Review On The Evaluation Of Efficacy Of Foot And Mouth Disease Vaccine

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Abstract: Foot and mouth disease (FMD) is one of the most economically devastating diseases affecting cloven-hoofed livestock worldwide. It is among the widespread endemic diseases in Ethiopia. The control strategies for FMD vary between countries based on status of the disease in the country, the financial and technical ability of the country. Vaccination is an effective method of control of FMD especially in FMD endemic countries but its effectiveness is not evaluated routinely. This seminar is done with the objective of reviewing approaches to veterinary vaccine efficacy evaluation. Although present conventional foot-and-mouth disease (FMD) vaccines can prevent clinical disease, protection is short lived (□6 months), often requiring frequent revaccination for prophylactic control. Monitoring of the field effectiveness of a vaccination program is important for the control of FMD by vaccination. Some of the methods used for this purpose include challenge studies; randomized control trials; observational studies and serological studies were discussed under this review. Recommendations are made for the development of effective FMD control program and maintaining the efficacy of a FMD vaccine and effectiveness of a vaccination program.

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1. Introduction

Foot and mouth disease (FMD) is one of the most economically devastating diseases affecting cloven-hoofed livestock worldwide (Quinn *et al.,* 2005). FMD is caused by a highly variable RNA virus of the genus Aphthovirus and family Picornaviridae (Arzt *et al*., 2011). Seven serotypes (A, O, C, Asia 1, SAT 1, SAT 2, and SAT 3) and a large number of topotypes (Mort *et al*., 2005) were identified. Further, new subtypes of FMDV are continuously evolving due to an infinite mutation rate in the RNA genome of the virus (OIE, 2008). FMD is widely distributed with high prevalence in developing countries. In Ethiopia it is endemic and distributed in most part of the country (Ayelet *et al*., 2012).

The control strategy of FMD varies based on the status of the country and its neighbor country to this disease. Generally, it can be controlled by movement control/quarantine (animals, animal products and infected materials), diagnostics and surveillance, vaccination, slaughtering of infected and in-contact animals, biosecurity measures etc. (Aitken, 2007).

Vaccination has proven to be a very effective way of controlling and eliminating FMD from certain regions of the world, such as Western Europe and parts of South America (Saraiva and Darsie, 2004). If used strategically, vaccination can create a barrier between infected and disease-free areas, provided that FMDV vaccine serotypes and subtypes match with those causing outbreaks in a given area. Vaccination against one FMDV serotype does not usually protect animals against other serotypes of the virus or other strains of the same serotype (Pattnaik *et al*., 2012).

Different types of vaccination programs are implemented in different regions of the world, with varying challenges to their success. One key challenge is the limited availability and high cost of the vaccine. Furthermore, the duration of immunity induced is short and booster inoculations need to be administered at 4 to 6 monthly intervals in most animals, including young cattle. The vaccine also needs to contain a large quantity of specific antigen (1 μg per dose or perhaps closer to 5 μg per dose) and the production of large volumes of FMD virus needs to be conducted in a biosecure facility that will prevent virus escape into the environment, this makes it expensive to produce (Dungu, 2002).

Despite the advantages the vaccination may provide by reducing the number of animals culled/lost due to the disease; there are inherent factors which may offset the likely effectiveness of a vaccination strategy. For example, the vaccine requires 4-5 days for immunity to develop and the vaccine efficacy is related to the antigenic match between the vaccine strain and the circulating strain and the effectiveness of vaccination program (Barnett and Carabin, 2002). These limitations render the effectiveness of vaccination policies (Traulsen *et al*., 2011).

Complementing the required control measures with vaccination-to-live has the potential to reduce disease spread by protecting the susceptible population, leading to shorter epidemics, and fewer animals culled. Given the enormous scale and implications of vaccine use in terms of both health and economics, it is clearly important that their effectiveness should be thoroughly evaluated. FMD can be controlled using various strategies and veterinary vaccines are evaluated in very different ways. Therefore, this review was done with the objective of:

- Reviewing approaches of FMD vaccine efficacy evaluation

2. Evaluation Of Efficacy Of Foot And Mouth Disease Vaccine

2.1. FMD Vaccine Efficacy and Effectiveness of Vaccination program

Vaccines are crucial in both human and animal disease control and it is estimated that veterinary vaccines are available for over 400 diseases affecting mammals, birds and fish, including farm animals, pets and wildlife (Van Aarle, 2010). Designing a monitoring system for vaccination needs indicators of success of the preventive or control measures to be defined in terms of one or more of the following: the expected extent of reduction of disease or virus circulation; the acceptable incidence of disease, below which a program is considered successful and the absence of disease or circulation of the agent (Giancarlo *et al*., 2016).

