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Review

Non-specific effects of veterinary vaccines: a systematic review

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ABSTRACT

The benefits of vaccines have been centred on their specific effects on subsequent infections by target pathogens. Recent studies, however, have opened up new insights into additional effects of vaccines known as non-specific effects (NSEs) or heterologous effects of vaccines. While several articles have reviewed epidemiological and immunological evidence for NSEs of vaccines in humans, similar works on veterinary vaccines are scarce. The objective of this paper was to review the findings of published studies on NSEs of vaccines developed or repurposed for use in animals. In total 8412 titles were retrieved from PubMed and CABI databases on the 30th of April 2021. After the final stage of screening, 45 eligible articles were included in the review. Data from these articles were summarised and presented here. In general, most of the vaccines studied in the reviewed articles have beneficial NSEs against multiple pathogens and disease conditions. There were, however, fewe studies reporting detrimental NSEs from both non-live and live vaccines which is in contrast to the currently existing evidence of beneficial NSEs of live vaccines and detrimental NSEs of non-live vaccines. This review may be used as a complement for future review of RCT studies of NSEs of vaccines in animals and provide a useful addition to the evolving understanding of the NSEs of vaccines.

Contents

BCG, Bacillus Calmette-Guérin; DTP, Diphtheria-tetanus-pertussis; MMV, Mumps-measles vaccine; NSE, Non-specific effect; RCT, Randomised Clinical Trial.

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1. Introduction

Vaccines are amongst the most significant discoveries in medicine [1]. Infectious disease morbidity and mortality drastically decreased with the widespread use of vaccines in the 20th century [2]. Examples of vaccines that have played a significant role in the eradication and/or control of fatal diseases include vaccines against smallpox, polio, and measles in humans [3] and rinderpest and rabies in animals [4]. Vaccines also aided the intensification of livestock production and improvement of the health and longevity of pets [5]. Vaccines are used routinely in veterinary medicine to enhance animal health and production (e.g., vaccines against feline immunodeficiency virus, lumpy skin disease, porcine reproductive and respiratory syndrome) and in veterinary public health (e.g., rabies, tuberculosis, and anthrax).

The benefits of vaccines have been centred on the specific immune response against the vaccine-targeted pathogens [6,7]. Recent studies, however, have opened new insights into additional effects of vaccines, other than the specific response, known as non-specific effects (NSEs) or sometimes referred as ‘‘heterologous” or ‘‘off-target” effects [8,9]. Several studies on the NSEs of vaccines challenge the existing vaccine paradigm [10]. For example, immunizations of children with live vaccines such as bacillus Calmette-Guérin (BCG), measles vaccine or oral polio vaccine in high mortality settings were associated with a reduced risk of death, while children receiving non-live vaccines such as diphtheria-tetanus-pertussis (DTP) vaccine were at higher risk of death from all causes [11,12]. Moreover, it has been suggested that NSEs of vaccines vary by sex. Several studies have showed that the detrimental NSEs of non-live vaccines are more severe in girls than boys [13–15].

Animal populations with high mortality are usually located in low-income areas where vaccination is not affordable or accessible for animal owners. Therefore, studies of veterinary vaccines in high mortality settings are rare. In 2015, an observational study in a free-roaming dog population with high mortality reported lower mortality rates in dogs vaccinated against rabies in the absence of rabies outbreaks [16,17]. A follow-up randomised controlled trial, however, showed contradictory result with a detrimental effect of rabies vaccine in female puppies [18]. These inconsistent results highlight the need for more clinical research on NSEs of veterinary vaccines. Several reviews of the literature have collected epidemiological and immunological evidence for NSEs of vaccines in humans, mostly focusing on vaccines such as BCG, mumps-measles vaccine (MMV) and DTP [11,12,15,19,20]. While several articles have reviewed epidemiological and immunological evidence for NSEs of vaccines in humans, similar works on veterinary vaccines are scarce. The objective of this paper was to review published studies on NSEs of vaccines developed or repurposed for use in animals.

2. Methods

2.1. Study design and eligibility criteria

In the present systematic review, we aimed to identify, evaluate, summarize and discuss the findings of published studies on NSEs of vaccines developed or repurposed for use in animals. We conducted search of the literature using the United States National Library of Medicine and the National Institutes of Health Medical Database (PubMed, https://pubmed.ncbi.nlm.nih.gov) and the Centre for Agriculture and Biosciences International databases (CABI, https://www.cabi.org). We did not search grey literature and non-peer reviewed documents. We used the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA, www.prisma-statement.org) statement guide to report the findings. All titles that matched the search terms (Supplemental Table 1) and which were available in the databases as of 30th of April 2021 were retrieved for screening. All languages were considered (see below for the specific protocol for non-English papers).

