4 Forensic Science and Applications to One Health

Lloyd Reeve-Johnson[1]* and David Bailey[2]*
[1]*Institute of Health and BioMedical Innovation, Queensland University of Technology, Brisbane, Australia and Principal Research Fellow, Translational Research Institute, Brisbane, Australia;* [2]*Department of Forensic and Crime Science, Staffordshire University, Stoke-on-Trent, Staffordshire, UK*

4.1 Introduction

David Bailey

Currently (in 2015) in the UK there are scientific databases being constructed and built for the use and application of evidence-based veterinary medicine. But while the hierarchy of evidence for evidence-based medicine leaves expert opinion as the lowest-ranked in terms of quality, it does not provide any criteria to define the term 'quality' of evidence. The pyramid in Fig. 4.1 is widely used as an accepted tool to rank the *quality and strength* of evidence used to base clinical decisions upon in veterinary science, yet it is a tool that demonstrates caution in the over-use of personal experience in the application of evidence-based medicine and the construction of an evidence-based medicine tool.

*Corresponding authors: lloyd@goydpark.com; daysbays@yahoo.co.uk

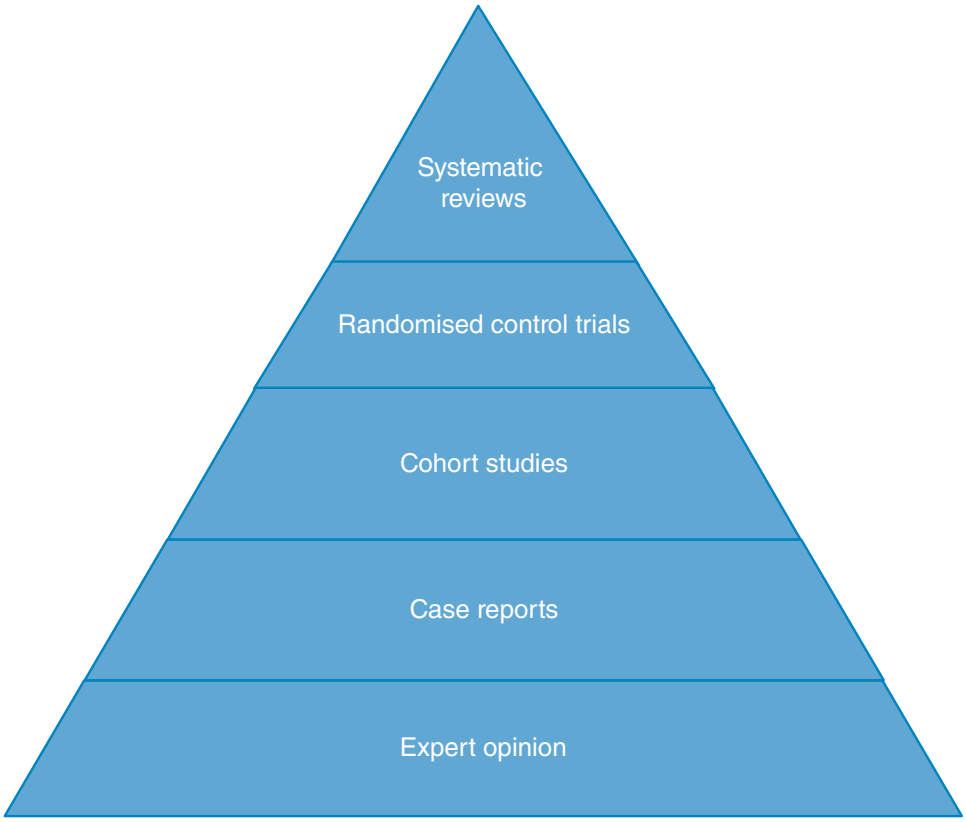

Fig. 4.1. Schematic representation of the 'hierarchy of evidence'.

