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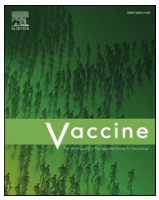

Short communication

Opportunities and challenges for the adoption of novel platform technologies to develop veterinary bacterial vaccines

Gary Entrican [a,*], Helba Bredell [b], Johannes Charlier [c], Adam F. Cunningham [d], Michael A. Jarvis [e,f], Paul R. Wood [g], Brendan W. Wren [h], Jayne C. Hope [a]

[a] The Roslin Institute at University of Edinburgh, Easter Bush Campus, Midlothian EH25 9RG, UK
[b] Afrigen Biologics and Vaccines, 5 Kestrel Park, Longclaw Drive, Montague Gardens, Cape Town, South Africa
[c] Kreavet, Hendrik Mertensstraat 17, 9150 Kruibeke, Belgium
[d] Institute of Immunology and Immunotherapy, University of Birmingham, Edgbaston, Birmingham B15 2TT, UK
[e] The Vaccine Group Limited, 14 Research Way, Derriford Research Facility, Plymouth Science Park, Plymouth PL6 8BU, UK
[f] School of Biomedical Sciences, University of Plymouth, Drake Circus, Plymouth PL4 8AA, UK
[g] Department of Microbiology, Monash University, Clayton, VIC 3800, Australia
[h] London School of Hygiene and Tropical Medicine, Keppel Street, London WC1E 7HT, UK

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ABSTRACT

Vaccine platform technologies provide standardised vehicles for the delivery of diverse antigens to elicit specific immune responses. The deployment of these platforms for novel vaccine development is influenced by a wide range of factors that must meet end-user needs for uptake, which includes cost, frequency of delivery and dependency on cold-chain storage. These factors can be identified by constructing a vaccine target product profile (TPP) that helps to direct the research effort towards the desired goal. The COVID-19 pandemic has exemplified how viral vectored and nucleic acid-based platforms can be rapidly deployed for population disease control. While successful for viral vaccines, the applicability of these platforms for bacteria is less well defined. Bacteria present different challenges to vaccine design from viruses due to their diversity and complexity. Other platform technologies are under development to address these challenges. The more we understand about vaccine platforms, the more adaptable they become, particularly for deployment across species with benefits for One Health. A Workshop was held at the 13th International Veterinary Immunology Symposium (IVIS) in South Africa in November 2023 to discuss the opportunities and challenges in deploying novel platform technologies for vaccine development against bacteria, particularly those that are affordable to low-middle income countries (LMICs). We report here on the outcomes of the presentations and discussions at the Workshop, highlighting the gaps and potential solutions through collaborative global efforts.

1. Introduction

Transformative technologies have been pivotal in the evolution of solely empirical approaches into those that utilise rational vaccine design, replacing a reliance on culture and propagation of pathogens with expressed recombinant antigens delivered in strategic ways to elicit the desired protective immune responses [1]. The past decade has seen a rapid expansion in the development of novel vaccine antigen delivery systems including adjuvants, nucleic acid formulations and viral vectors. The threat of human pandemics with the associated need for rapid vaccine development has been a major driver for research into vaccine platform technologies, the 2014–2016 Ebola epidemic and COVID-19

Abbreviations: AdV, adenoviral vector; AMR, antimicrobial resistance; CBPP, contagious bovine pleuropneumonia; DISCONTOOLS, Disease Control Tools; GHG, greenhouse gas; GMMA, generalised modules for membrane antigens; HIC, high income country; LMIC, low-middle income country; LNP, lipid nanoparticle; LPS, lipopolysaccharide; OMV, outer membrane vesicle; PAMP, pathogen associated molecular pattern; RVF, Rift Valley fever; STAR-IDAZ IRC, Strategic Alliances for the Coordination of Research on Infectious Diseases of Animals and Zoonoses International Research Consortium; STEC, Shiga toxin producing enterohaemorrhagic *Escherichia coli*; TPP, target product profile; VLPs, virus-like particles; vPTMF, vaccine platform technology master file; WHO, World Health Organisation; WOAH, World Organisation for Animal Health.

* Corresponding author at: The Roslin Institute at University of Edinburgh, Easter Bush Campus, Midlothian EH25 9RG, UK.
E-mail address: gary.entrican@roslin.ed.ac.uk (G. Entrican).

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pandemic being cases in point [2,3]. Vaccine platform technologies are defined as 'technologies that utilise a common backbone or vector to deliver specific antigens for vaccine [s] against different diseases' [4]. Once regulatory approval has been given for a vaccine incorporating a novel platform technology and the safety profile and functionality of that platform is defined, the approval of further vaccines that incorporate that technology can be accelerated by collating this information in a vaccine platform technology master file (vPTMF) within the regulatory product dossier [4].