Vaccine efficacy is a measure of how well a vaccine protects an animal against a given undesirable outcome, for instance disease, virus replication, virus shedding or virus transmission, when tested under controlled conditions such that the circumstances of vaccination and challenge infection are well characterized. Vaccine efficacy can also be expressed as the amount of reduction of disease in the vaccinated population compared with a control population administered with a placebo (OIE, 2012).

Vaccine efficacy is sometimes confused with vaccine effectiveness, which is an indicator of how well animals are protected in the field by a program of vaccination (Knight-Jones *et al*., 2014a). Vaccine effectiveness is defined as the reduction in risk in vaccinated individuals compared to similarly exposed unvaccinated individuals under field conditions (Plotkin *et al*., 2008). It is not only depends upon the initial (intrinsic) quality of the vaccine, as supplied by the manufacturer, but also upon extrinsic factors, such as the impact of vaccine storage and distribution, the vaccine match, the vaccination schedule and indirectly vaccine coverage (Giancarlo *et al*., 2016; OIE. 2012).

One of the reasons why vaccine efficacy and effectiveness are sometimes incorrectly used inter changeably may be because both can be estimated by comparing incidence in vaccinated animals to incidence in unvaccinated animals that received a similar level of virus exposure using the equation: VE = (*R*U-*R*V)/*R*U where *R*U is the incidence in the unvaccinated population, and *R*V is the incidence in those vaccinated (Giancarlo *et al*., 2016). Although the two concepts are related, they should be as distinct because they differ in the approach used for their estimation: (i) vaccine efficacy is estimated mostly through an RCT; while (ii) vaccine effectiveness is estimated through field observational studies or sometimes field trials under normal program conditions. The need for vaccine effectiveness studies is particularly acute when veterinary vaccines are authorized during emergency or exceptional circumstances with minimal efficacy data, and where outbreaks are occurring within a vaccination program (Giancarlo *et al*., 2016).

In order for veterinary vaccines to obtain market authorization, they are subjected to safety and immunogenicity studies on a limited number of individuals of the target species (European Medicines Agency, 2003; European pharmacopoeia, 2012). Although they are used in the assessment of efficacy, the scale of veterinary vaccine field studies are limited compared to human vaccine trials. Field studies play a very limited role in veterinary vaccine authorization and are typically used to evaluate safety rather than efficacy (OIE, 2013).

2.2. Methods for Evaluating the Protective Effects in Vaccinated Animals

2.2.1. Challenge studies

The evaluation of veterinary vaccines relies heavily on challenge studies. Typically, protection is assessed using a high level of pathogen challenge with the lowest vaccine antigen content permitted under the authorization. Although this will provide some confidence that the vaccine will protect even in extreme situations, the controlled conditions of a challenge study will not reflect sometimes suboptimal application of vaccines in the field. For some important veterinary pathogens like FMDV the design of these challenge studies is prescribed by official standards using 50%Protective Dose (PD50) as indicated below (European pharmacopoeia, 2012; OIE, 2013).

FMD 50% Protective Dose (PD50): In Europe FMD vaccines are routinely evaluated using the Protective Dose (PD50) test. Three groups of at least five cattle, are given different doses of vaccine (typically a full, a quarter and a sixteenth dose). Two unvaccinated control animals are also used. After three to four weeks, animals are given a standard dose of

FMD virus injected into the tongue. Animals are observed for foot lesions. From these data the fraction of the standard dose of vaccine that would protect 50% of exposed cattle is then estimated. The reciprocal of this is the PD50 value (European pharmacopoeia, 2012; OIE, 2013). This is a measure of vaccine potency, reflecting protective efficacy.

2.2.2. Randomized controlled trials (RCT)

This approach is employed more routinely in the evaluation of human vaccines. In a RCT, a study group that represents the population of interest is identified, preferably with a high incidence of the disease. Individuals within this population are then selected at random to be vaccinated, or to receive either no vaccine, a placebo, or an alternative vaccine. The protective efficacy of the vaccine can then be calculated by comparing the incidence in the vaccinated and control groups (VE = (*R*U-*R*V)/*R*U) (Plotkin *et al*., 2008).

