Are the knowledge, tools and resources to control foot and mouth disease available?

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Summary

Foot and mouth disease (FMD) is a highly contagious viral disease of cloven-hoofed animals. Together with other diseases highlighted in this special issue, the circulation of FMD virus in different parts of the world has shaped the work of the World Organisation for Animal Health (WOAH, founded as OIE) over the past hundred years. In 2012, the Global Framework for the Progressive Control of Transboundary Animal Diseases, led by WOAH and the Food and Agriculture Organization of the United Nations, established a joint FMD working group and a strategy for the control of FMD. Control of FMD requires political commitment to deliver the sustained investment and deploy the resources required to break the cycle of infection. This brief review highlights recent improvements in diagnostic and genomic tools, as well as new vaccine platform technologies that, if strategically deployed, have the potential to improve the control of this disease. The review also reflects on global and regional initiatives using the Progressive Control Pathway for FMD, which remains relevant and has wider positive benefits for the control of other transboundary animal diseases.

Keywords

Diagnostics – Disease control – Foot and mouth disease – Outbreaks – Surveillance – Vaccines.

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Introduction

Foot and mouth disease (FMD) is a transboundary disease that affects cloven-hoofed animals, such as cattle, sheep, goats and pigs. The causative agent is an RNA virus, FMD virus (FMDV), in the Picornaviridae family (genus *Aphthovirus*) that exists as seven different serotypes: O, A, C, Asia 1, Southern African Territories (SAT) 1, SAT 2 and SAT 3. The disease is highly contagious and difficult to control due to the multiple serotypes and species affected, low infectious dose, rapid virus replication and opportunities for spread between animals via direct contact and indirect (fomite) transmission routes. In high-income countries, such as those in mainland Europe, FMD freedom has been achieved through the wide-scale use of vaccination coordinated with zoo-sanitary measures on farms. In contrast, in low- and middle-income countries, there are more resource constraints and fewer immediate incentives to control the disease. These different economic perspectives shape the current distribution of FMD, namely in Africa, Asia (including the Middle East) and Venezuela (Fig. 1). In these settings, the epidemiology of FMD is divided into seven component endemic pools representing different ecosystems that maintain specific FMD viral serotypes and lineages [2]. Serotype O is present in all seven pools and has the widest distribution, while the SAT serotypes are normally restricted to the African continent and Asia 1 is found only in Asia. Serotype C has not been detected in any of the pools since 2004 and is now considered extinct [3]. This compartmentalisation of FMDV is dynamic and thought to reflect regional trade patterns in live animals and animal products.

The epidemiology of foot and mouth disease is very dynamic

Viral genomic data collected by FMD Reference Laboratories are routinely used to understand the global distribution and epidemiological events of FMDV [4], such as the emergence of new lineages, or to identify where FMDVs have spread to cause outbreaks in new geographical locations (Fig. 1). Longer-distance viral movements have the potential to completely change the virus risks in a region. These trans-pool events often pose challenges for the deployment of vaccines to get ahead of outbreaks and may be presaged by upsurges in infection by the causative lineage at the point of origin.

Currently, the O/ME-SA/Ind-2001e lineage continues to dominate over other serotype O lineages in parts of Asia. For example, in mainland South-East Asia (Pool 1), four genetic lineages of serotype O previously circulated; however, since 2020/2021, O/ME-SA/2001e has been the main lineage reported. Indonesia, which had previously been free from FMD (since 1990), reported FMD cases due to O/ME-SA/Ind-2001e in 2022 [5],

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and incursions of this lineage have also been detected in previously FMD free zones in Kazakhstan (2022) [6] and Russia (2021) [7].

Sequence data demonstrate that many of the FMDV lineages that spread between pools arise from South Asia (Pool 2), reinforcing the importance of FMD surveillance in countries such as India to identify virus strains that may spread more widely. In this context, the detection of an emerging lineage called O/ME-SA/SA-2018 in India, Nepal, Bangladesh and Sri Lanka and the first evidence of its spread to Pool 3 (Oman and the United Arab Emirates) provide evidence of a potential new risk for other regions. Elsewhere in Pool 3, a new clade within the O/ME-SA/PanAsia-2^{ANT-10} sub-lineage has caused outbreaks in Eastern Mediterranean countries and territories (Jordan, Palestine and Israel). These FMDVs are most closely related to viruses found in Pakistan and appear to have become more dominant than the sub-lineage O/ME-SA/PanAsia-2^{QOM-15} previously found in this region.