The global response to the COVID-19 pandemic exemplified the portability and functionality of novel vaccine platform technologies (in particular viral vectors and nucleic acids) for inducing protective immunity at scale. Indeed, WHO estimates that national COVID-19 vaccination programmes saved an estimated 1.4 million lives in Europe alone, an unprecedented achievement for vaccinology within such a short time-frame [6]. Valuable lessons have been learned from the COVID-19 pandemic on the comparative immunogenicity of different vaccine platforms and how they are deployed, informing on future vaccine roadmaps with One Health benefits, including veterinary vaccines [7]. Platform technologies vary in a number of fundamental properties, such as thermostability, cost-of-goods, requirements for boosters for protective efficacy and capacity for repeated use. All of these factors will influence how vaccines are deployed in the target population, be that in humans or animals, emphasising the importance of considering the vaccine target product profile (TPP) at all stages of research and development [8]. Our knowledge of the functionality of vaccine platform technologies and their ability to induce different immune responses is expanding rapidly, creating a solid base for informed decision-making on platform selection for vaccine development. To date, viral-vectored and nucleic acid platforms have largely been used for vaccines against viral diseases, whereas vaccines against bacteria have relied largely on killed organisms, bacterial fractions (including toxoids) and protein conjugate-based technologies for both human and veterinary medicine [9].

With this backdrop, a number of funders and networks came together to organise a vaccinology workshop at the 13th International Veterinary Immunology Symposium (IVIS) in Kruger, South Africa in November 2023 to discuss the opportunities and challenges for adopting novel platform technologies to develop next-generation vaccines against bacteria in veterinary species. Of particular focus was addressing gaps and unmet needs for antibacterial vaccines for farmed animals that can improve One Health, reduce antimicrobial usage and subsequent antimicrobial resistance (AMR) and be deployed in low-middle income countries (LMICs).

2. Gap analyses for identifying and addressing unmet needs in veterinary vaccinology

Community-driven gap analysis conducted by an expert working group is an informed way of identifying unmet needs for disease control through vaccination. Such gap analyses can help funders make strategic decisions on research priorities and can focus the efforts of applicants for that funding. The Workshop comprised seven short presentations designed to stimulate thought processes for the breakout discussion groups focussing on key challenges and gaps in current capability (Box 1). Part of this process is ensuring that vaccine will be fit-for-purpose for the relevant end-users by considering the TPP.

3. Constructing a vaccine TPP

The construction of a TPP is the starting point for any commercial vaccine project to ensure that the final product will be fit for purpose and can also be used to market the product to the target population. The earlier the TPP is constructed, the more focussed the research effort will be; TPP development therefore has value even at the earliest stages of academic research [8]. The TPP should address the unmet need for a new product and take into account any barriers that might prevent deployment in the target population. Generally speaking, the cost-of-goods and purchase price need to be lower for veterinary livestock vaccines than for vaccines for companion animal vaccines and humans. These cost demands become even more challenging when developing affordable vaccines for deployment in LMICs as opposed to (or in addition to) deployment in high-income countries (HICs).

Construction of the TPP should follow a defined process by systematically evaluating the product profile against a list of vaccine attributes, taking into account the variables for each attribute and also clearly defining any characteristics that are unacceptable for the final product profile. As an exemplar, Table 2 shows the TPP for development of a novel vaccine to reduce greenhouse gas (GHG) emissions from farmed ruminants as part of the efforts of The Global Methane Hub to combat climate change, with methane emissions estimated to have contributed to 30 % of the current global warming [10]. The various criteria can be evaluated using existing products or procedures that are known to be acceptable to regulators and end users, such as comparative safety, number of doses and incorporation of adjuvant formulations or platform technology in a vPTMF that accelerate time to market (Table 2).

Most livestock producers would like cheap, thermostable, single-shot, multivalent, DIVA-compliant vaccines. Incorporation of a TPP into the vaccine research roadmap helps to identify gaps along the development pipeline. These gaps can sit anywhere along the pipeline

Box 1
Presentations at the Workshop.