In contrast, the use and application of expert opinion is the preferred method of dealing with disputes as they arrive and progress through the judicial process, and the use and reliance of meta-analyses and other higher 'quality' indicators are not the preferred tools for use in a legal dispute. The hierarchy of 'quality' of evidence is flipped upside down in a legal dispute, with professional opinion being the preferred tool on top of this judicial pyramid of strength and quality of evidence. Here is an important difference in the acceptance of forensic science into the scientific world. The higher 'quality' indicators reserved for non-legal academic disputes are fixed in dried ink and are set like concrete, unable to answer, bend, yield or provide answers to that single inevitable marginal example query that is asked of an opposing barrister, that a person can process, analyse and construct the appropriate answer to only under oath. Courts prefer scientists, and not science, to answer questions. Evidence-based medicine is very good at telling you what would have happened and what has happened, but very poor at predicting what is going to happen in biological systems. Evidence-based medicine will tell you what *should* happen, but it is precise at telling you exactly what *has* happened and therefore what you should expect to happen if you follow the same process, conditions and methodology. A scientist should be able to tell you the outcome under different processes, dates, times and places based on the available evidence, and the available evidence cannot do this. Only the scientist can.

Personal opinion can be stress-tested under examination-in-chief and cross-examination, and all the randomized controlled trials and meta-analyses cannot do what an expert can do under questioning – that is, to change its mind and deliver a different possible outcome, result, interpretation or conclusion under appropriate adversarial questioning. This is a major difference between evidence-based medicine and evidence-based testimony. In evidence-based medicine, one allows the findings of the studies and trials to navigate our opinion toward a reliable, accepted and verifiable outcome and conclusion. It is

safe, but sometimes narrow in application. In evidence-based testimony, one reads the appropriate studies, literature and available material and provides another layer of reliability that science despises: we allow our interpretation and our own experiences and application of this material to cover areas which may not be presented in the available literature. It is not as safe, but has a wider application. In the former, you have your opinion handed to you and it is flanked by descriptors such as 'best practice', 'gold standard' and 'good guidance', along with the inevitable inclusion 'the available evidence leads us to conclude … '. In the latter, you seek your own interpretation and opinion from your own analysis of the available evidence as it applies to the dispute, the material and the questions in front of you.

And while the use of the word 'evidence' is being used in both evidence-based medicine and evidence-based legal disputes, a translation is required of what the two uses of the word 'evidence' mean; this translation can be summed up visually by inverting the pyramid of evidence hierarchy.

Translational research is the term adapted to explain the difference between evidence-based medicine and bridging the research results between species, pathogens and situations. And while One Health can be used as a descriptor to bridge the research results between human and non-human species, the use and application of forensic science to research of the species is also a translational research relationship that requires an inverting of the hierarchy of quality evidence that is used in all research. You need to know the subject, know it well and provide interpretation to the relevant questions; and while your opinion is of little value in evidence-based medicine, it is of the highest value in a legal dispute of evidence-based medicine.

This translational research requires the hierarchy of 'quality' evidence to be flipped upside down when making the transition from evidence-based medicine to evidence-based legal disputes. The two are not the same, and an understanding of the concept is required before an understanding of translational research can be enjoyed.

While One Health can be used to describe a world with no boundaries between species in terms of disease, health and welfare, the understanding of the One Health concept requires an understanding of the scientific evidence-based medicine process. Any potential application of legal issues that can potentially stem from One Health issues require a translation and transition away from how we understand and apply science to One Health research and how we again apply this science differently to legal disputes. The science doesn't change between evidence-based clinical science on the one hand and forensic science on the other, but the application and understanding of how it is applied between clinical science and forensic science does change.

An understanding of science allows us the tools to evaluate the scientific use of certain advances, methods and research. The forensic application of science allows us to apply what we know to a legal arena. Translational science is a descriptor which allows us to understand the journey through scientific research into legal application, when the science has not changed but the application has. Problems can arise when one person has the ability or power to evaluate all of the available material, and make a decision based on his or her translation and interpretation of that material into practice. Politicians are usually best placed to make these decisions, and errors in translation are often seen at this political level. Where there are political factors involved in any scientific process, then the hierarchy pyramid is not inverted; it may be replaced with other non-scientific factors that reinforce the political stance on a certain scientific argument. It is at this level, where scientific process is no longer useful and forensic opinion hierarchies are not required, that the scientist in us is allowed to be removed from the decision-making process. Thus there is the emergence and translation of pure science through the forensic application into a tool of the political process; understanding this limit of our input is as important as the understanding of how we

input into decisions and findings as scientists, and how we alter our application of science as legal scientists.