2.2. Definition of non-specific effects

In the scope of the present review, non-specific effect of a vaccine refers to effect on morbidity and/or mortality that is beyond the specific effect on the target pathogen or disease for which the vaccine is designed. In the literature, heterologous vaccine immunity may refer to immune responses directed against different strains of pathogens (cross-protective immunity) within the same, related or different genera of pathogens. However, in our context, to consider any effect of a vaccine as non-specific, the target pathogen should not be closely related to the organism(s) contained in the vaccine. Therefore, in this review, we defined the term NSEs of a vaccine as the effects against pathogen(s) that is not within the same genus as the vaccine pathogen(s) and it is not included in the vaccine. The vaccine pathogen and the challenge pathogen are assumed to be antigenically unrelated. We consulted the International Committee on Taxonomy of Viruses (ICTV, https://talk.ictvonline.org/taxonomy) and the List of Prokaryotic Names with Standing in Nomenclature (LPSN, https://www.bacterio.net) to determine the relatedness of pathogens at the genus level. The effects of vaccines against tumours were not considered as NSE if the vaccine components included an antigen used as a model for tumour antigen (e.g., the model antigen ovalbumin, OVA).

2.3. Search terms

A list of search terms was prepared using three search term topics (Supplemental Table 1). The first and second topics included terms related to 1) vaccination and 2) NSEs, respectively. While the third topic included a list of diseases with known vaccines (in development or commercialized) in domestic mammals. This list was obtained by screening the books ‘‘Infectious Diseases of Livestock” [21] and ‘‘Infectious Diseases of the Dog and Cat” [22]. For each pathogen, we read the vaccination description, and the names of the diseases were included in the list if a vaccine has been developed in the past or was under development. Alternative and derivative terms referring to a specific disease were included in the list; for example, the search terms for lumpy skin disease included ‘‘lumpy skin disease”, ‘‘Capripox”, and ‘‘Capripoxvirus”. The Boolean operators ‘‘OR” and ‘‘AND” were used between search terms and between topic groups respectively.

2.4. Inclusion and exclusion criteria

The inclusion criteria were: (1) studies of NSEs of vaccines (based on our definition above) in animals; (2) all types of vaccines (recombinant vaccines were considered when NSEs were evidenced by a comparison between the recombinant vaccine with vector and a vaccine of the targeted pathogen without a vector); (3) both experimental and observational studies; and (4) biological products used either as the primary component of immunization or used as adjuvants. Research articles in languages other than English were included for screening after translation to English by professional translators whenever full texts were available. Studies that used animals as a model to test vaccines being developed for use only in humans were excluded. For example, experimental studies of measles vaccine in mice were not included. Studies on influenza or BCG vaccines in laboratory animals were also excluded if the potential use of the vaccines were clearly sta-

Table 1
Summary of studies included in systematic review of the non-specific effects of vaccines in animals.