1. Introduction, background and the challenge (Jayne Hope[1] and Gary Entrican[1,9])
2. The importance of designing the vaccine TPP for translational research (Paul Wood[2])
3. Outer membrane vesicles (OMVs) for bacterial vaccinology (Adam Cunningham[3,4])
4. Bacterial glycoconjugate vaccines (Brendan Wren[5])
5. Viral vectors for veterinary vaccinology (Michael Jarvis[6,7])
6. mRNA platforms for veterinary vaccinology (Helba Bredell[8])
7. STAR-IDAZ vaccine roadmaps (Gary Entrican[1,9])
8. DISCONTOOLS bacterial vaccines gaps (Johannes Charlier[9,10,11])

The presentations were designed to provide background to the challenge of developing anti-bacterial veterinary vaccines and set the context for the questions addressed by the discussion groups (see Box 2). Speaker Affiliations: [1]The Roslin Institute at the University of Edinburgh, UK; [2]Monash University, Melbourne, Australia; [3]Global Bactivac Network; [4]University of Birmingham, UK; [5]London School of Hygiene and Tropical Medicine, UK; [6]The Vaccine Group Ltd, Plymouth, UK; [7]University of Plymouth, UK; [8]Afrigen Biologics and Vaccines, Cape Town, South Africa; [9]STAR-IDAZ Global Research Alliance; [10]DISCONTOOLS; [11]Kreavet, Kruibeke, Belgium.

and may include fundamental research into the biology of the pathogen and host immune response if such knowledge is lacking. In such cases the TPP may have to be loosely defined and should not preclude the development of first-generation protective vaccines. Second-generation vaccines that improve on their predecessors can be developed as new platform technologies emerge to address market needs. An example is vaccination against human hepatitis B when the vaccine based on inactivated purified virus was superseded by a highly efficacious recombinant antigen vaccine delivered in virus-like particles (VLPs) [11].

4. Platform technologies for vaccines against bacteria

An undoubted positive outcome of the COVID-19 pandemic is the improved knowledge that has been acquired on the functionality of different vaccine platform technologies, including their ability to induce cellular and humoral immune responses [12]. The rapid deployment of those platforms during the pandemic was based on prior knowledge of coronavirus biology and host immunity since neutralising antibodies to spike protein were known to be protective [13]. Thus, once the spike sequence of novel SARS CoV-2 was known, the route to recombinant expression or incorporation into vaccine platform delivery platforms became open. A viral-vectored vaccine based on vesicular stomatitis virus had already proven successful for preventing Ebola virus disease in humans [14], whereas the efficacy of mRNA-based vaccines (or other nucleic acid-based platforms) had yet to be proven at a population level.

Can the lessons from the COVID-19 vaccination programmes be translated more widely, not just for other viral diseases but also for bacterial diseases, and be deployed in veterinary species? Common themes re-iterated throughout the Workshop were: (a) bacteria are not viruses - meaning that there is often not a single target for neutralising antibodies and protective antigens are not always proteins; and (b) the TPP requirements of human vaccines do not necessarily apply to veterinary vaccines, particularly for deployment in LMICs with dependency on a cold chain supply and cost-of-goods per dose. A main challenge for bacterial vaccines includes the diversity and structural complexity of antigens, that can also include serotypic variants. The presentations at the Workshop addressed these points for four different platform technologies.

4.1. Nucleic acid vaccines

Veterinary vaccinology has led the way in nucleic acid vaccine platform technologies, with the first three DNA vaccines commercialized for use in horses, fish and dogs [15]. However, DNA vaccination has not been widely-adopted and none of the existing vaccines are anti-bacterial. As previously mentioned, mRNA vaccines have come to the fore as a result of COVID-19, but their deployment is influenced by a number of practicalities, including cost-of-goods for production, purchase cost per dose and ultra-cold-chain dependency. These factors influenced the global use of mRNA-based vaccines for COVID-19, particularly in LMICs. These same factors arguably have greater impact for livestock vaccination in LMICs since these generally need to be much cheaper than human vaccines to be cost-effective.

In 2021 WHO signed a letter of intent with a consortium of funding agencies, industry, government and academia to establish a mRNA Technology Transfer Hub [16]. Expanding the portability of vaccine platform technologies for use in both humans and animals has multiple benefits, particularly for controlling zoonotic infections for improving One Health. An example is vaccines for controlling Rift Valley fever (RVF), which is one of the WHO priority diseases in humans and also a notifiable disease for World Organisation for Animal Health (WOAH) (Fig. 1). A number of platform technologies are currently being deployed for next-generation RVF vaccines [17]. Notably, within the mRNA Technology Transfer Hub there is a RVF mRNA vaccine under development for deployment in small ruminants that is stable above freezing point. Should this be successful, there will be more opportunities for