Lloyd Reeve-Johnson

The majority of the world's population live in urban or semi-urbanized environments. In the 21st century, humans tend to perceive the world around them as being shaped more by culture, industry and themselves than by natural history. Vital to understanding, controlling or eradicating disease is a sound understanding of the origins, evolution and reservoirs of infection, and interactions between different species and potential pathogens. Translational research implies understanding the health, husbandry and physiology of different species, as well as the influence of their local environment, before findings can be applied to different situations. This increases the chances of achieving medical research outcomes that are sustainable, effective in practical situations, and attuned to the impact on other species and the environment. Incorporating a broad perspective of the epidemiology of diseases results in improvements in research quality and efficiency. Consideration of multiple dimensions of host–pathogen interactions and the physiology of health greatly strengthens the objectivity of evidence upon which medical decisions are ultimately made.

Research in humans is constrained by personal preferences, lifestyle, religion, culture and ethical boundaries. These factors limit enrolment, restrict randomization, decrease experimental control, confound results and slow progress in comparison to the experimental study conditions typical of animal science research. Evidence-based medicine has been strongly advocated for many years, yet human studies used to generate medical evidence are undermined by the above factors and rely on sample populations that differ from patient populations in health-status, age, race and multiple other ways, due to unavoidable sources of study bias. This was highlighted in a review of 49 of the most-cited papers on the effectiveness of medical interventions in highly visible journals between 1990 and 2004. It was found that by 2005 a quarter of the randomized study trials and five out of six non-randomized studies had already been contradicted (Young *et al.,* 2008).

Human health care is transforming, largely to seek more cost efficiency. Funding is increasingly linked to superior societal outcomes. Technology is necessary, but not sufficient, and is constantly adapting to the reality of competing for resources and optimizing resource reallocation. The true value of time, knowledge and insight of translational approaches to societal goals, including preclinical phases of human health care and the innovation that underpins incremental food production, remains to be fully captured. Animals suffer from many of the same chronic diseases as humans, including heart disease, cancer, diabetes, asthma and arthritis. Sometimes a disease entity is recognized in animals long before it is recognized in humans. The concept of comparative medicine was understood by the ancient Greeks and dissection and studying of animals has long been used to understand human diseases (Olsson, 1969). Comparative anatomical and physiological studies have been responsible for significant advances in medicine: Banting and Best discovered insulin through such work, and Edward Jenner developed the smallpox vaccination based upon observations of cow pox.

While translational research considers issues of bridging research results between species, pathogens or situations, the macroview of interconnectedness between all health issues has been branded with titles such as World Health, One Medicine, Global Health and more recently One Health. Definitions embrace a common theme of collaboration between multiple disciplines, working locally, nationally and globally to attain optimal health for people, animals and the environment (American Veterinary Medical Association, 2008). In an era of specialization, the alarming breadth of this definition should not detract from the importance of communicating collaborative cross-disciplinary approaches to medical research, and of stimulating funding bodies to provide necessary incentives for collaboration to occur. As illustrated in the list below, the importance of collaborations has been formally accepted by many international organizations.

What remains to be seen is how effectively these collaborations will be organized, which ultimately determines whether they will fulfil their potential.

Examples of major organizations which have formally adopted One Health in their formal agendas include the following.

1. USA: American Medical Association, American Veterinary Medical Association, American Academy of Pediatrics, American Nurses Association, American Association of Public Health Physicians, American Society of Tropical Medicine and Hygiene, Centers for Disease Control and Prevention (CDC), United States Department of Agriculture (USDA), US National Environmental Health Association (NEHA), and a number of university centres focused on One Health research.
2. European Union: Belgium: Institute of Tropical Medicine, Antwerp. Sweden: Department of Animal Health; The Infection, Ecology and Epidemiology Network, University of Uppsala, founded an inaugural Chair in 2012 in Integrative Biology. UK: British Veterinary Association; a new Veterinary School at the University of Surrey has pledged to differentiate by making One Health central to their teaching of veterinary students; the Royal Veterinary College in London and the Royal (Dick) School of Veterinary Studies of Edinburgh University recently established new academic staff positions in One Health. The European Association for Veterinary Pharmacology and Toxicology held its first session on the topic in Amsterdam in 2012.
3. Other global organizations: The World Bank, World Health Organization, Food and Agriculture Organization, World Organization for Animal Health, Global Alliance for Rabies Control and The Gates Foundation.

