes with the possibility of adding up to more than 100% of the actual burden. Thus, accounting for comorbidity is an important process in the estimation of production losses attributable to specific causes, and there are several methodological approaches.

One approach to address comorbidity is to attribute to the most likely cause by aetiological fractions, with any undefined abortions classified as 'other' and not assigned specific causes [31]. For example, abortion causes considerable production losses in Ethiopian livestock, with estimates of annual abortion percentage of 16.1% in goat flocks, and 12.6% in sheep flocks [30]. In a theoretical population without abortion, the annual parturition rate would increase from the current value 59.0% to 67.5% for sheep in crop-livestock mixed systems [25], which forms the abortion envelope. Abortion aetiology is broadly categorised into infectious diseases including zoonotic brucellosis, peste des petits ruminants, *Chlamydophilia abortus*, *Listeria monocytogenes* and *Coxiella burnetii*, non-infectious diseases such as nutritional deficiencies and external causes such as toxins or extreme weather events such as high ambient temperature manifesting as heat stress [12]. In the study above, farmers were asked the cause of abortion, similar to a verbal autopsy in the human burden of disease study. As perceived by farmers from crop-livestock mixed systems 20% were due to infectious diseases, 22% extreme weather events, 19% malnutrition (feed shortage), 12% trauma and 1% plant poisonings, whilst 27% remained unknown and thus left as 'other causes' [30].

The second approach uses population attributable fractions (PAF) to calculate the production loss for a specific disease [32]. If the individual disease PAF are used, then there is the possibility that added together the total production loss would be more than 100% of the animal health loss envelope. To correct for this the PAF is multiplicatively combined ensuring the combined value does not exceed 100%, but assumes that the diseases occur independently, which may not always be the case. To use this approach data on the prevalence of each disease and the relative risk of the resulting sequalae occurring is required in the population under investigation.

The third approach is to consider the conditional probability as described by Rasmussen *et al.* [15] using odds ratios to estimate comorbidity and assumes that adjusted sequela and health states are in the same proportion as the individual values obtained from the literature. This approach is applicable to health outcomes that manifest in changes in production parameters such as reduction in milk production, which are not as easily bounded by a theoretical maximum. It allows for dependency between diseases, for example cows with hypocalcaemia having twice the risk of ketosis than normocalcaemic cows. If data on inter-disease risks such as odds ratios are available, the assumption that diseases occur independently made in the second approach is no longer required.

All three approaches are used by GBADs, the decision on which approach to use is made on the availability of data and the type of parameter that is being measured.

Conclusions

Whilst the total burden (the AHLE) provides advocacy for animal health budgeting and research into new technologies for improving animal health, disaggregated burden estimates are needed for specific diseases as the baseline from which to evaluate the potential benefits of interventions [1]. Calculations based on individual diseases that do not account for comorbidity can result in an overestimation of the true burden. This may lead to cost-benefit analyses overestimating the benefits. The development of useful mathematical models for estimating the burden of animal disease requires an understanding of the complexity of the system that the model will represent, and identification of the choices available for translating this understanding of complexity into credible conceptual and mathematical models. The methodological framework for attributing the burden of animal disease to specific causes or groups of causes incorporates different approaches depending upon data availability. In making the approach used transparent. will enable comparable estimates and avoid overestimation. It serves as a starting point for an informed discussion on the philosophical and methodological choices used, enabling the framework to be updated and refined.

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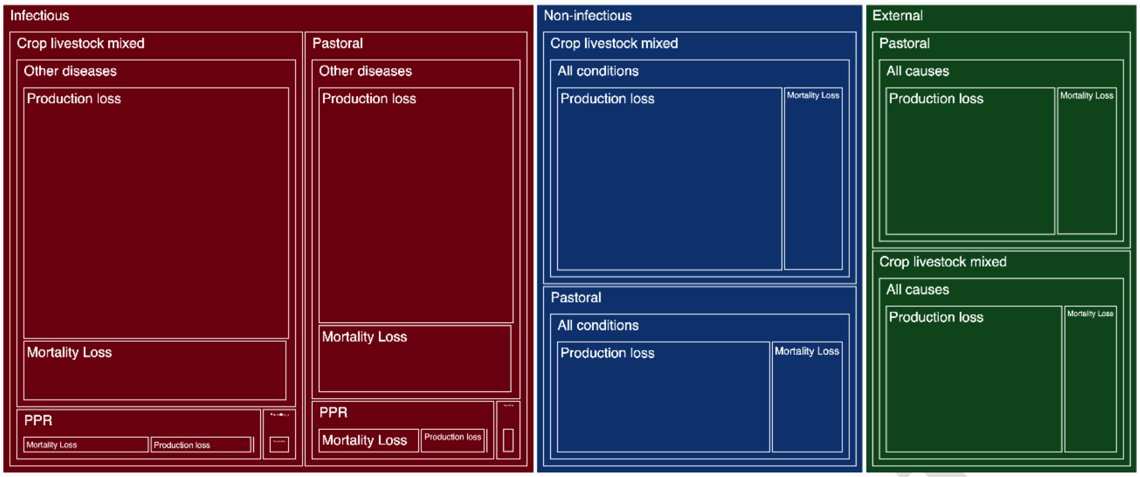
Table I