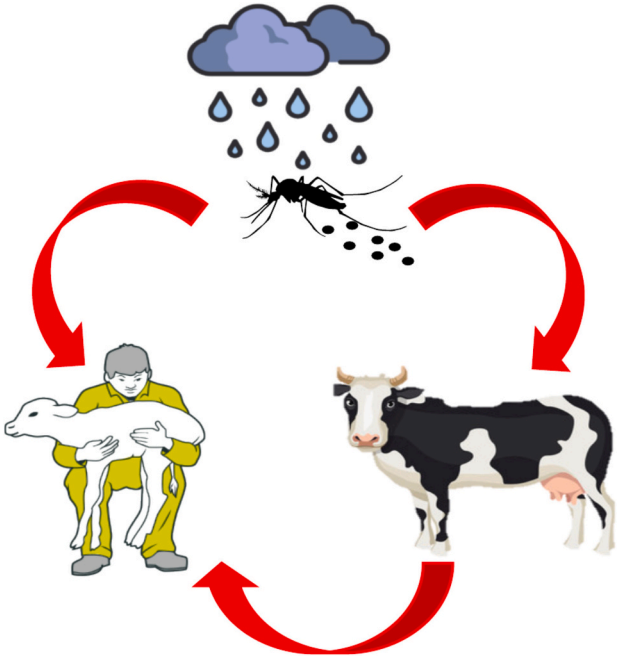

Fig. 1. Vaccination against Rift Valley Fever (RVF) in animals and humans can prevent virus transmission between the insect, animal and human hosts of the RVF triad to benefit One Health.

mRNA vaccines to be deployed more widely in veterinary species, which could include anti-bacterial vaccines. Indeed, there is preclinical evidence of mRNA vaccine efficacy against a number of bacterial pathogens in humans (Table 3), evidence that this platform technology can induce protective immune responses against bacteria [18]. One of these mRNA-LNP (lipid nanoparticle) vaccines showed full protection against lethal *Yersinia pestis* infection after a single dose [19].

4.2. Viral vectored vaccines

The adoption of viral-vectored vaccines is much more advanced in veterinary medicine compared to human medicine, with many more licensed products [9]. Viral-based platforms have been largely deployed for control of viral diseases to date, but novel viral-vectored vaccines are being developed against bacterial pathogens in livestock. *Streptococcus suis* (*S. suis*) has been identified as one of the pathogens with unmet needs for a new vaccine in pigs (Table 1). *S. suis* is a zoonotic pathogen that causes meningitis and septicaemia in pigs and humans with a global distribution; thus, a novel vaccine has One Health benefits and also potential to reduce antibiotic usage [20]. Autogenous vaccines are often deployed locally, but are expensive and do not provide cross-protection against different serotypes or heterologous strains [21]. *S. suis* is therefore a good exemplar pathogen for constructing a TPP for a novel viral-vectored vaccine.

The TPP of a such a *S. suis* vaccine should be multivalent for multiple serotypes, induce both cellular and humoral immunity for optimal protection and be affordable to HICs and LIMCs. Two candidate antigens that are highly-conserved and shown to be protective in recombinant form have already been identified [21]. A viral vector that meets the TPP for delivery of these antigens is bovine herpes virus-4 (BoHV-4), a double-stranded DNA virus of the gamma herpesvirinae sub-family with the capacity of accommodating large amounts of foreign genetic material. The prototype *S. suis* vaccine has been shown to be induce antibody, cellular immunity (production of both IFN-γ and IL-4) and confer protection in a rabbit model, meeting the requirements for future development [21].

Table 1
Bacterial diseases of livestock requiring new or improved vaccines as a component of integrated control strategies to improve animal health and/or reduce zoonotic transmission.

Disease/pathogen	Species
Bovine tuberculosis (*Mycobacterium bovis*)	Cattle
Paratuberculosis (*Mycobacterium avium* subspecies *paratuberculosis*)	Cattle, sheep
STEC (Shiga toxin producing enterohaemorrhagic *Escherichia coli*)	Cattle
Leptospirosis (*Leptospira hardjo*)	Sheep
Brucellosis (*Brucella abortus, B. melitensis, B. suis*)	Cattle, pigs
Chlamydiosis (*Chlamydia abortus*)	Sheep, goats
Salmonellosis (*Salmonella enterica*)	Poultry
Mycoplasmosis	Cattle
- Contagious bovine pleuropneumonia (CBPP: *Mycoplasma mycoides* subspecies *mycoides*)	Sheep, goats
- Contagious agalactia (*Mycoplasma agalactiae*)	Cattle, pigs
- Pneumonia (*Mycoplasma bovis, Mycoplasma hypopneumoniae, Mycoplasma hyorhinis, Mycoplasma hyosynoviae*)	Cattle, sheep
Mastitis (*Staphylococcus aureus*, *Escherichia coli*, *Streptococcus uberis)*	Poultry
Anthrax (*Bacillus anthracis*)	Pigs
Campylobacter (*Campylobacter jejuni*)	Pigs
Porcine pleuropneumonia (*Actinobacillus pleuropneumoniae*)	
Porcine meningitis/septicaemia (*Streptococcus suis*)	