4.2 The Need for Translational Research and One Health Collaborations

In 2010, the human population surpassed 7 billion and is set to reach 9 billion by 2050. Four billion people earn less than US$3000 per year (the majority of the world's population). The world's poorest have the greatest potential to benefit from health care, nutritional and other medical innovations. They are also likely to live in closest proximity to animals often to the point of interdependence for economic, nutritional and health goals. Besides ethical imperatives there are commercial opportunities to offer health solutions to this population. Empirical measures of the behaviour of the world's poorest consumers 'and their aggregate purchasing power suggest significant opportunities for market-based approaches to better meet their needs, increase their productivity and incomes, and empower their entry into the formal economy' (Hammond *et al.*, 2007, p. 3). Besides altruistic motives, eradicating infection among the poorest makes disease transfer to others less likely. Increasing occurrence of viral and bacterial resistance to treatments that are only affordable in affluent communities, provides motivation to minimize reservoirs of infection elsewhere. Translational approaches to health care are highly relevant to many macro-economic challenges of the future including: food production, poverty, disease spread, disaster relief, sustainability, affordable health care provision, antimicrobial resistance and psychosocial issues.

In 2010 global GDP approached US$70 trillion with human health care expenditure of US$5.95 trillion (pharmaceuticals accounted for US$850 billion) and human retail food expenditure $4 trillion. The capitalized value of animal health delivery was tiny in comparison at US$20 billion. The point is that animal health is substantially undervalued in terms of market capitalization when the value added to other industries is taken into account. Animal research has a vastly disproportionate influence on other markets. It is firmly placed at the meeting point of two dominant markets: human health and nutrition, and impacts other major markets including energy production (see Fig. 4.2). Animals provide: the test-bed for mammalian genetic research into food productivity and reproduction; testing of human medical and surgical innovations; pre-clinical pharmacology and toxicology; and function as sentinels in disease surveillance. Pharmaceutical companies recoup development costs of products which fail regulatory scrutiny for human use,

