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Using economic and social data to improve veterinary vaccine development: Learning lessons from human vaccinology

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ABSTRACT

The drivers of vaccine development are many and varied. They include, for example, recognition of the burden of a vaccine-targeted disease, prioritisation of the multiple problems associated with a disease, consideration of the differing socio-economic situations under which vaccines are used, the influence of advocacy groups, and assessment of the feasibility of large-scale vaccine manufacture and distribution. In the field of human health, data-driven development of vaccines is becoming increasingly common through the availability of reliable information on the Global Burden of Disease (GBD) and stringent evaluations of vaccination programmes utilising empirical data on costing and effectiveness, and standardised cost-effectiveness thresholds. The data generated from such analyses allow policymakers, implementing partners, industries and researchers to make decisions based on the best, and most contextually relevant, available evidence. In this paper, we wish to explore the current use of economic and social data for the development of veterinary vaccines. Through comparison with the development of human vaccines, we will look for opportunities in animal health sciences to better integrate socio-economic data and analyses into the process of veterinary vaccine selection, development, and field implementation. We believe that more robust animal health impact assessments could add value to veterinary vaccine development by improving resource allocation and animal disease management.

1. Introduction

Investment in health interventions – be that in humans or in non-human animals, at the individual or group-level (e.g. farm, region, and nation) – requires decisions to be made on resource allocation within a finite budget. Making these health decisions evidence-based requires on the one hand, data on the burden of diseases and on the other, data on the cost and acceptability of the interventions used to combat these diseases within particular contexts. With such data, the optimal combination of interventions can be developed and implemented. In addition, disease control programmes require data on the safety and effectiveness[1] of vaccines, the quality of which depends on the robustness of pharmacovigilance systems and the monitoring of adverse events in vaccinated populations [1].

In the field of human health, there has been vast progress made on understanding and quantifying the global burden of diseases across populations, time and space [2]. There are guidelines to help countries making decisions about vaccination [3], as well as specific guidance on the socio-economic evaluation of vaccine and vaccination strategies [4]. In this regard, cost-effectiveness analyses are the most commonly used economic tool in human health care settings. This approach uses proxy outcomes, such as $ per disability adjusted life years (DALYs) saved or quality adjusted life years (QALYs) averted, to judge the cost-effectiveness of vaccination programmes in human populations. For the adoption of monovalent rotavirus vaccine alone, sixty cost-effectiveness analyses were to date performed [5], demonstrating the high degree to which this

Abbreviations: BNP, Bovine Neonatal Pancytopenia; DALYs, Disability Adjusted Life Years; GAVI, Global Alliance for Vaccines and Immunisation; GBADs, Global Burden of Animal Diseases; GBD, Global Burden of Disease; ICER, Incremental Cost-Effectiveness Ratio; PAHO, Pan-American Health Organization; QALYs, Quality Adjusted Life Years; VE, Vaccine Effectiveness; OIE, World Organisation for Animal Health; zDALYs, Zoonotic Disability Adjusted Life Years.

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[1] Throughout this paper we use the term 'Vaccine Effectiveness', being the 'vaccine efficacy measured by observational studies under field conditions within a vaccination programme' [11].

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type of analysis is integrated into human vaccinology. Yet, the same cannot be said for veterinary vaccinology. A search in Web of Science [6] on the 19th July 2018 showed, for instance, that by using the string search ('human vaccin*' AND (cost-effectiveness OR profitability OR cost-benefit)) 1104 results were obtained, while ('animal vaccin*' AND (cost-effectiveness OR profitability OR cost-benefit)) only provided 160 results. This observation underlines the paucity of socio-economic analyses in veterinary vaccinology. Similarly, the data available from pharmacovigilance systems to explore the safety and effectiveness of veterinary vaccines in the field are, for the most part, of poor quality. In fact, the data on adverse effects and vaccine effectiveness are generally absent due to high under-reporting [7]. So, why are the approaches to the development of veterinary and human vaccines so different?

2. What are the main differences between human and veterinary vaccine development?

The path from the identification of an immune stimulating agent to a marketable vaccine requires significant investment of finance and time, whether the vaccine is intended for human or non-human animals [8,9]. We highlight here however, two specific areas where development of veterinary vaccines lag behind. These being the ability to prioritise potential vaccine targets based upon the quantified burden of diseases and the use of extensive observational field studies in the post-licensure phase to evaluate vaccine safety, effectiveness, and cost-effectiveness under field conditions [10–12].