4.3. OMVs/GMMA vaccines

The platforms considered so far (nucleic acid and viral vectors) have largely been used to develop vaccines against viruses. Given that bacteria tend to be larger, more complex and occupy different anatomical niches from viruses, other platform technologies can deliver antigens in different ways that may stimulate immune responses that are more aligned with protection, depending on the bacterium in question (Fig. 2). Current subunit single-antigen bacterial vaccines tend to target capsules or secreted toxins as these are accessible to antibody. However, the bacterial cell wall is much more complex, comprising outer membrane antigens and carbohydrates such as lipopolysaccharide (LPS), hence vaccines targeting these also need to be more complex, as exemplified by current human vaccines (Fig. 3).

Bacterial outer membrane vesicles (OMVs)/ generalised modules for membrane antigens (GMMAs) is one such platform technology. At around 20-200 nm in diameter, these particles contain membrane proteins in their native conformation and pathogen-associated membrane patterns (PAMPs) such as LPS that can act as adjuvants. OMVs/GMMAs have flexibility for modification through targeted removal of antigens or reactive PAMPs or insertion of foreign antigens, these features have made them a particularly effective platform for vaccines against Gram-negative bacteria [22]. OMVs have been successfully deployed within vaccines against meningococcal B strains in humans [23]. OMVs/GMMAs are yet to be deployed in veterinary vaccinology, but their immunogenic properties, manipulability and low production costs make them feasible and attractive future candidates.

4.4. Bacterial glycoconjugate vaccines

Carbohydrate-based vaccines require specific processes for production and presentation to the immune system to induce protection, which includes delivery in OMVs as described above [24]. Traditional production methods rely on growth of the pathogen, cleavage and purification of the glycan polysaccharide or O antigen), production and purification of the carrier protein and then chemical conjugation of carrier protein and glycan. This process has underpinned highly successful human vaccines against *Haemophilus influenzae* type b, *Streptococcus pneumoniae*, *Neisseria meningitidis* and *Salmonella typhi* [25]. However, the production process involves multiple quality control steps adding to the time and cost for vaccine production, which has put these vaccines out of reach for deployment in livestock.

Table 3
mRNA vaccines against bacteria in preclinical development in humans.

Bacterial pathogen	Vaccine antigen
Borrelia burgdorferi	OspA
Listeria monocytogenes	LMON_0149
Listeria monocytogenes	EF-Tu
Listeria monocytogenes	LLO_E262K + LMON_2272
Mycobacterium tuberculosis	Hsp65
Pseudomonas aeruginosa	OprF-1
Pseudomonas aeruginosa	PcrV
Staphylococcus aureus	AdsA
Yersinia pestis	Caf1

Table 2
Designing a target product profile (TPP) for an anti-methanogen vaccine.

Vaccine attribute	Desired Profile		Variables		Unacceptable profile
	Base Profile	Differentiation	Upsides	Downsides	
Overall description	An inactivated vaccine that reduces methanogens without negatively affecting productivity	Incorporates a safe adjuvant that induces long duration of immunity	Reduces methane emissions	Affects production, increases susceptibility to diseases	High production costs
Claims	Contributes to the reduction of methane emissions	Has synergistic impact with other interventions	Long lasting effect	Methane reduction is short-lived	
Species	Cattle	Effective in all ruminants	Effective in buffalo		Only effective in some cattle breeds
Formulation	Incorporates an existing registered adjuvant, one ml per dose	Can be delivered with other vaccines	Stable at room temperature	Short shelf-life	Requires storage at minus 20 °C
Administration	Intramuscular or subcutaneous, two doses, four weeks apart with annual booster. Delivered to animals six months or older	Single dose, can be delivered to young animals and pregnant animals for passive transfer of immunity	Can be formulated with other vaccines		More than three doses required for effect
Comparative efficacy	30 % reduction in methane emissions	50 % reduction in methane emissions			Less than 20 % reduction in methane emissions
Safety profile	Injection site reactions no greater than those with clostridial vaccines			Negative impact on productivity	More severe site reaction following injection
Time to Approval	Proof-of-concept within three years, registration within seven years			Requires FDA approval in the USA	Projected registration is over twenty years away