Reference	Author + year of pub.	Vaccine pathogen (pathogen as adjuvant or vector)	Type of pathogen responsible for NSE	Type of vaccine	Animal Species	Outcome measured to assess NSE	Non-Specific Effect
[26]	Knobel DL.-*2021*	Rabies virus	Virus	Inactivated	Dog	Survival	Detrimental
[18]	Arega S.-2020	Rabies virus	Virus	Inactivated	Dog	Survival	Detrimental
[17]	Knobel DL,.-2017	Rabies virus	Virus	Inactivated	Dog	Survival	Beneficial
[71]	Dolan TT.-1980	BCG	Bacteria	Live attenuated	Cattle	Survival and clinical parameters	Not observed
[44]	Manickam R.-1983	*Corynebacterium parvum*	Bacteria	Inactivated	Cattle	Survival and clinical parameters	Beneficial
[27]	Juste RA,.-2021	*Mycobacterium avium* subsp. *paratuberculosis*	Bacteria	Inactivated	Cattle	Survival and culling rate	Beneficial
[79]	Dineen JK.-1977	*Trichostrongylus coiubriformis*	Parasite	Live attenuated	Sheep	Recovery of mature worms	Beneficial
[33]	Jensen KJ.-2019	*Mycobacterium avium* subsp. *paratuberculosis*	Bacteria	Inactivated	Pig	Pathology of the lungs, recovery of pathogens and body weight	Detrimental
[28]	Jensen KJ.-2021	Rabies virus	Virus	Inactivated	Pig	Survival and need for treatment.	Variable
[35]	LeRoith T.-2011	Porcine reproductive and respiratory syndrome virus	Virus	Live attenuated	Pig	Pathology	Detrimental
[73]	Bwala DG.-2018	*Mycoplasma gallisepticum*	Bacteria	Live attenuated	Chicken	Clinical parameters and pathology	Beneficial
[74]	Huang HJ,-2000	Newcastle disease virus	Virus	Live attenuated	Chicken	Survival and bacterial load	Beneficial
[45]	Bigland CH.-1975	*Erysipelothrix insidiosa*	Bacteria	Inactivated	Turkey	Serum plate agglutination reaction	Beneficial
[60]	Kato G.-2012	BCG	Bacteria	Live attenuated	Japanese flounder	Survival and bacterial load	Beneficial
[50]	Kim CH.-2000	Snakehead rahbdovirus	Virus	Inactivated Subunit	Rainbow trout	Survival, clinical parameters and viral load	Beneficial
[75]	Norqvist A.-1989	Spring viremia of carp virus *Vibrio anguillarum*	Bacteria	Live attenuated	Rainbow trout	Survival	Beneficial
[40]	Scott CJ.-2013	*Yersinia ruckeri*	Bacteria	Inactivated Subunit	Rainbow trout	Survival	Beneficial
[67]	Tabbara KJ.-1975	BCG	Bacteria	Live attenuated	Rabbit	Clinical parameters, parasitaemia and pathology	Beneficial
[68]	Behin R,.-1977	BCG	Bacteria	Live attenuated	Guinea-pig	Pathology	Beneficial
[81]	Davydova VM.-1967	*Brucella* spp. (1) *Yersinia pestis* (2) Tetanus toxoid (3) Diphtheria toxoid (4)	Bacteria	Live attenuated (1,2) Toxoid (3,4)	Guinea-pig	Survival, bacterial load and pathology	Beneficial (1,2) Detrimental (3,4)
[34]	Zhalgasbayeva GT.-1976	BCG (1) Simian virus 40 (SV40) (2)	Bacteria (1) Virus (2)	Live attenuated (1) Live (2)	Hamster	Pathology	Detrimental
[64]	Spencer JC,.-1977	BCG	Bacteria	Live attenuated	Mouse	Survival	Beneficial
[65]	Weintraub J.-1977	BCG	Bacteria	Live attenuated	Mouse	Survival, parasite load and pathology	Beneficial
[62]	Ujiie A,.-1966	BCG	Bacteria	Live attenuated	Mouse	Survival and bacterial load	Beneficial
[41]	Sulitzeanu D.-1962	BCG	Bacteria	Inactivated Live attenuated	Mouse	Bacterial load	Beneficial
[70]	Clark IA.-1977	BCG	Bacteria	Inactivated Live attenuated	Mouse	Parasite load	Beneficial
[63]	Ortiz-Ortiz L.-1975	BCG	Bacteria	Live attenuated	Mouse	Survival, parasite load and pathology	Beneficial
[42]	Ghadirian E,.-1986	BCG (1)	Bacteria	Live attenuated (1)	Mouse	Parasite load and pathology	Beneficial
[24]	Dubos RJ,.-1957	*Listeria monocytogenes (2)* *Corynebacterium parvum* (3) BCG (1) *Mycobacterium fortuitum* (2) *Bordetella pertussis* (3)	Bacteria	NA (2) Inactivated (3) Live attenuated (1) Inactivated (1, 2, 3) Subunit (1)	Mouse	Survival and bacterial load	Beneficial

(*continued on next page*)

Table 1 (*continued*)

Reference	Author + year of pub.	Vaccine pathogen (pathogen as adjuvant or vector)	Type of pathogen responsible for NSE	Type of vaccine	Animal Species	Outcome measured to assess NSE	Non-Specific Effect
[25]	Schaedler RW.-1957	BCG (1) *Mycobacterium fortuitum* (2) *Bordetella pertussis* (3) *Serratia marcescens* (4)	Bacteria	Live attenuated (1) Inactivated (1, 2, 3) Subunit (1) Toxoid (4)	Mouse	Survival	Detrimental
[29]	Bruley-Rosset M,.-1976	BCG (1) *Mycobacterium smegmatis* (2) *Salmonella typhi* (3) *Lentinus edodes*(4) Levamisole (5)	Bacteria (1,2,3) Plant (mushroom) (4) Drug (5)	Live attenuated (1) Subunit (1,2,3) NA (4,5)	Mouse	Phagocytic activity of macrophages on tumour cells	Beneficial
[30]	Germain RN,.-1975	BCG (1) *Mycobacterium tuberculosis* (2) *Listeria monocytogenes* (3)	Bacteria	Live attenuated (1,2) Subunit (1) Inactivated (3)	Mouse	Tumour regression	Beneficial
[61]	Ujiie A.-1966	BCG (1) *Salmonella enteritidis* (2) corticosteroid (3) Carbon (4)	Bacteria (1,2) Hormone (3) NA (4)	Live attenuated (1,2) NA (3,4)	Mouse	Survival and bacterial load	Not observed
[54]	Kato K.-1984	BCG (1) *Listeria monocytogenes*(2)	Bacteria	Inactivated (1,2) Subunit (1) Live attenuated (2)	Mouse	Parasite load	Beneficial
[49]	Kong D.-1997	BCG	Bacteria	Subunit	Mouse	Parasite load and pathology	Beneficial
[55]	Iida T.-1971	*Bordetella pertussis*	Bacteria	Toxoid	Mouse Rat	Survival	Beneficial
[72]	Herod E.-1978	*Brucella abortus*	Bacteria	Live attenuated	Mouse	Survival and parasite load	Beneficial
[46]	Rolph MS.-2004	*Coxiella burnetii*	Bacteria	Inactivated	Mouse	Viral load	Beneficial
[43]	Orme IM.-1983	*Mycobacterium tuberculosis*	Bacteria	Inactivated Live attenuated	Mouse	Bacterial load	Beneficial
[80]	Gorshunova LP.-1970	Rabies virus	Virus	Live attenuated	Mouse	Survival	Beneficial
[47]	Raettig H.-1976	*Salmonella typhymurium*	Bacteria	Inactivated	Mouse	Survival	Beneficial
[77]	Penarete-Vargas DM.-2010	*Toxoplasma gondii* *Neospora caninum*	Parasite	Live attenuated	Mouse	Survival	Beneficial
[32]	Levine S.-1972	*Bordetella pertussis*	Bacteria	Inactivated	Mongolian gerbil Mouse Rat	Pathology	Detrimental
[69]	Langley RJ.-1989	BCG	Bacteria	Live attenuated	Gerbil	Parasite load	Beneficial
[31]	Pauwels R.-1983	*Bordetella pertussis*	Bacteria	Inactivated	Rat	Immunoglobulin E (IgE) response	Beneficial