The European Medicines Agency (EMA) specifies guidelines and standards for RCT designs for veterinary vaccines (European Medicines Agency, 2001). Although field trials are used for veterinary vaccines, unlike human medicine, they are sometimes thought of as inferior methods of efficacy evaluation compared to the standardized and highly controlled conditions of the challenge study (OIE, 2013).

2.2.3. Observational vaccine effectiveness evaluation

Although observational studies have limited application in animal populations, there are some examples of its use (Hogerwerf, 2011). During observational studies vaccinated individuals are likely to differ from those not vaccinated in ways that may confound the vaccine effect (Knight-Jones *et al*., 2014b). Observational studies are used for the evaluation of the effectiveness of a vaccination program. Several different observational study designs exist of which some key designs are described below.

Cohort studies: In a cohort study, incidence is compared in vaccinated and unvaccinated groups over the period of observation. Where national databases with health records for all individuals exist they can be used for national studies of vaccine effectiveness (Leval *et al*., 2013). Large cohort studies are less common for livestock, partly due to cost. Retrospective studies, using either farm records or after outbreaks amongst small-holders, are more feasible (Knight-Jones *et al.*, 2014b).

Case-control studies: It is possible to estimate vaccine effectiveness by comparing prior vaccination status of affected individuals with the vaccination status of controls that were similarly exposed, but failed to contract the disease (Grassly *et al*., 2007). This is a common method of human vaccine effectiveness evaluation. As it is relatively quick and inexpensive to perform the method would be suitable for veterinary vaccines provided that accurate vaccination and disease data are available (O'Loughlin *et al*., 2010). However, a lack of vaccinated and unvaccinated animals on the same premises and increased likelihood of vaccination in high risk groups may prevent identification of a suitable control group. The method may also not be possible within a highly effective control program due to a lack of cases (Knight-Jones *et al*., 2014a).

Case-cohort studies*:* In a case-cohort study, the odds of vaccination in cases are compared to the odds of vaccination in a sample representing the population at large; this gives an estimate of the risk ratio and thus vaccine effectiveness. Occasionally it is used for human vaccines, like other field evaluation methods, in veterinary it is used for a high incidence disease like FMD (Knight-Jones *et al.*, 2014a).

Outbreak studies: When there is a lack of unvaccinated animals, inadequate protection may be identified by outbreaks in vaccinated populations without comparison to a control group. This may be the case when evaluating outbreaks in commercial farms with uniform management. Evaluation of reactive vaccination performed in response to outbreaks can be challenging as the investigator may be unsure if individuals were already immune before vaccination, challenge may occur before vaccinated individuals have responded to the vaccine and those left unvaccinated may have a different risk of pathogen exposure (Knight-Jones *et al.*, 2014b).

Thorough investigation of outbreaks that occur in vaccinated animals, where protection would have been expected, is an important aspect of monitoring the performance of vaccination. A systematic approach is recommended in order to check off all the steps where problems could potentially have occurred from initial vaccine quality and suitability, through vaccine storage, delivery and vaccination, vaccine coverage, induced immunity and the nature of the challenge, long post-vaccination interval or change in antigenic phenotype (Figure. 2). The timing of outbreaks in relation to vaccination is a key consideration, as immunity takes time to develop and then wanes (Giancarlo *et al*., 2016).

2.2.4. Serological evaluation

Sero-prevalence surveys are often used for livestock as an unbiased measure of disease burden where under-reporting is a problem. However, sero-positivity owing to infection must be distinguishable from vaccine-induced sero-positivity (Giancarlo *et al*., 2016). Some of the serological methods of evaluation of vaccine performance are discussed below.