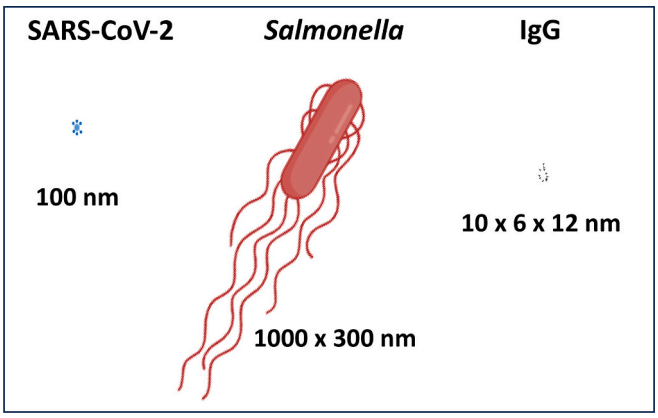

Fig. 2. Proportional representation of a virus, bacterium and immunoglobulin. Representative approximate relative sizes of a SARS-CoV-2 virion, a flagellated *Salmonella* bacterium and IgG molecules Sizes described in nanometres and represent a 'typical' size that is not meant to be definitive. The graphic representation demonstrates the potential capacity of a bacterium to bind many more IgG molecules than a single virion.

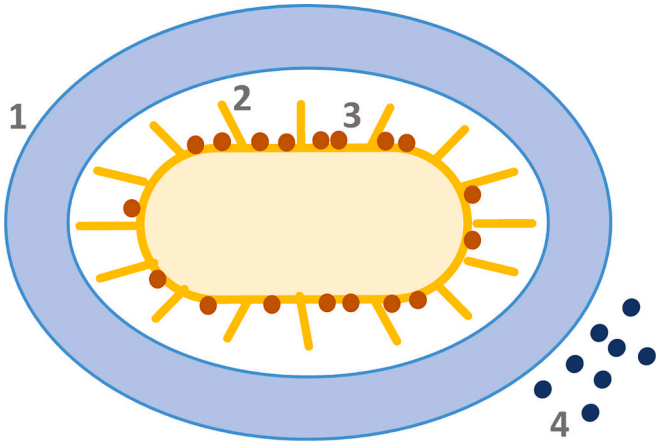

Fig. 3. Location of bacterial antigens incorporated into vaccines. The 'classes' of antigens included in bacterial vaccines licensed for use in humans. [1] Capsular polysaccharide; [2] Outer antigens [such as LPS]; [3] Cell membrane-proximal antigens; [4] Secreted antigens. All bacterial vaccines licensed for use in humans include exposed antigens, with capsular polysaccharide antigens forming the majority of single antigen bacterial vaccines.

Protein glycan coupling technology (PGCT) is a recent innovation that circumvents the complex and expensive processes involved in chemically synthesising glycoconjugate vaccines by engineering expression in endotoxin-free *E. coli* in a single-step procedure (Fig. 4). The flexibility of PCGT to mix-and-match all combinations of glycan with protein greatly expands the range of potential vaccine candidates [26]. This system also permits the immortalisation of clones once they are established and the potential to make OMVs from the *E. coli*, reducing production costs further. This puts the technology within potential reach of livestock vaccine producers and is currently being evaluated to prevent *Campylobacter jejuni* colonisation in chickens [27].

mRNA vaccine technologies are unlikely to be applicable for glycoconjugate vaccines. Unlike protein synthesis, polysaccharide synthesis is non-template driven and requires a complex biosynthetic pathway of many enzymes to sequentially assemble the target polysaccharide correctly. In the future it will be a combination of the recent platform technology platforms that will accelerate the new generation of veterinary vaccines.

5. Resources for developing veterinary vaccinology roadmaps and conducting gap analyses

5.1. STAR-IDAZ

The Secretariat for the global Strategic Alliances for the Coordination of Research on Infectious Diseases of Animals and Zoonoses (STAR-IDAZ) International Research Consortium (IRC) is funded by the European Union to address the coordination of research programmes at an international level to develop new and improved strategies to control at least 30 priority diseases/infections/issues that adversely affect animal health [28]. STAR-IDAZ IRC activities include the construction of interactive research roadmaps that represent pipelines for vaccine development for the target diseases. For each vaccine, the TPP is the end point of the roadmap, with the research pipelines punctuated by critical 'nodes' that highlight the criteria that need to be met for progression to the next step. The criteria set out in each node have been identified by gap analyses conducted by expert STAR-IDAZ Working Groups. The underlying vision being one of maximising the impact of global research investment in veterinary vaccine development. Crucially, this requires input from the research community to maintain state-of-the-art knowledge of the gaps and is linked to DISCONTOOLS gap analyses [29].