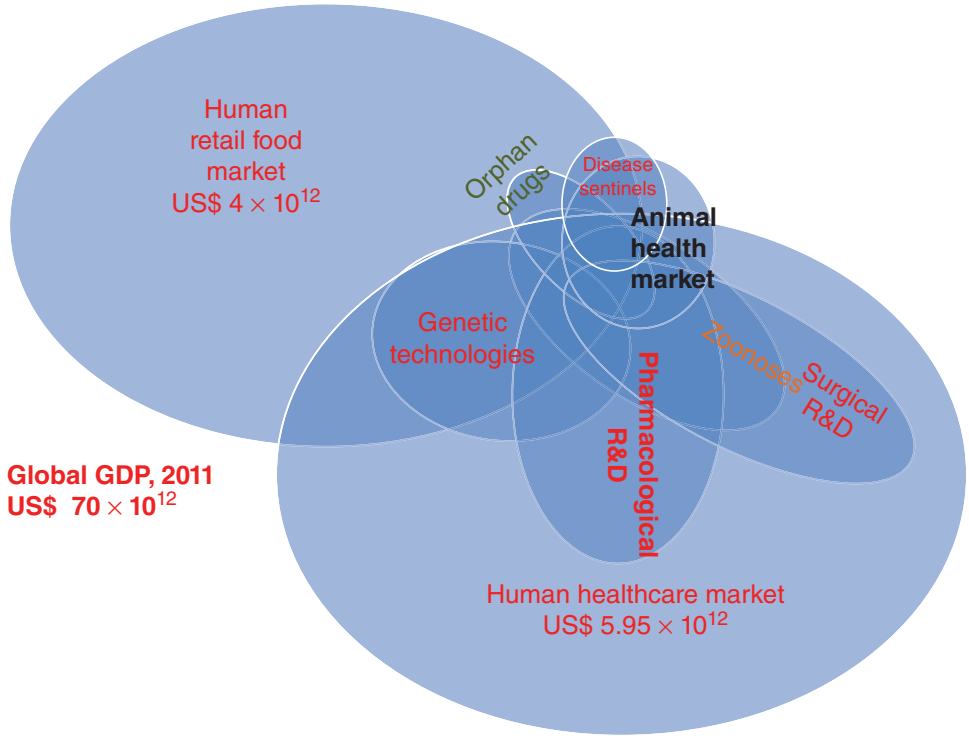

Fig. 4.2. Schematic diagram of approximate market sizes and the interrelationship between expenditure on human health care, human food, animal health care and subsidiary markets.

and commercialize related molecules in animal health that were developed alongside lead candidates for human use. When patent protection in humans expires the animal health market provides additional patent opportunities against generic competition. There is huge value remaining to be captured through improving our ability to 'translate' animal physiology to relevant human contexts and vice versa. Animal models are much more flexible, scientifically controllable, repeatable, less costly and results can generally be obtained much more rapidly with shorter generation times than in human research (Reeve-Johnson, 1998).

Medical and surgical interventions pioneered in animals contribute greatly to the quality of life and longevity of humans. There is a traditional 'linear' view of pre-clinical testing from animals to humans which loses sight of the continuum of results relevant to multiple health issues that can be interpreted across species. No animal is an exact replica of another, yet each animal species provides a new window of enlightenment – each a different perspective of an incomplete picture into potential applications for products, adaptation of physiology, possible toxic reactions, or different ways to harness biological systems. Participants in animal aspects of comparative medicine have for many years failed to adopt a macro-economic approach to quantify their societal impact and ensure this is valued as effectively as contributions by medical professionals. This includes knowledge management and the downstream impact of information and subsequent technological development.

The majority of the world's population still lives in close proximity to animals, and control of zoonotic disease remains vital to public health. The propensity to travel internationally extends the risk of pandemic infection to all communities. Despite this, clinical veterinary and medical research have remained remarkably independent with significant lag-time in adopting innovation between professions. The musculoskeletal system is well suited to comparative medicine. Information gained from one species can be translated to others, advancing diagnosis and treatment.

Since the early 1930s, comparative orthopaedic research has incorporated the One Health concept. Otto Stader, a veterinarian,

used a comparative medicine approach and developed the first form of external skeletal fixation, the Stader splint to stabilize fractures in dogs. During the Second World War, Navy surgeons improved the treatment of fractures in sailors by incorporating Stader's advances. During the 1940s and 1950s, another veterinarian, Jacques Jenny, performed one of the first intra-medullary pinning procedures in animals and significantly advanced fracture repair strategies in horses and humans. In 1966, Sten-Erik Olsson and John L. Marshall, both of whom had medical and veterinary medical degrees, founded the first laboratory dedicated to comparative orthopaedic research at the Hospital for Special Surgery in New York. In the 21st century, comparative orthopaedic laboratories are located throughout the world and use both comparative and translational research approaches in an effort to improve diagnostic capabilities, enhance preventive and therapeutic strategies, and advance the understanding of disease mechanisms. Advances in fracture fixation, total joint replacement, and cartilage repair are examples of how knowledge flows in both directions, to benefit both human and animal health (Cook and Arnoczky, 2009).

4.3 Why Interest in One Health Now?

The cost of human health care coupled with ageing populations is a major economic burden to developed countries. Diseases such as diabetes mellitus and dementia represent a growing threat, not only to patients, but to our ability to keep human health care affordable. A critical role for new medicines will be prevention, treatment and management of diseases suffered by an increasingly ageing population. There are animal models for many 'human' diseases. What is often lacking is relating clinical reference points and applying these across species. As one example, research into the objectivity of using traditional clinical signs to measure disease severity in animals with respiratory infections showed poor correlation between three species, yet these measures are routinely used to justify regulatory approval of new antibiotics and other therapeutic products for use in animals (Reeve-Johnson, 1999). Given that it was possible to gain elective necropsy comparisons at each stage of the disease in these animals to compare clinical and pathological measures directly (which clearly could not be done in humans), this highlights the importance of understanding differences in the way diseases manifest in different species. It also raises the question of validity of a variety of traditional clinical signs used in humans as prognostic indicators.