Descriptions of column titles in Table 1:
Reference: reference of the paper (numbered as cited in the body of the review paper).
Author + year of pub.: name of first author and year of publication.
Vaccine pathogen (pathogen as adjuvant or vector): the test vaccine, adjuvant, or vector as vaccine to which NSEs was investigated.
Type of pathogen responsible for NSE: the type of organism in the vaccine.
Type of vaccine: the type of vaccine (described as live attenuated, inactivated, subunit or toxoid).
Animal Species: the species of animal used in the study.
Outcome measured to assess NSE: specific outcome measured and used as a basis to determine the presence of NSE of the vaccine.
Non-Specific Effect: the presence or absence and type of NSEs.

ted to be for human use. In addition, review articles and comment papers as well as studies of NSEs of vaccines conducted only *in vitro* were excluded.

2.5. Output screening

Screening of the search output was carried out in three stages. In stage 1, two reviewers (SA and AC) screened the list of titles independently. A third reviewer (DK) settled disagreements. The same process was followed in stage 2 for abstract screening. If there was no abstract of selected papers, the full text was screened at stage 2. Finally, all selected articles were read and discussed for inclusion or exclusion by SA and AC during stage 3 of the selection process. Table 1 presents a summary of data extracted from all papers included in the review after stage 3 screening (a more detailed summary of this data is presented in Supplemental Table 2). A few of the articles were written in languages other than English. In most cases, these had English translations of the abstracts (French, German, Japanese, Polish, Romanian, and Russian, etc.). Articles written in other than English languages and that were selected during stages 1 and 2 were translated by a professional translator and the full texts were screened by AC and SA.

2.6. Description of selected papers

A summary of data from selected articles are presented in Table 1. A list of articles without available full text are described in Supplemental Table 3. Each of the included articles was summarised in a table with reference to our review objective (NSEs of veterinary vaccines). Therefore, our summary did not always follow the same pattern as the information provided by the author(s) of the article but focused on the observation of NSEs by the author (s). This means that experiments about vaccine development or specific effects of the vaccine were not described in the tables. Details of the data collected from selected articles is presented in Supplemental Table 2. This table contains eight parts, which refer to (i) reference of the article (5 columns), (ii) the aim and objectives (2 columns), (iii) the vaccine and challenge pathogen or antigen (6 columns), (iv) the study subjects (5 columns), (v) the treatment groups compared (2 columns), (vi) measured outcomes (3 columns), and (vii) conclusion and reviewers' comments (2 columns).

The aims/objectives (ii) of the reviewed articles were retrieved directly from the selected articles, and authors are quoted. The second column described the initial intention of the author(s) to describe a NSE. The columns under the vaccine and challenge