5.2. Discontools

DISCONTOOLS (DISease CONtrol TOOLS) is a resource for STAR-IDAZ IRC, identifying gaps in knowledge that accelerate the development of new diagnostics, vaccines and pharmaceuticals to reduce the burden of 57 infectious diseases of animals, supported by national funders within Europe and industrial stakeholders [30]. DISCONTOOLS is an open-access resource for the animal health research community, with the gap analyses underpinning research calls and subsequent funding applications, engaging with over 400 expert, stakeholders and funders [31]. Examples of livestock bacterial diseases with an identified need for new/improved vaccines as part of integrated control strategies by DISCONTOOLS is listed in Table 1. Common barriers to developing many of these vaccines are manifold, but include: a poor understanding of protective host immune mechanisms, lack of delivery systems that induce mucosal immunity, overcoming pre-existing immunity including maternal antibodies, novel approaches to antigen identification, good challenge models in the target species, and, where feasible, animal-free models. Aspirational vaccines will be ideally be safe, effective, single-shot, thermostable, multivalent, and DIVA (discrimination between infected and vaccinated animals)-compliant. Safety and efficacy are mandatory requirements for regulatory approval of a vaccine, but meeting these other aspirations remains challenging and may not be feasible with existing technologies (but these may become available in the future). Hence the need for designing a realistic vaccine TPP that addresses the challenges with current capability and with the potential of being improved upon as technologies improve.

6. Breakout discussion groups

The purpose of the Workshop was to discuss the gaps and unmet needs for bacterial vaccines against bacteria for deployment in farmed livestock that meet the TPP requirements for LMICs (and by inference, HICs) with benefits for One Health and/or have potential to combat antimicrobial resistance (AMR) by reducing antibiotic usage. Each group was asked to address two of the questions that are described in Box 2. Every group addressed question 1 plus one other and an appointed rapporteur the collective views of each group to the Workshop delegation.

The consensus opinions were:

1) The vaccine TPP needs to be considered very early in R&D and should take into account geographical location (LMICs and HICs

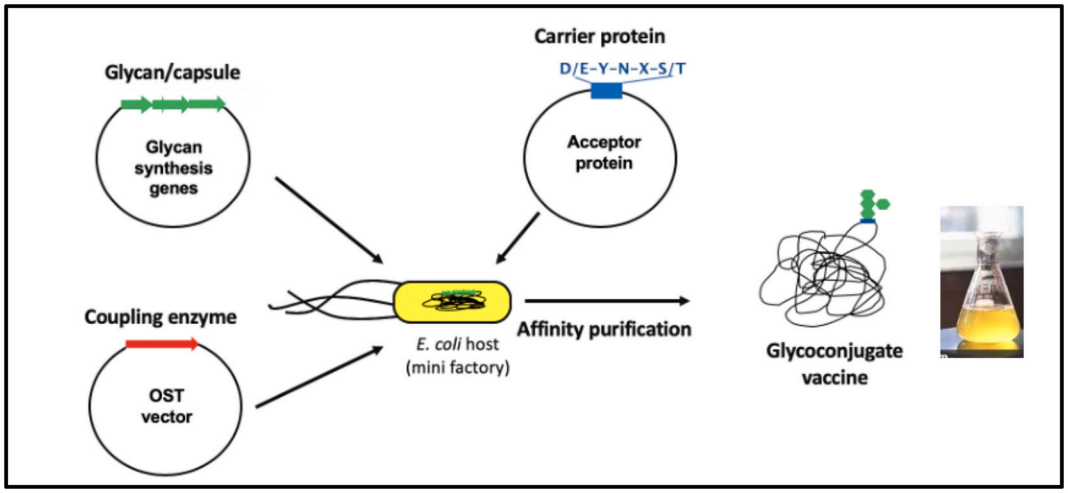

Fig. 4. Principles of Protein Glycan Coupling Technology (bioconjugation) to produce glycoconjugate vaccines. The target bacterial glycan (*e.g.* capsular polysaccharide of O antigen) is cloned into detoxified *E. coli* cells containing a carrier protein (*e.g.* protein vaccine candidate using reverse vaccinology). The glycan is coupled to the protein through the oligosaccharyl transferase (OST) cloned on the *E. coli* chromosome. After culture, cells are lysed, and the vaccine is purified by affinity chromatography.

Box 2
Questions discussed by the Workshop breakout groups. Every group discussed question 1 (in bold) plus one other.