2.1. Defining priorities for veterinary vaccine development

The context in which human and non-human animal vaccines are developed differs and relates to the diverse value propositions attached to vaccine recipients (i.e. humans and non-human animals). The value of non-human animals has always been dictated by human society and its culture [13] and have varied across time and space, in relation to different roles attributed to non-human animals in society (e.g. food production, leisure, labour and company) [11]. In fact, the willingness to invest in non-human animal health interventions (e.g. in research, development, and health programme implementation) often reflects the different values (e.g. sentimental, and financial) attached to non-human animal species and possible fears related to their diseases (e.g. health). Today, pets have become important companions in life for humans – hence the term 'companion animals' – and their integration into human society has increased, especially in modern Western societies. The market of companion animal vaccines has grown fastest, reflecting an increase in Western investments and concerns in pet wellbeing and healthy practices, as well as in the number of pet owners worldwide. By contrast, the market growth of farmed animal (i.e. livestock and fish) vaccines has mostly been driven by zoonotic diseases (i.e. diseases transmissible to humans) and diseases with significant effects on international trade (i.e. diseases affecting the market share of dominant powers) [14,15]. Including, for instance, highly pathogenic avian influenza (HPAI), foot and mouth disease (FMD), and porcine reproductive and respiratory syndrome (PRRS). In other words, farmed animals have been somewhat marginalised from the debates on veterinary vaccine development and their vaccines promoted purely as objects of human safety and the global economy [16,17]. The individual value of farmed animals as living beings, as well as their contextual value to specific human populations has therefore been neglected. Although largely absent from discussions of veterinary vaccines, many subtle and chronic diseases that are restricted to farmed animals (i.e. enzootic diseases) have, however, a significant impact on farmed animal health and welfare and represent a significant burden for multiple societies, especially in the poorest and most vulnerable countries [17].

Initiated in 1991, the Global Burden of Disease, Risk Factors & Injuries (GBD) study has provided decision makers with 'timely, local, and valid estimates' of the burden of many human diseases, injuries and sequelae of diseases [2]. From this work, priorities can now be set according to the context and the quantified burden of a disease upon a human population in terms of DALYs [18]. Following the same approach, some work has been conducted to quantify a global burden of animal diseases. This initiative has so far been limited to zoonotic diseases with the creation of a Zoonotic Disability Adjusted Life Years (zDALYs) metric [19,20]. Therefore, we are still lacking of a standardised process to quantify the global burden of animal diseases as a whole [21,22]. This paucity of data results, in turn, in an inability to accurately prioritise animal diseases or establish a baseline for the cost-effectiveness assessment of animal disease interventions, such as vaccination, thereby giving space to dominant and powerful voices in the allocation of resources for the control of animal diseases, such as FMD and HPAI [15].

Similarly, although commonly used as a tool for the post-licensure evaluation of human vaccine effectiveness, large-scale post-introduction observation studies are rarely conducted for veterinary vaccines due to a lack of resources and poor demonstration of return on investment [11,23]. In addition, when they exist, as for FMD vaccines in Turkey [24], they are rarely coordinated as part of a national policy, making their implementation more difficult.

2.2. Evaluating safety, effectiveness, and cost-effectiveness of veterinary vaccines under field conditions

With a handful of notable exceptions, socio-economic analyses of veterinary vaccines have mostly relied on *ex-ante* modelling studies [25], including models demonstrating the economic benefit of vaccination programmes against Rift Valley Fever in Kenya [26], rabies in Tanzania [27], brucellosis in Mongolia [28], FMD in Denmark [29], UK [30] and the USA [31,32], as well as a variety of analyses for HPAI vaccination campaigns [33–37]. To maximise their utility, there is, however, a need for further validation of these models with empirical data collected in the field during the roll-out of vaccination campaigns; something that remains relatively rarely applied in the veterinary sciences.

Although several studies exist which analyse the social and/or economic impact of veterinary vaccines, it is very difficult, if not impossible, to compare them due to the variety of methods used and inconsistency in the outcomes measured. This includes, for instance, outcomes such as the determination and comparisons of the total costs of various national vaccination strategies against HPAI [38–42], the savings made on alternative mitigation strategies after the adoption of a vaccine [43], or the increase in household expenditure attributable to a vaccine adoption [44]. Despite the inherent importance of these analyses on an individual basis, the lack of: (1) a standardised metric for quantifying the global burden of animal diseases; (2) standardised methods for determining the cost-effectiveness of veterinary vaccines; and (3) standardised cost-effectiveness thresholds within the veterinary sciences, prevents the comparison and prioritisation of vaccine interventions across animal species, pathogens and geographical localities.