Glossary of terms and definitions

Term	Definition	Synonyms	Mapping to UMLS concept
Aetiology	The relationship between causes and the effects they produce	Etiology	UMLS concept: C1314792
Burden of animal disease	The impact of disease in a farmed animal population, including morbidity, mortality, and health expenditure. For GBADs this incorporates the impact on the wider economy and human health. This impact refers to various metrics to measure death, loss of health due to, and expenditure on diseases and risk factors		UMLS concept: C4277729
Comorbidity	The coexistence of two or more disease processes in the same animal	Multimorbidy	UMLS concept: C0009488
Conceptual disease model	Computational models, schematically represented as an outcome tree, that describe the significant outcomes (termed sequelae or syndromes) of each aetiological cause, the various health states that best represent the health loss from each sequela, as well as the time spent in each health state	Outcome tree	
Disease	An inability to perform physiologic functions at normal levels in the presence of sufficient nutritional supply and environmental quality the outcome of which is a decreased efficiency of converting inputs such as feed and water, into outputs such as milk and meat		UMLS concept: C0012634
Health state	Reflects a combination of sequelae that result in production loss which is not necessarily unique to a particular disease. Each health state is associated with a change in the value of a production parameter that reflects the severity and is conceptually similar to a disability weight		
Litter size	The number of animals born per litter. It is measured as a distribution, for example proportion of single, twins and multiple lambs in a litter per adult ewe	Birth type, type of birth, prolificacy rate	UMLS concept: C2239272

Morbidity	A measure of disease incorporating a disease frequency, the clinical manifestation of the disease, resulting health states and changes in the value of production parameters		
Mortality rate	The proportion of the population that die during the study period. Mortality is a complex and multi-faceted parameter and may be defined differently depending on circumstances. In GBADs 1.0 the parameter 'mortality rate' is used to refer to deaths directly due to animal health-related causes including: disease, injury, predation, acute nutritional deficits (e.g. starvation), and environmental catastrophe (e.g. droughts, flooding, wildfire). It does not include emergency slaughter or salvage slaughter as these are included in offtake if they have financial value	Death rate	UMLS concept: C0205848
Parturition interval	The time interval between successive parturitions in the same female animal	Birth interval	UMLS concept: C0005605
Parturition rate	The inverse of the parturition interval. The value is the median or mean number of litters per adult female per time interval		
Sequela	The pathological condition (such as abortion) resulting from a specific aetiology. Each sequela may be a consequence of multiple aetiologies and can be mapped to one or more health states resulting in a change in the value of a production parameter (such as reduced parturition rate)	Syndrome	UMLS concept: C0543419
Zoonotic brucellosis	Infection of a particular host species by *Brucella melitensis*, *B. abortus*, *B. suis* or *B. canis*	Brucellosis*	UMLS concept: C0006309

GBADs: Global Burden of Animal Diseases
UMLS: Unified Medical Language System
* although termed brucellosis within the UMLS, it is mapped to the broader concept 'bacterial zoonosis'