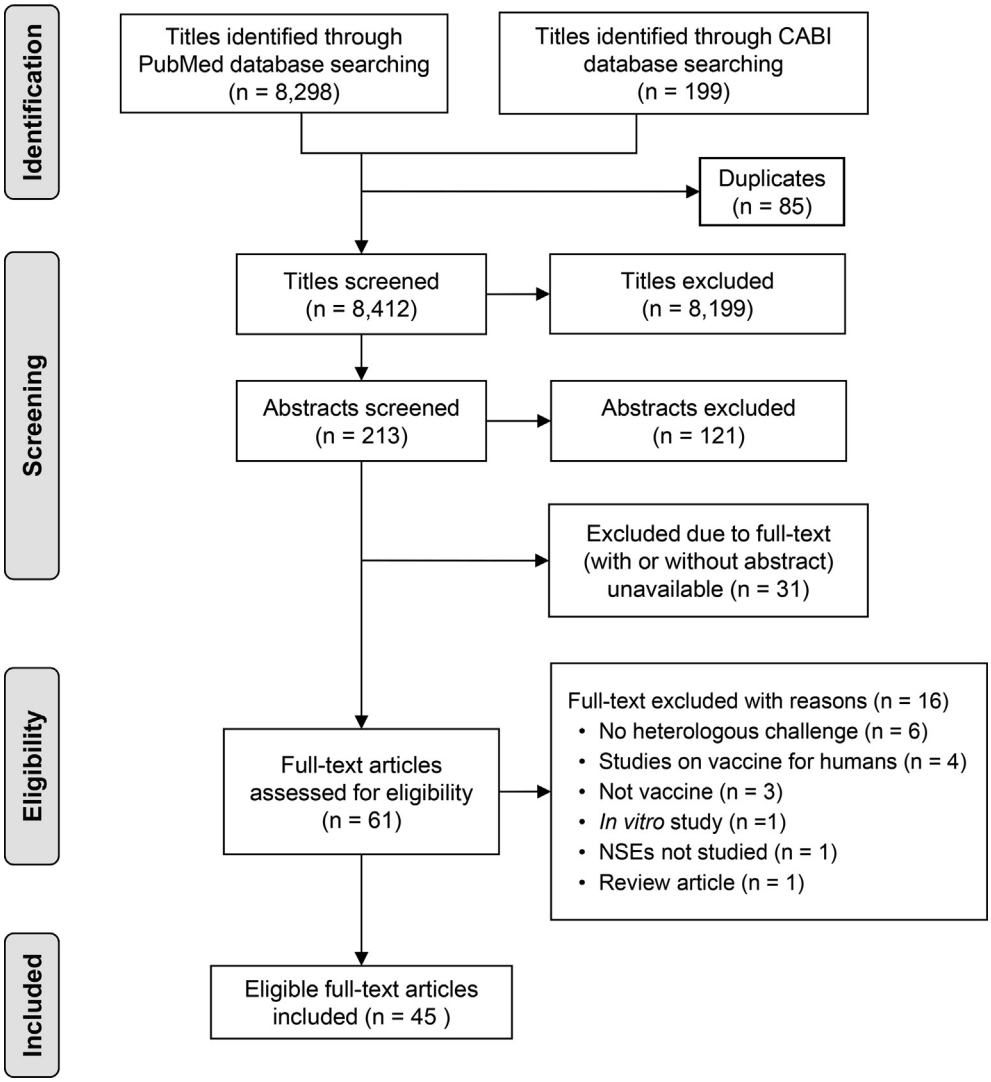

Fig. 1. Flow diagram of identification, screening and selection of literatures for systematic review of non-specific effects of veterinary vaccines.

pathogen or antigen title (iii) describe the vaccine and challenge pathogens, type of the vaccine and routes of administration. Vaccines were categorised into four main types according to previous classification [23]: live attenuated, inactivated, subunit (includes recombinant DNA vaccines or those in which the antigen is produced in bacterial expression systems), and toxoid. When the vaccine component responsible for NSEs was a vector or an adjuvant in the vaccine, the name was included in parentheses. The name of the challenge pathogen/disease in the experiment as well as its route of administration were also described in this part. Study subjects (iv) were described by important features such as species, sex, and breed (or strain for laboratory animals). The intervention and control groups (v) were defined by the reviewers as the groups which were studied for the assessment of NSEs. In some studies, comparisons might have been made between groups for specific effects but not NSEs (e.g., response of a vaccine against its homologous pathogen); however, these experiments were mostly excluded from our table. The columns for measured outcomes (vi) list the major clinical and immunological measurements used for comparing groups, and describe the conclusion as beneficial, detrimental or not-observed NSEs. To determine whether NSEs were observed or not, we looked at if clinical outcomes (such as parameters related to morbidity or mortality), with or without immunological parameters, were observed in the studies. The conclusion (vii) was retrieved directly from the paper (quote from the author) when it was clearly described, while in the comments column we summarised interesting points that might not have been included in the authors' concluding statements.

3. Results

Overall, 8412 titles were retrieved from PubMed and CABI databases on the 30th April 2021. After title, abstract and full text screening, 45 papers were included in our systematic review (Fig. 1). The full text of a further 31 papers that fulfilled the criteria of selection at the title (n = 12) or abstract (n = 19) screening stages were unavailable (Supplemental Table 3). Among the papers included for review, four articles were not written in English (2 in Russian and 2 in Japanese). A summary of the selected papers is presented in Table 1.

The majority of the included articles (n = 28, 62%) described studies of vaccines in an experimental setting using laboratory animals, while the remaining studies (n = 17, 38%) were conducted in natural condition. The majority of experiments were performed in mice and rats (n = 23, 51%). Other laboratory animals that were used include rabbit, hamster, gerbils, and guinea pigs (n = 5, 11%). Vaccine on domestic animals and fish were studied less frequently (cattle = 3, dog = 3, chicken = 2, fish = 4, pig = 3, sheep = 1 and turkey = 1) Table 1.