After the thalidomide disaster of the 1960s, pharmacovigilance came to the fore in human health placing heavy responsibility on vaccine manufacturers, public health officials, vaccine programme managers and front line staff to monitor, report and act on human vaccine adverse events [45,46]. By contrast, although recognised and supported by different legislations around the world, veterinary pharmacovigilance schemes in Europe, USA, Canada, Australia and South Africa (e.g. European directive 2004/28/EC and regula-

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tion (EC) no.726/2004) have so far only consisted of spontaneous reporting of suspected adverse events [47]. In this context, the UK is seen as the exemplary scheme within the EU, with the Veterinary Medicines Directorate (VMD) regularly publishing reported events in the Veterinary Record [7]. Interestingly, the majority of adverse events reported in the UK and France are in companion animals and the majority of reports are from veterinarians with similar patterns observed elsewhere, indicating a lack of engagement from various stakeholders outside the veterinary practise of companion animals [47,48]. Moreover, studies in Europe have demonstrated a large degree of under-reporting by veterinarians, undermining the strength of the current systems [7,48]. As a result, the success of veterinary pharmacovigilance remains today questionable, especially given past crises related to the introduction of new veterinary vaccines in the field. A particularly striking example, highlighting the need for both larger scale post-introduction studies and stringent pharmacovigilance in animal health, was the increased incidence in Bovine Neonatal Pancytopenia (BNP) in calves born to dams previously vaccinated with PregSure® Bovine Viral Diarrheal Vaccine (Pfizer animal health) after its introduction in several European countries and New Zealand [49–53]. This severe haemorrhagic disease of calves was characterised by massive thrombocytopenia and some degree of leukopenia, resulting in external and internal haemorrhage around 10 days of age. The cause was elucidated to be vaccine-induced maternal alloantibodies, with an incidence of between 6 and 200 per 100,000 vaccinated dams [52]. Importantly, there was an approximately 3-year delay between the launch of the PregSure® vaccine and the increased incidence of BNP, and the incidence of disease has differed enormously between and within countries due to differences in genetics and/or vaccine protocols [52,53]. Factors such as these indicate why safety decisions based on the results of clinical trials on small numbers of homogenous animals – as are often performed in veterinary vaccine development [11] – are not sufficient for the detection of potential adverse events at a population level. In addition, although current legislation obliges pharmaceutical producers and end-users to report adverse effects, including lack of vaccine effectiveness, frequent non-reporting of adverse events makes such a system particularly weak in monitoring the lack of expected vaccine effectiveness [7,23].

Having examined some of the main differences between human and non-human animal vaccine development, we now present an example of impact assessment conducted in human vaccinology and discuss its implications for the future of veterinary vaccine research and animal health policy. In doing so, we wish to challenge the current processes of socio-economic data collection and analysis in veterinary sciences for the development and implementation of new vaccine policies.

3. Learning lessons from human vaccine development: The socio-economic analysis of rotavirus vaccination in Malawi

Diarrheal disease is one of the leading causes of death in children under 5 worldwide, with rotavirus as the number one causative agent [54]. Rotaviral enteritis was estimated to be responsible for 1,865,000 (95% Uncertainty Interval [U.I.]: 14,43100–22,74600) DALYs lost globally in 2010 [10]. In the sole region of Africa, rotavirus has been estimated to cause around 2,557,000 (95% U.I.: 1,901,000–3,026,000) episodes of severe diarrhoea and 95,000 (95% U.I.: 52,500–151,300) deaths every year [55]. The global alliance for vaccines and immunisation (GAVI) provides support for vaccination programmes in eligible countries, based upon their gross national income [56]. Prior to the introduction of rotavirus vaccination in GAVI-eligible countries, the programme was the subject of an *ex-ante* modelling study. This study suggested that, across eligible countries, the vaccine would be very cost-effective ($43/DALY averted) [57]. Malawi was one of the first African countries to introduce monovalent rotavirus vaccine within their national childhood vaccination programme with the support of GAVI. In collaboration with the Malawi National Immunisation Technical Advisory Group (NITAG), a national vaccine evaluation programme was established, comprising of several interlinking studies. These included sentinel surveillance to investigate changing disease incidence and distribution of rotavirus genotypes, matched and unmatched case-control studies and a large prospective population based cohort study investigating vaccine effectiveness and cost-effectiveness [58]. These studies provided country-specific empirical data on vaccine effectiveness (VE), including within sub-populations, such as those with co-morbidities (e.g. HIV and stunting), and the cost-effectiveness of the vaccination campaign. Cost-data were captured at the level of the patient, household, healthcare provider and national vaccination campaign, and using the TRIVAC 2.0 model projected the incremental cost-effectiveness ratio (ICER) over a 20-year period (2014–2033). Overall, the Malawi's monovalent rotavirus vaccine demonstrated 63% VE, with no significant reduction in VE in HIV-infected or stunted children. This resulted in a 43% reduction in the burden of rotavirus in hospitals. To date, no specific genotype has emerged to suggest vaccine escape and the incremental cost-effectiveness ratio of introducing the vaccine was determined to be $10/DALY averted [59,60]. Given Malawi's 2016 GDP per capita of approximately $300, this vaccine appears, therefore, to be highly cost-effective according to the WHO threshold [61].