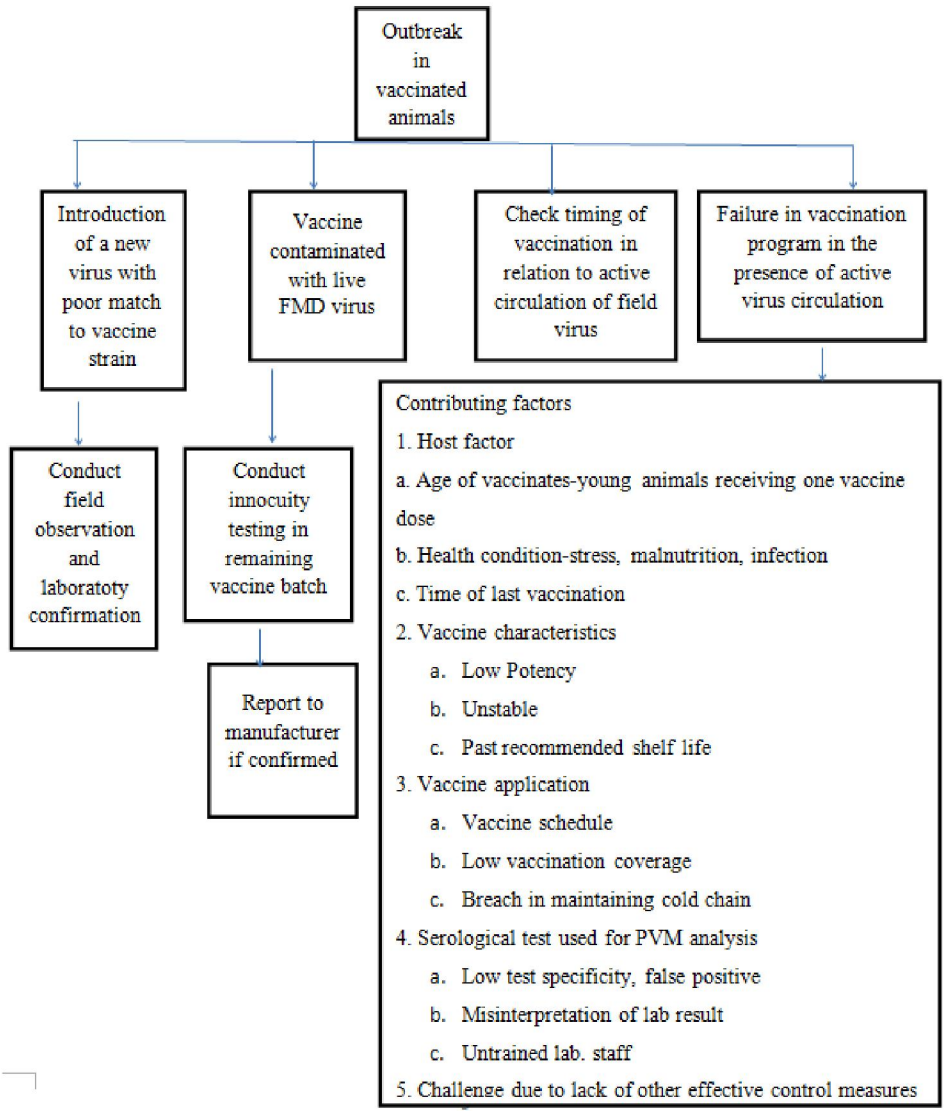

Figure 2. Disease outbreak investigation- Considerations and contributory factors (Source: Giancarlo *et al*., 2016).

Correlates of protection: Vaccines often induce a measurable response (e.g. antibody titer). If this response is correlated with protection against disease or infection it can be used as an alternative outcome for vaccine evaluation (Plotkin *et al*., 2008; Nguipdop-Djomo *et al*., 2013). Correlates of protection are widely used for both human and veterinary vaccines. There is pressure to minimize the use of animal challenge studies; evaluating serological measures of protection instead (Reeve *et al*., 2011).

The Expected Percentage of Protection (EPP): is a standardized test used to assess the potency of FMD vaccines using serology rather than pathogen challenge. In this method, the sera from 16 to 30 cattle between 18 and 24 months of age, taken 30 days post vaccination are assessed for their ability to neutralize or bind virus (typically the vaccine strain) using a virus neutralization (VN) tests or an ELISA. The proportion of animals expected to be protected is then estimated by referring to serological titers and observed protection from multiple previous challenge studies (Paton *et al*., 2005; OIE, 2013).

Post-vaccination sero-conversion surveys: Sero-conversion surveys using only sera collected post-vaccination are common in livestock. The proportion with an antibody titer above a specified threshold associated with protection is then determined (Robiolo *et al*., 2010).

Sero-prevalence surveys: This involves assessing sero-status for a representative sample of the population irrespective of vaccination status after a vaccination campaign. Not widely used for human vaccines, these surveys are used in veterinary settings to assess the level of "population immunity" (PNEFA,

2007), under the assumption that sero-positivity implies protection. Sero-prevalence is a function of the proportion vaccinated, the proportion that sero-convert post-vaccination and the proportion sero-positive following natural infection. In endemic populations, it is therefore difficult to infer if high levels of sero-positivity reflect high coverage with an effective vaccine or widespread infection, or a combination of both vaccination and infection. Where vaccine protection is short-lived or population turnover is rapid, studies need to be regularly updating (Knight-Jones *et al*., 2014a).