A summary of the period and the types of journals the studies were published is presented in Table 2. Investigation of NSEs of vaccines was a primary or secondary objective of the study in 35 (77.8%) articles. In the remainder, the report of NSEs was a fortuitous observation. The earliest articles date from 1957 [24,25]. They are from the same authors who investigated the NSEs of *Mycobacterium* and BCG. Since then publications related to NSEs of vaccines have been sporadic, with a peak in numbers in the 1970s (n = 16; 35.6%). A large number of the studies were published by journals of general medicine or infectious diseases (labelled as general in our table) and by immunology journals (n = 19; 42%, in each journal). Seventeen studies were conducted in domestic animals or fish, but only seven of them were published exclusively in veterinary science journals (Supplemental Table 2).

Most of the studies in the reviewed articles investigated vaccines that contained antigens or whole organisms from bacteria (n = 35, 77.8%), followed by vaccines that contained virus or component of a virus (n = 8, 17.8%) and those that contained parasite (n = 2, 4.4%) (Table 3). Overall, 35 various species of vaccine pathogens were tested for their response in the reviewed articles. By far the most frequently studied vaccine was BCG/*Mycobacterium* spp. (n = 23). Other vaccine pathogens that were investigated include *Bordetella pertussis* (n = 5), rabies virus (n = 5), *Listeria monocytogenes* (n = 3), *Corynebacterium parvum* (n = 2), and several other vaccines were investigated in a study. The observed NSEs were generally beneficial (n = 35), but detrimental effect was reported in seven studies. The most recent report of detrimental effect was from a study in dogs with the use of inactivated rabies vaccine [26].

There were forty various types and species of challenge pathogens targeted by most of the test vaccines, whereas no challenge pathogen was used in five studies [17,18,26–28]. In the latter studies, NSEs of vaccines were assessed by the effects of vaccines on all-cause mortality or culling rate and need for treatment against other diseases. In four other studies, NSEs of vaccines were assessed by measuring response to tumour [29,30], allergy [31] or brain injury [32].

The studies used animals of either both or single sex, however, the sex of study animals was not clearly specified in 17 studies (37.8%). Where the sex of animals was specified, only one of the sexes was used in 15 studies (female, n = 10; male, n = 5); while in 13 (28.9%) of the studies both sexes were used. In the studies where apparent detrimental NSE was reported, both female and male animals were used [18,24,26,33,34] while in one study effect was studied only in male animals [32] or the study did not specify the sex of the animals used [35].

4. Discussion and conclusions

Studies on NSEs of vaccines have been extensively reviewed before [12,20,36–39]; however, the focus of these reviews has been on human vaccines such as measles, BCG and DTP. In the present review, we showed that evidence for NSEs of vaccines in animals

Table 2
Year of publication and type of journals included in the systematic review of non-specific effects of veterinary vaccines.

Time Period	Number of papers n (%)	Objective to investigate NSE, n (%)	Journal Scope, n (%)		
			General	Immunology	Veterinary
1957–1970	7 (15.6)	7 (15.6)	6 (13.3)	1 (2.2)	0 (0)
1971–1980	16 (35.6)	15 (33.3)	7 (15.6)	7 (15.6)	2 (4.4)
1981–1990	7 (15.6)	3 (6.7)	2 (4.4)	4 (8.9)	1 (2.2)
1991–2000	3 (6.7)	2 (4.4)	2 (4.4)	0 (0)	1 (2.2)
2001–2010	2 (4.4)	1 (2.2)	1 (2.2)	1 (2.2)	0 (0)
2011–2020	7 (15.6)	4 (8.9)	2 (4.4)	3 (6.7)	2* (4.4)
2021–2021	3 (6.7)	3 (6.7)	0 (0)	0 (0)	3 (6.7)
Total (%)	**45 (100)**	**35 (77.8)**	**20 (44.4)**	**16 (35.6)**	**9 (20)**

* Both veterinary and immunology journals.

Table 3
Type of vaccines, target pathogens, and number of NSEs observed in the reviewed articles.

Pathogen	Live attenuated,n (%)	Inactivated,n (%)	Subunit,n (%)	Toxoid,n (%)	NSEs observed, n (%)				Total, n (%)
					Beneficial	Detrimental	Variable	Not observed	
Bacterium	24 (53.3)	17 (37.8)	7 (15.6)	3 (6.7)	28 (62.2)	4 (8.9)	1 (2.2)[#]	2 (4.4)	35 (77.8)
Virus	4 (8.9)	4 (8.9)	1 (2.2)	0 (0)	4 (8.9)	3 (6.7)	1 (2.2)	0 (0)	8 (17.8)
Parasite	2 (4.4)	0 (0)	0 (0)	0 (0)	2 (4.4)	0 (0)	0 (0)	0 (0)	2 (4.4)
Total	**30 (66.7)**	**21 (46.7)**	**8 (17.8)**	**3 (6.7)**	34 (75.6)	7 (15.6)	2 (4.4)	2 (4.4)	**45 (100)**

Note: Some articles used multiple vaccine organism and vaccine formulations.
NSEs: non-specific effects.
[#] NSE was variable according to the different types of bacterial vaccines studied.

has been demonstrated since the 1950s [24,25]. Although the number of publications increased in the 1970s, most of these studies reported NSEs of vaccines with few details and no further investigations were attempted. This was followed by a dearth of publications on this subject during subsequent 40 years. Out of the 35 studies of animal vaccines with a primary objective of investigating NSEs, 60% of them were published before 1980.