1. **Vaccine Platform Technology gaps: what platforms are currently being deployed in this area, what are the future opportunities we are currently missing?**
2. What other technology gaps need to be addressed to accelerate veterinary vaccine development (production systems, adjuvants, delivery systems, immunology)?
3. Can we address AMR using novel vaccine platform technologies? If so, how do we achieve that?
4. How do we measure and demonstrate the One Health benefits (knowledge from vaccine platforms in different species, reduction in zoonoses, improved food safety, reduction in methane emissions)?
5. How can novel vaccine platform technologies meet the desired TPP for different countries/infrastructures (cost, stability, boosters, multivalency, duration of immunity, mucosal immunity)
6. In what situations (and how) should DIVA capacity be incorporated into vaccine development to ensure effective deployment (taking into account the need for suitable diagnostic capability)?

have different requirements) when deploying different platforms (with cost-of-goods and cold chain delivery being identified as decisive differential factors).

2) Bacteria are not viruses and not all bacteria are the same. The identification of protective antigens is challenging and selection of appropriate delivery platforms for those antigens may be different for vaccines against intracellular and extracellular bacteria to elicit appropriate protective immune responses. Broadly cross-protective vaccines are one way to align needs of HICs and LMICs where geographically-restricted serotypes are an issue.
3) There is a need for greater understanding of the immune system in different veterinary species and also the functionality of vaccine platform technologies in those species. This includes understanding species-specific adjuvants, platform performance in different species, the influence of co-infections, duration of immunity (*e.g.*, single shot vaccines are desirable), mechanisms for site-specific delivery (particularly to target mucosae) and neonatal vaccines that overcome passively-acquired maternal antibody.
4) Reverse vaccinology and machine learning should be more widely exploited for antigen identification for vaccine design and could be identify conserved protective antigens for bacteria with multiple serotypes.
5) Multivalent/syndromic vaccines are highly desirable in livestock vaccinology, but requires deep understanding of mechanisms of protective immunity against each pathogen to determine which combinations of antigens/platforms can be successfully combined.
6) Effective vaccines are one of the best tools at our disposal to reduce reliance on antibiotics and thereby reduce antimicrobial resistance.

7. Conclusions

The presentations and breakout discussions at the Workshop collectively highlighted the challenges in identifying protective antigens and in understanding specific host immunity for designing unmet needs for anti-bacterial vaccines, particularly for vaccine TPPs that meet the criteria for successful deployment in LMICs. While safe, effective single-shot DIVA-compliant multivalent vaccines that give lifelong protection are the desirable goal, this is very ambitious and may not be feasible. The two vaccinology networks represented at the Workshop were BactiVac and the International Veterinary Vaccinology Network (IVVN) that were funded initially through the UK Global Challenges Research Fund Network. BactiVac aims to accelerate the development of vaccines against bacterial infections that are relevant to LMICs and can be involved in the entire vaccine development pipeline [32]. IVVN aims to address the challenges impeding vaccine discovery, evaluation and

delivery for controlling priority livestock and zoonotic diseases in LMICs [33]. Crucially, both networks provide catalyst pump-prime funding to stimulate vaccine development projects that benefit One Health through improved food safety, reduced zoonotic transmission and reduced antibiotic usage.

On the host side, our relatively poor understanding of immune function in veterinary species represents a major gap that impacts on anti-bacterial vaccine development. On the pathogen side, identification of protective bacterial antigens remains challenging. Solutions include the adoption of reverse vaccinology for identification of protective bacterial antigens and also carrier proteins, while synthetic biology (engineering biology) can optimise expression of bacterial glycans for glycoconjugate vaccines [34,35]. Databases such as DISCONTOOLS help to identify gaps for novel or improved livestock vaccines for controlling diseases as part of a coordinated approach including novel diagnostics and therapeutics.

CRediT authorship contribution statement

Gary Entrican: Writing – review & editing, Writing – original draft, Conceptualization. **Helba Bredell:** Writing – review & editing, Writing – original draft. **Johannes Charlier:** Writing – review & editing, Writing – original draft. **Adam F. Cunningham:** Writing – review & editing, Writing – original draft. **Michael A. Jarvis:** Writing – review & editing, Writing – original draft. **Paul R. Wood:** Writing – review & editing, Writing – original draft. **Brendan W. Wren:** Writing – review & editing, Writing – original draft. **Jayne C. Hope:** Writing – review & editing, Writing – original draft, Conceptualization.

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Declaration of competing interest

BW is Cofounder and shareholder in ArkVax. MAJ is employed by TVG Ltd., which develops viral vectored vaccines against agricultural infectious diseases. MAJ has received I-UK funding for development of *S. suis* vaccines in pigs.

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Data availability

No data was used for the research described in the article.

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