Changes in antimicrobial resistance patterns have been highlighted as a serious threat to global public health. The World Health Organization raises the possibility of a post-antibiotic era in the 21st century where common infections and minor injuries are fatal (World Health Organization, 2014). This is an area of mutual concern to both human and veterinary health. However, the answer is not as simple as restricting antibiotic use. Treatment and prevention strategies differ between species and this relates to husbandry as much as to pathogenesis. Hospital antibiotic use poses the highest risk of selecting for resistant pathogens in human populations. The practicalities of entire flock medication in feed or watering systems for animals dismay medics; however, repeated studies generally fail to show a link to human health. Although initially counter-intuitive, this is better understood in the context of strictly enforced antibiotic withdrawal periods before slaughter and food-chain entry, competitive exclusion of human pathogens by natural flora better suited to the gut of healthy animals, lack of contact on commercial farms with typical human pathogens, the lack of viable human pathogens in situations that antibiotics are used on farms, and even the potential for benefit through use due to a decrease in bio-burden (e.g. *Salmonellae* and coliform bacteria) that may become pathogenic if allowed to persist to the time of meat processing.

Advances in health-oriented telecommunications, medical imaging, massive database capacity, memory miniaturization, satellite technology, and other information systems are all fundamentally changing the organization of health care. These technologies allow doctors to communicate more easily and quickly and facilitate multidiscipline collaboration.

Health care managers can drive systems in real time. Consumer awareness about health is better than ever before and through the use of interactive cable systems, online forums, and personal health information systems, this can occur easily in remote locations, as occurs with the Telehealth and e-Health initiatives, such as that run by the Australian College of Rural and Remote Medicine (ACRRM). Between 2000 and 2005 the number of mobile phone subscribers globally grew more than fivefold to 1.4 billion. The greatest growth is now in developing countries. This provides massive opportunities for outreach, training and remote medical access in disadvantaged communities.

Electronic medical records, once developed into national databases, have the ability to radically change the way patients interact with health professionals and provide patients with the ability to engage more fully in their own health care. They allow costs to be monitored and more cost-efficient ways of allocating public funding to be derived. Patients can schedule appointments, receive reminders or review test results. The explanation of medical terminology can be included, taking cost out of the system and allowing the savings to be reallocated to areas of need. This is already in place with current software for veterinary patient care which provides a useful prototype with less concern on potential privacy issues and an ability to make refinements before application in human medicine. Algorithms, predictive modelling to draw on billions of specific health indicators, outcomes from laboratory data and clinical information, and even insurance claim history can comprehensively describe an individual patient's health status. Using the rules of probability, a computer can weigh the data against a patient's particular needs and help the clinician determine which treatment option is most likely to work. Other algorithms take sets of rules for how to treat a disease or condition and translate them into formulae derived by a peer-reviewed system within each health speciality, which generates a comprehensive list of treatment options useful for remote diagnosis and treatment. Using a computer or handheld device, the physician can use an algorithm to get a treatment plan that is based on best practices and the patient's unique needs. The capability is already available in the databases of the largest veterinary practices, yet this prototype for much larger and more costly human versions has not been fully leveraged.

The expectation of 'personalized medicine' is that screening will reveal whether an individual is likely to respond well to a drug, highlight risk factors and avoid toxic side effects. A targeted approach to treatment can ensure that each patient receives the right medicine at the right time. One example is screening for Human Estrogen Receptor (HER) display to determine treatment and prognosis in the management of breast cancer. Since molecular diagnostic tests can reveal a patient's susceptibility to disease, they can also guide preventive treatment before symptoms arise. The emergence of personalized medicine will shift the focus of medical care from 'disease treatment' to 'health care management'. Many animal genomes were mapped before the human genome. The use of genetic markers to screen populations for risk factors are being developed. Increasingly, therapeutics will be guided by predictive evidence from genetic and other molecular tests. Safety evaluations will continue to use animal toxicology as a final screen, and disease models in animals will continue to play a role in the evaluation of the safety and efficacy of new pharmaceuticals in the future.