One of the main hypotheses about NSEs of vaccines is that live vaccines have beneficial NSEs while non-live vaccines have detrimental NSEs [39]. In contrast to this proposition, the NSEs of vaccines reported in the reviewed articles are mixed. Some live vaccines presented detrimental effects [25,34,35] while some non-live vaccines showed beneficial effects [17,24,27,30,31,40–47]. In most of the subunit vaccines studied, a beneficial NSE was demonstrated [24,29,30,40,48–54]. On the other hand, detrimental [25] as well as beneficial effect [55] was reported for toxoid vaccines. Although most of the evidence of NSEs of vaccines reviewed in these papers were from either live or inactivated vaccines, the fact that both toxoid and subunit vaccines demonstrated evidence of NSEs shows the need for more investigation of NSEs on these type of vaccines as well. Moreover, as new technologies and better understanding of the immune process have led to the development and use of a wider range and more advanced vaccines, similar studies on NSEs of these new-generation vaccines should be encouraged.

Although BCG vaccine is used in both humans and animals, in this review we looked at studies evaluating NSEs of BCG when it was used or was intended to be used exclusively in animals. Consistent with numerous reports of beneficial NSEs of live BCG vaccines in humans [56–59], animal studies also suggested a similar effect of live BCG vaccine in fish [60], mice [24,25,29,30,42,49,61–66], rabbits [67], guinea pigs [68] and gerbils [69]. Experimental studies in mice that received live BCG vaccine generally showed beneficial NSEs against a large number of pathogens. These effects include decreased severity of diseases following infection with *Leishmania tropica* [65,68], *Trypanosoma cruzi* [63], *Entamoeba histolytica* [42], *Babesia microti* [70] and *Toxoplasma gondii* [67]; reduced bacterial multiplication following infection with *Brucella abortus* [41], *Salmonella enteritidis* [61] and *Staphylococcus* spp. [24,25]; or an increase in local and systemic protection to influenza virus [64]. Protection against non-infectious pathology was also reported for BCG vaccine where it conferred protection from tumours [29,30], although effects on the development of tumours was also reported as detrimental one in another study [34]. Despite a large number of evidence in laboratory animal models, a study in cattle failed to detect a NSE of BCG after challenge with *Theileria parva* [71]; however, the authors acknowledged a serious limitation due to a small sample size. Collectively, these results highlight the need for clinical trials of BCG in farm animals. With an ever-increasing need for vaccination in animal production, optimizing immunization strategies could address the benefits of NSEs of vaccines.

Although less frequently studied than BCG, the other test vaccines in the reviewed articles were more diverse in their nature, type and the study subjects used. Vaccines against bacteria in general focused on diseases that can affect humans and animals: *Bordetella pertussis* [24,31,55], *Brucella abortus* [72], *Corynebacterium parvum* [42,44], *Coxiella burnetii* [46], *Erysipelothrix insidiosa* [45], *Listeria monocytogenes* [30,42,54], *Mycobacterium fortuitum* [24,25] and *Salmonella* serotype Typhimurium [47]. NSEs were also observed for vaccines that are used only in animals including *Mycoplasma gallisepticum* and Newcastle disease virus vaccines used for poultry diseases [73,74]; and *Vibrio anguillarum* [75], *Yersinia ruckeri* [40], Snakehead rhabdovirus and Spring viremia of carp virus [50] used for diseases in fish.

A protective NSE was reported for *Toxoplasma gondii* vaccine, a live vaccine targeting *Neospora caninum* [76,77]. However, this effect was not strong enough to prevent foetal death. Innes et. al. [76], suggested that the vaccine and pathogen parasites share a common epitope exposed in host cells that would explain the heterologous effect (thus, cross-protection rather than a true NSE). NSEs of *Toxoplasma gondii* vaccine were observed with both the live [76,77] and the non-live form of the vaccine [78]. Similarly, protective NSEs were demonstrated with nematode vaccine. Dineen et al [79] reported a protective NSE against adult *Nematodirus spathiger* worms in sheep which were vaccinated with irradiated larvae of *Trichostrongylus colubriformis*.

Vaccines used as adjuvant had also been shown to confer NSEs. This adjuvant property was shown for BCG and other *Mycobacteria* spp. [29]. Apart from bacterial vaccines, NSEs were reported from some viral vaccines such as Newcastle disease virus vaccine [74], porcine respiratory and reproductive syndrome virus vaccine [35] and rabies virus vaccines [17,18,26,28,80]. The evidence for NSEs of rabies vaccines was mixed in the reviewed studies. Some studies including our work from 2017 [17] and another study from 1970 [80] reported beneficial effects while follow up study to our previous study showed detrimental effects [18,26]. Another current study in pigs showed variable NSEs of rabies vaccine depending on the status of rabies vaccination of mother sows and the sex of the piglets from these sows [28]. In this study, rabies vaccination tended to be detrimental in males, but beneficial in female piglets from non-vaccinated sows, whereas maternal vaccination reversed the beneficial effect of rabies vaccination in female piglets to a detrimental one [28]. In fish, DNA vaccines targeting snakehead rhabdovirus (SHRV) and spring viremia of carp virus, induced a non-specific antiviral protection at early stages followed by specific protection at later stages of infection [50].