Overall, these data have provided a strong evidence-base for continued support of the vaccination campaign, especially as Malawi will be required to increase the proportion of their co-payment for the vaccine over time (the GAVI-alliance currently subsidises much of the vaccine cost). Moreover, the TRIVAC model developed with the support of the Pan-American Health Organization (PAHO) has also been made available to the majority of low and middle-income countries. It is used by national teams to evaluate the impact of new childhood vaccinations, and specifies parameters to calculate costs of vaccination, prevented healthcare costs, number of cases averted and the incremental cost-effectiveness ratio in terms of $/DALY averted [62]. Fig. 1 demonstrates the breath of data collected in post-introduction studies and incorporated into the TRIVAC model, which influence the context-specific incremental cost-effectiveness ratio. Parallel to these specific models and systems of impact assessment, a project led by the World Health Organization, assisting members to choose health interventions that are cost-effective (WHO-CHOICE project), has developed threshold guidelines. These latter suggest that an intervention costing less than 3 times the per Capita GDP per DALY averted is cost-effective, while interventions costing less than 1 should be considered highly cost-effective [61]. There is debate, however, around the validity of these thresholds recommended by WHO-CHOICE, with some suggesting that, as an independent metric, it hardly considers what a country can actually afford or is willing to pay for an intervention. Other ways of determining the cost-effectiveness of interventions have therefore been suggested [63]. Yet, the underlying requirement still remains a need for robust and empirical data on both the global burden of disease and the cost-effectiveness of interventions.

By using this example, we illustrate how post-marketing observational field evaluations provide an ideal opportunity to collect empirical data allowing the determination of vaccine safety, effectiveness, and cost-effectiveness. We selected an example from the sciences of human vaccinology as, to our knowledge, there is no equivalent study that would demonstrate an economic analysis being embedded into a veterinary vaccination campaign. Building on this, we wish to highlight the current data needs for animal