New modes of pharmaceutical research go beyond high throughput screening trial-and-error approaches to molecular design: microorganisms may be genetically modified to carry out specific tasks, lock onto specific receptor sites in the body, or target pathogens. Nanotechnology, the science of building molecular-scale machines, also holds the promise of a completely new type of treatment, from a translational science approach between engineering and medicine. Tiny machines with the tools and intelligence to perform specific tasks are being developed to kill viruses, repair cells, and manufacture proteins or enzymes.

The biggest immediate impact of health care innovation is likely to be more effective use of the techniques that we already have. Improvements in efficiency require integrating our understanding across different paradigms

and the willingness to implement changes to current practice. This includes better pharmaco-vigilance data, leading to changes to dosage regimens, management of external sources of infection, and immune modulation of patients. There is still much progress to be made in refining the use of existing treatment options. In developing countries, many easily solvable health problems require improved access to treatment and innovative ways of providing cheap and locally available preventive measures rather than new technology per se. Approaches that also incorporate the interdependent health status of humans who live in close proximity with animals (including vectors) will have most effect. In human medicine, despite huge budgets, reducing cost is a major driver for change. In contrast, veterinary medicine has always been cost-constrained and has evolved with a culture of seeking cost-efficiency, limiting diagnostic testing to the essential, and the ability to demonstrate return on investment to a full fee-paying clientele (akin to countries where there is no social security safety net). There are also differences in diagnostic tradition, where human medicine prioritizes clinical history above the physical examination, while veterinarians have been shown to minimize collateral history-taking from owners and rely predominantly on physical examination of patients to form initial diagnoses (Reeve-Johnson, 2012). There are still huge amounts that each medical discipline can learn from the other.

4.4 Macro-economic Issues of the 21st Century Where Animal Health-based Innovation is Integral to Human Survival

4.4.1 Food production and security

Food and Agricultural Organization figures indicate that total demand for food will rise 70% in the 44 years from 2006 to 2050. Meat demand in particular is predicted to increase strongly and it is forecast that, by 2050, double the current level will need to be produced (The Economist, 2011, p. 6).

The scale of problems that can arise when an integrated approach is not taken to either biological or chemical contamination is vast. Many cooked meat factories can process in excess of 1000 t of meat each week (approximately 20 million individual servings). These meat products move rapidly into a very diverse range of products distributed internationally, e.g. sandwiches, tinned foods, pizza toppings. In 2008 a product from a cooked meat factory in Canada became contaminated with *Listeria monocytogenes* and resulted in 26 deaths (Attaran *et al.*, 2008). The same year in China, contamination of dairy products with melamine caused over 300,000 babies to fall ill, with 53,000 being hospitalized, six deaths, and mass product withdrawals in many countries (Wall, 2014).

4.4.2 Energy demands

The only market that exceeds human food sales or health care in size is the consumption of energy. In 2008 global energy use was 11.29 billion t of oil equivalent, at 7.33 billion barrels/t. This equates to 82.8 billion barrels (bbl). Multiplied by US$85–100/bbl = US$7.0–8.3 trillion, or 10–12% of global GDP. This is relevant to food production because in 2011 it was reported that 40% of America's wheat crop was being used to provide just 8% of their fuel needs for vehicles (The Economist, 2011, p. 4). The European Union has a target of 10% biofuel. This has a substantial effect by pushing up the price of food for humans and animal production. Veterinary drugs used to alter fermentation in the rumen have been applied to selectively enhance fermentative ethanol production, decreasing the amount of wheat diverted to the biofuel market. This market is sustained by the world's developed economies, but results in increases in the price of food, causing a disproportionate burden on the world's poorest.

4.4.3 Poverty

Four billion low-income people, the majority of the world's population, constitute the