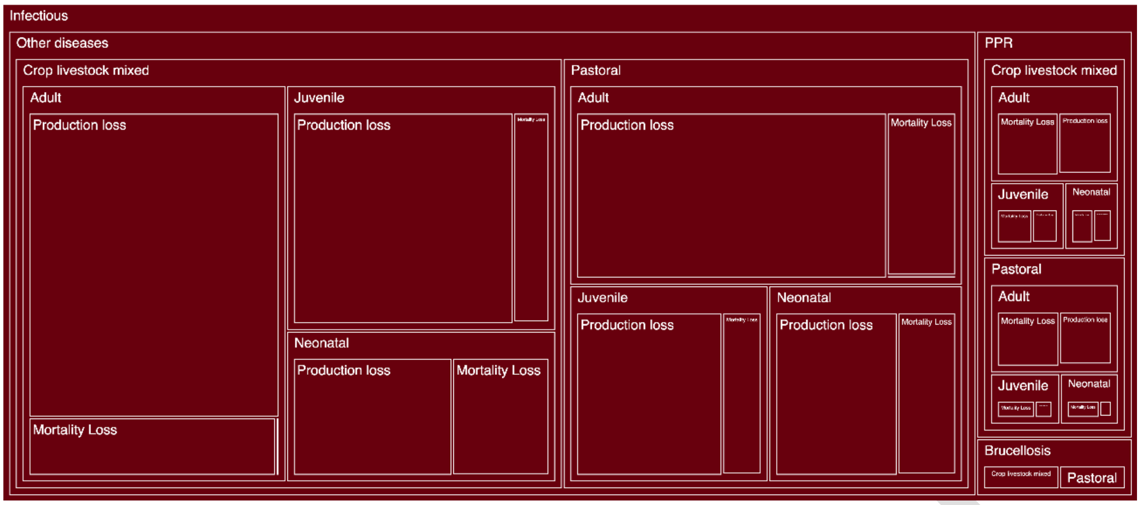


PPR: peste des petits ruminants

Figure 1

The Level 1 attribution of the burden of disease in Ethiopian small ruminants to infectious, non-infectious and external causes

Level 1 is disaggregated by production systems (crop-livestock mixed and pastoral) by component (production loss, mortality loss and health expenditure, and by age-sex category. Health expenditure accounted for less than 1% of the burden and is therefore not visible

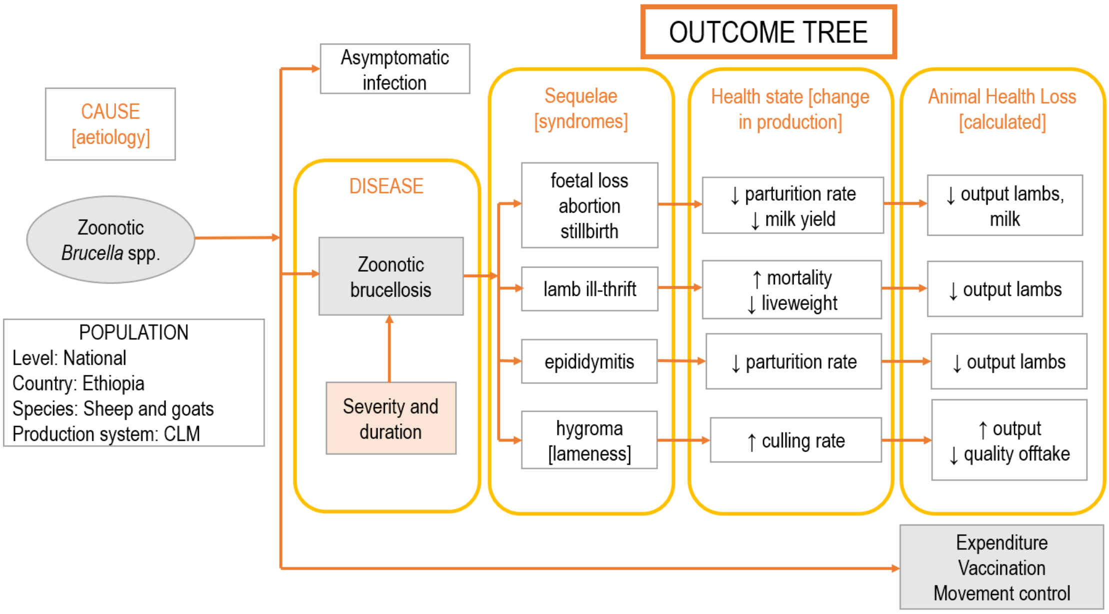


PPR: peste des petits ruminants

Figure 2

The burden of infectious diseases in Ethiopian small ruminant production systems including production loss, mortality loss and health expenditure

Within this total burden envelope, cause-specific burden is estimated for PPR (top right thick white box) and zoonotic brucellosis (bottom right white box)



CLM: sedentary crop-livestock mixed systems in rainfed temperate and tropical highlands of Ethiopia as defined by Jemberu *et al.* [25]

Figure 3

An example of a conceptual disease model for zoonotic brucellosis in sheep

In this example, the sequelae of a symptomatic infection are age-sex dependent; a proportion of infected pregnant adult females suffer abortion whereas a proportion of adult males suffer epididymitis, however both manifest as decreased parturition rate (health state)