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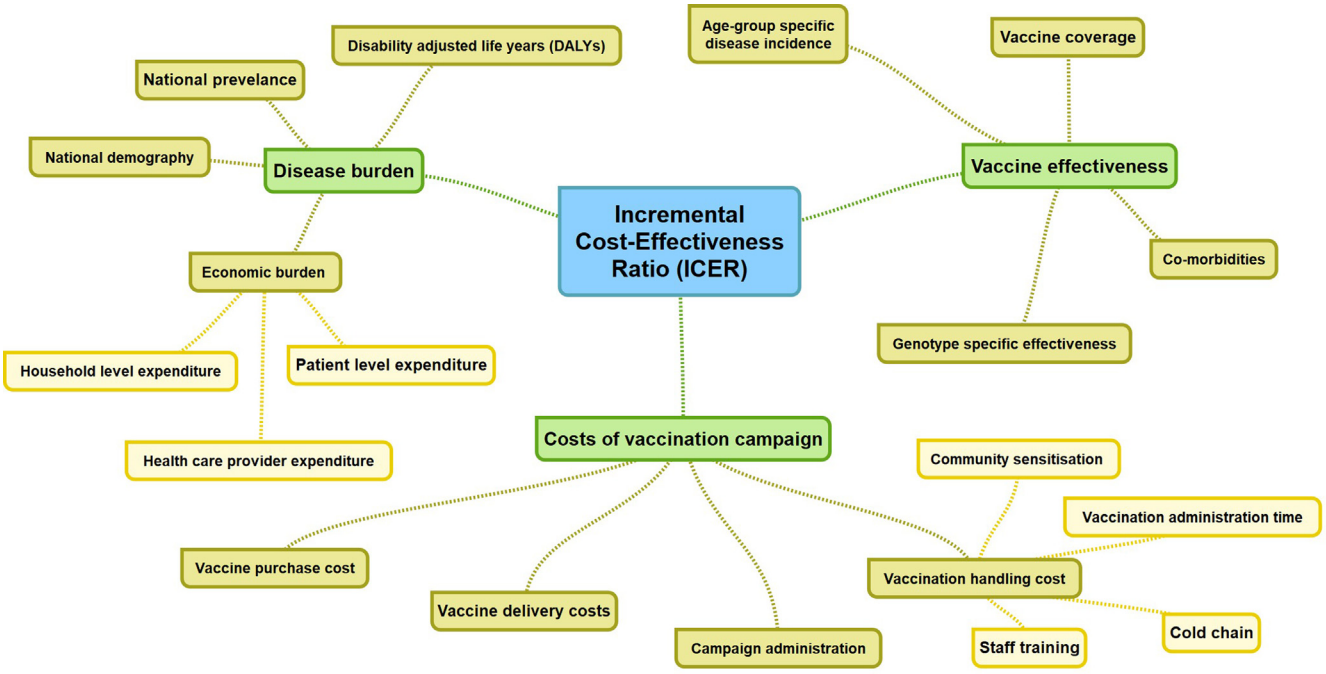

Fig. 1. Data influencing the national level incremental cost-effectiveness of a vaccination programme. (Adapted from the TRIVAC 2.0 model as presented in Bar-Zeev et al. [59,60]).

health, and, more specifically, vaccination decisions, and propose recommendations for moving forward and improving the development of veterinary vaccines.

4. What are the opportunities for improving the use of economic and social data in veterinary vaccinology?

A better understanding of the socio-economic benefits of animal health interventions, starts from an understanding of the burden of animal diseases in specific contexts of animal use and value attribution, along with the demand for and acceptability of different intervention options. In the particular context of vaccine, it is subsequently important to evaluate their safety, effectiveness and cost-effectiveness, since each of these aspects influence the acceptability of the end-user vaccination.

Following the precedent set by the human GBD project, the first planning workshop of the Global Burden of Animal Diseases (GBADs) programme was held this year at the World Organisation for Animal Health (OIE), in Paris [64]. This initiative aims to develop a system that regularly collects, validates, analyses and disseminates information on the socio-economic impacts of animal diseases and disease interventions at global, national and sector levels. GBADs will draw on the core principles of the GBD programme to assess animal disease losses and will incorporate principles of economics and other social sciences to look at net losses and explore current levels of expenditure. In addition, GBADs will support a process of impact differentiation between species and production systems at a national, regional and global level in order to identify points of weak resource allocation between diseases and within specific disease programmes. In quantifying the global and relative burden of different animal diseases, this project will present a strong social and economic case for animal health investments and sustainable vaccine interventions.

Currently, post-introduction studies are rare in veterinary vaccinology because of their high cost and resource requirements and are not perceived as being a good value for money investment. This type of work, however, represents one of the best ways in which data can be collected to better understand the safety, effectiveness, acceptability and cost-effectiveness of vaccines under field conditions. Learning from the useful information generated in human vaccinology, animal health would benefit from vaccination campaigns being designed with integrated post-introduction observational studies. This includes conducting long-term, field-based, prospective cohort studies that capture the full costs of intervention at different levels (e.g. individual, local, regional, national, or international) and assess the occurrence of possible adverse outcomes and externalities, such as those observed during the FMD crisis in the United Kingdom [25]. These studies also provide an opportunity to understand the dynamics, the logistics and the distribution chains of vaccine interventions and the possible challenges of their implementation, especially in terms of societal acceptability. By engaging with various stakeholders, faced with the potential impacts of new vaccine interventions and policies, these studies would also increase the representation of these actors in the design of new vaccine policy and strengthen their participation in the reporting of adverse effects [23]. When public funds are being utilised in vaccination programmes, these analyses, and the engagement with stakeholders, are essential for ensuring value-for-money to society, and this societal value should be considered from the very decision whether to develop a candidate vaccine through to delivery. This way, the re-parameterising of *ex-ante* models with empirical data can improve the quality of our predictive modelling work, the vaccine interventions we design, as well as the decisions we make (Fig. 2). Dialogue with stakeholders and an understanding of willingness-to-pay (from the private and the public sectors) may also foster the development of cost-effectiveness guidelines such as those available from WHO-CHOICE, against which interventions can be measured.