In vitro vaccine matching assays: The likely performance of vaccines may sometimes be predicted via *in vitro* serological methods. However, these matching studies do not consistently predict effectiveness. A veterinary assay used for predicting FMD vaccine-induced protection is the "r-value" (Paton *et al*., 2005) (see next paragraph). Combining information on vaccine potency and antigenic match improves the prediction of efficacy with identification of genetic predictors under development (Reeve *et al*., 2010).

r value test: the "r value" is an *in vitro* assay of FMD vaccine match; this is a measure of the relative reactivity of sera from vaccinated cattle to the field virus in question compared to the reactivity of the same sera to the virus strain used to make the vaccine, performed by ELISA or VN (Paton *et al*., 2005; OIE, 2013). For FMD, a sub-optimal vaccine match may be compensated for, to a certain extent, by having a more potent vaccine that stimulates greater antibody production, e.g. one that contains more antigens per dose (Paton *et al*., 2005). The test provides rapid results, but there can be problems with test repeatability (Paton *et al*., 2005) and results do not tell you if the vaccine is actually protecting animals in the field. "r" stands for "relationship" and an r1 value assesses this relationship using antiserum to one of the viruses under comparison. Two-way relationships (r2) can also be assessed using serum against both viruses (OIE, 2013).

2.2.5. Direct versus indirect effects of vaccination

Direct vaccine protection is the reduction in risk in vaccinated compared to similarly exposed unvaccinated individuals. However, vaccinating some but not all members of a group can result not only in protection of those vaccinated, but also reduced pathogen exposure and morbidity in those not vaccinated. This indirect vaccine effect is due to a reduction in transmission within the group as a whole. Studies that only capture the direct effect of vaccination by comparing vaccinated and unvaccinated individuals in the same group may underestimate the overall effect of vaccination by not capturing the indirect effects (Knight-Jones *et al*., 2014b). The direct and indirect effect of vaccination can be examined using cluster randomized trials.

Cluster randomized trials: In cluster randomized trials (CRTs), the intervention is randomly allocated to entire clusters, rather than individuals. Certain CRTs and observational vaccine effectiveness studies can be designed so as to capture direct and indirect vaccine effects. By randomizing allocation to different clusters, rather than individuals within the same cluster, inferences can be made on the overall effect of vaccination on a community, rather just the direct effects afforded to the individual (Millar *et al*., 2008). Vaccinated and control clusters will tend to be similar due to randomization.

2.3. Vaccine Coverage

Vaccine coverage is often taken to mean the proportion of animals assigned to be vaccinated that are actually administered the vaccine, or proportion vaccinated in relation to the entire susceptible population and the figures calculated can then be used as an indicator of how the delivery system performs. It can be calculated using vaccine distributed method, administered method, survey and sero-prevalence studies (Knight-Jones *et al*., 2014a; Giancarlo *et al*., 2016).

The coverage necessary to stop the FMDV from spreading within a herd will depend upon the number of cases that one case generates on average over the course of its infectious period, in a totally susceptible population (the basic reproductive ratio, $R0$). If a proportion of the population is immune, transmission to these animals may be blocked and the net reproduction ratio (Rn) will decline. If it is reduced to a level at which each infected animal infects on average less than one new animal (Rn< 1), the proportion of the population that is infected will tend to decrease over time, ultimately leading to eradication. The proportion that is immune from vaccination will depend upon coverage and the protective effect of the vaccine (Giancarlo *et al*., 2016).

3. Conclusion And Recommendations

Currently FMD is endemic in many countries including Ethiopia. FMD can be controlled by different strategies based on the status of the disease in the country and the neighboring countries. Vaccination is one of the best options for the control of disease in veterinary medicine including FMD. Checking the matching of vaccine strain and the strain circulating in the region to be vaccinated is mandatory for effective control of FMD using vaccination. Both vaccine efficacy evaluation and monitoring the effectiveness of a vaccination program are essential for measuring protection actually achieved within a vaccination

program. Challenge studies under controlled conditions and sero-prevalence studies are widely used strategies when evaluating veterinary vaccines efficacy.

Based on the above conclusive ideas the following points are forwarded:

- In FMD endemic situations, for the efficient control of the disease, a country must apply routine mass vaccination together with the control of animal movement and other effective biosecurity measures.
- To check the efficacy of a vaccine a country needs to test each batch of a vaccine before application in to a whole population.
- It is better for a country to evaluate the effectiveness of FMD vaccination program as it is crucial for guiding policy and for securing funding for disease control.
- Regular surveillance and monitoring of the status of FMD in the country must be applied.

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