The lack of consistency in the type and degree of NSEs of vaccines observed in the current review may be due to factors that could modify these effects. NSEs of a vaccine may vary by factors including, among others, strain of the vaccine [44,73] route of administration [55,62], time period between vaccination and challenge [62,74], addition of adjuvants [28,36], sex [28], strain [31,62] and stress before challenge [74] and pre-vaccination muscle exercise

[81] of the recipient host animal and maternal immunity [28]. While all *Bordetella pertussis* vaccines in one experiment showed an effect on IgE production, the magnitude of the effect varied by strain and a synergetic effect was observed with added aluminium hydroxide [31]. NSEs may also depend on the dose of vaccine administered. This was noted in various vaccines (BCG, *Mycobacterium fortuitum* and *Bordetella pertussis*) in an earlier study by Schaedler and Dubos [25]. A higher dose of *Brucella abortus* vaccine induced a stronger non-specific immunity [69] and a higher dose of *Bordetella pertussis* vaccine enhanced the production of total serum IgE [31]. The direct dose–effect relationship was further demonstrated in BCG vaccine. When the dose of BCG was too low, non-specific protective effect was only partial [42]. The effect of BCG on tumour development also varies with the number of boosters [34]. A study by Langley and Gray [69] also indicated that protection by BCG against *Babesia divergens* was dose-dependent [69]. Moreover, the magnitude of NSEs of vaccines was observed to vary by the routes of administration used [29,55,61,64,67]. But in one study the route of administration had no such effect [70]. The route of administration playing a role in altering the magnitude of NSEs of vaccine may be explained partly by the fact that efficiency of the route of administration to increase bioavailability of the vaccine antigen or its components for uptake by patrolling antigen-presenting cells and to continuously stimulate the immune response. It has been suggested that vaccine-induced activation of immune cells in regional lymph nodes might lead to enhanced overall immune recognition. This is particularly important in inactivated vaccines [82].

The other factor that may affect the degree of NSEs of vaccines is the period between vaccination and challenge. Clark and co-workers showed that the BCG-induced suppression of infection was more effective when the interval between the vaccine and subsequent infection (challenge) was longer [70]. Similar observation was made with *Brucella* vaccine [72]. However, the contrary is described for the production of IgE after vaccination with *Bordetella pertusiss* [31]. A longer time period between BCG vaccination and a challenge with *Leishmania major* administration led to diminishing NSEs [49]. On the other hand, vaccination after challenge (even with patent infection) did not afford protection [70] or was detrimental [24,34,35].

In general, the studies on the NSEs of vaccines in animals were preliminary and the evidence of NSEs of veterinary vaccines is scarce. Most of the evidences available from animal studies focused on laboratory animal models. While small laboratory animal models contribute to important findings and breakthroughs in the understanding of the underlying mechanisms of NSEs of vaccines [83,84], their predictive value may not always be strong, leading to translational failure [85]. Hence, the investigation of NSEs of vaccines in animal populations with high morbidity and mortality in natural conditions is of paramount importance.

This systematic review suffers from some limitations due to intrinsic and extrinsic factors in our methods. For example, we might have missed some relevant papers during search and screening process. We attempted to decrease this limitation by using as many alternative vocabularies as possible in the search terms and limiting our search term to three groups of words and phrases. We also did the screening process by two reviewers independently. We believe that this has reduced the chance of missing articles. Another limitation is that, most of the studies in our review articles were non-randomized trials, observational studies and studies whose design and methodology were not clear. Evidence synthesized from a systematic review of RCT is considered to provide the best evidence, however, the number of RCT studies in our review were very limited. Another limitation was that in the majority of the literatures the sampling strategy and sample sizes were not clearly stated.

Despite the limitations, in this review we attempted to synthesise data from literatures published on possible NSEs of veterinary vaccines from 1975 to 2021. We hope this review could be used as a complement for future review of RCTs of NSEs of vaccines in animals and provide a useful addition to the evolving understanding of NSEs of vaccines. Moreover, this review has identified a number of potential vaccines that may have NSEs in various species of animals that have not been investigated before. This will likely initiate an increased interests to researchers to investigate NSEs in various vaccine types and animal species in the future.

5. Data statement

Data will be made available upon request.

CRediT authorship contribution statement

Sintayehu M. Arega: Conceptualization, Methodology, Writing – original draft, Writing – review & editing. **Darryn L. Knobel:** Methodology, Writing – review & editing. **Felix N. Toka:** Methodology, Writing – review & editing. **Anne Conan:** Conceptualization, Methodology, Writing – review & editing.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary material

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