Implementing our recommendations, both in terms of data collection and the establishment of large post-introduction studies for vaccine interventions may be difficult. Resources will be needed for the development of baselines on which to prioritise diseases and, once decided and selected, for the standardisation of the

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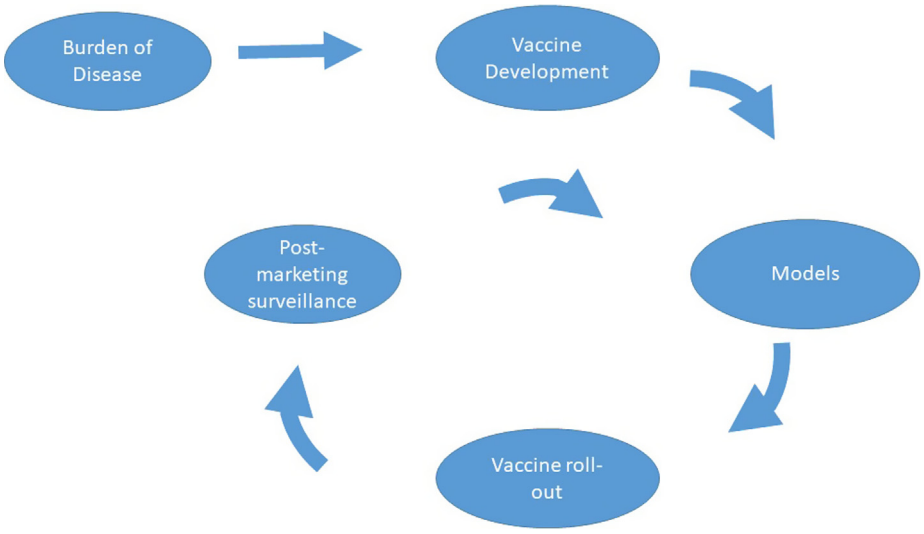

Fig. 2. Data driven veterinary vaccine development.

vaccine protocols and surveillance systems on which the vaccination programme evaluation will be based. These will require the interpretation and use of different sets of data, which in itself may pose challenges related to the requirement for transdisciplinary collaboration, including an understanding of the data, language and expectations of different disciplines and institutions [65]. In addition, ascertainment of animal vaccination status can be a major challenge [58], with valid individual data often lacking, especially in the global South where individual animal electronic records are not available [11]. Robust data, however, are available for larger farms and those involved in rolling out vaccination programmes should be strongly encouraged to improve record keeping for later analysis of vaccine coverage, efficacy and adverse events. The determination of vaccine effect in a setting where multiple interventions may be implemented at once might also be difficult, as well as adjusting for confounding effects between vaccinated and non-vaccinated individuals and assuring quality and consistency of data collection at large scales [58]. Nevertheless, such an initiative will allow the prioritisation of animal diseases and the evaluation of vaccination programmes based on empirical evidence, leading to more effective results for the health of animals and the moral development of societies. If the animal health sciences are to take up the challenge presented here, we believe that this will allow the evolution of thinking from advocacy based on expert opinion to that of multi-source decision-making based on data allowing optimisation and sustainability of intervention programmes at all levels.

5. Summary

The contexts of human and non-human animal vaccinology differ; yet, there is scope for the field of veterinary vaccinology to better utilise socio-economic approaches to demonstrate the value of population-based vaccination campaigns. Enhanced appreciation of the economic and social benefits of veterinary vaccination will assist their uptake by individual animal owners or national governments and, in turn, assist the attainment of the sustainable development goals. As a community, we have built strong predictive models, but these now need to be reviewed and validated with empirical data, preferably collected during large post-introduction studies. The type of work we suggest comes at a cost and requires vision and leadership from public bodies, industries and scientists. The benefits are, however, immense and will improve science, budget allocation and pharmacovigilance of veterinary vaccines.

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Contributions of authors

All authors contributed to the conception, drafting and revision of this article. All authors have approved the final version of this manuscript.

Conflict of interest

The authors declare no conflict of interest.

Authorship

All authors attest they meet the ICMJE criteria for authorship.

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