During 2023, epidemiological events in Pool 3 and the European neighbourhood were overshadowed by the emergence of SAT 2/XIV, caused by viruses that are closely related to those collected from Ethiopia in 2022. These are the first reports of the SAT 2 serotype in many of the affected countries, and since infection is occurring in naive animals without any history of infection or vaccination for this serotype, there are significant concerns about the potential for rapid onward spread to other countries in the region and to the FMD free buffer zone in Thrace via east-to-west virus conveyers that have been described for other FMDV lineages [8,9,10].

Recent FMD outbreaks in North Africa (Algeria, Libya and Tunisia) have been due to the O/EA-3 topotype, normally found in sub-Saharan Africa. Sequence data show that these cases are due to new introductions of the virus, distinct from earlier introductions in 2018 [11]. Elsewhere in North Africa, published reports of FMD cases in Egypt have been associated with viruses from the O/EURO-SA and A/EURO-SA lineages that were previously found only in South America [12,13]. These unexpected outbreaks need to be monitored closely since there is potential for onward spread in North Africa and the Eastern Mediterranean. For Southern Africa (Pool 6), the O/EA-2 topotype that has moved southward continues to cause outbreaks and has now been reported in Zambia, Namibia, Malawi and Mozambique. These cases represent the first detection of serotype O in southern Africa in more than 20 years [14]. These findings are important because serotype O vaccines are not widely used in this region. South Africa has lost its FMD free (without vaccination) status due to SAT 2 outbreaks in the provinces of

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KwaZulu-Natal and Free State and to SAT 3 outbreaks in Free State, Gauteng, Mpumalanga and the North-West Provinces.

Improved tools for foot and mouth disease surveillance: can these address inherent biases in sampling?

Serological tests have limited power to discriminate between the FMDV serotypes and strains responsible for infection in endemic regions [15]. Therefore, the ability to reconstruct patterns of viral movement is dependent upon the more laborious and targeted collection and analysis of virological samples, and on trust between laboratories and their national authorities to transparently share data and sequences. The World Organisation for Animal Health (WOAH)/Food and Agriculture Organization of the United Nations (FAO) FMD Laboratory Network (https://www.foot-and-mouth.org) was established in 2004 as a forum to collate laboratory data to help understand global virus distribution patterns and use these data to inform vaccine recommendations, as well as to harmonise and improve the quality of laboratory testing in FMD Reference Laboratories.

Control of FMD should be guided by surveillance, so that the limited resources available are directed towards mitigating the most important risks [16]. However, there are important biases in surveillance activities that impact the use of the data generated. In endemic countries, virological sampling is often *ad hoc*, responding to only a minority of outbreaks, perhaps when outbreaks are severe or there is external funding from specific projects. Furthermore, clinical signs are difficult to spot in vaccinated populations and small ruminants. Due to these biases, reliance on outbreak counting or poorly designed serosurveys to assess FMD prevalence or the success of control programmes is not accurate. These factors motivate the use of well-designed serological surveys for non-structural protein antibodies and the development of novel non-invasive sampling and sequence-based approaches to estimate burden of disease in endemic settings [17,18,19,20].

To enhance FMD surveillance, more cost-effective approaches to sequence FMDV are urgently needed. FMDV-specific pipelines using the MinION platform (Oxford Nanopore) may be suitable for deployment to laboratories in countries where FMD is endemic [21,22,23]. For FMDV detection, the development of pen-side or field tests also continues to be an active area of research (reviewed in [24] and [25]). Lateral flow devices (LFDs) are easy to implement, and results can be obtained in 10–30 minutes. FMDV LFDs have been reported to have similar sensitivity and specificity as the antigen enzyme-linked

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immunosorbent assay [26,27,28] and can detect FMDV in tissue homogenates, vesicular fluid, oral fluids and lesion swabs. Intact viral RNA can be recovered from such devices for further characterisation (e.g. using reverse transcription polymerase chain reaction and sequencing) [29,30], and field validation of such cost-effective sample-to-sequence pipelines continues to be a high priority [31].

These new test formats have often been developed for use in emergency settings (such as virus incursions in FMD free countries or zones) but may be particularly suited for use in FMD-endemic areas with high ambient temperatures and where the time to collect and dispatch samples to a laboratory for disease investigation is sometimes protracted. However, their use is currently constrained by limited availability of the required reagents and equipment, along with a lack of trained scientists and funding.

Will the next-generation foot and mouth disease vaccines provide a paradigm shift for control programmes?

Although FMD vaccines are technically difficult and expensive to produce, it is estimated that more than 2 billion doses are used annually [32]. Since the 1960s, most vaccines have comprised chemically inactivated antigen prepared by growing large amounts of virus in cell culture (such as BHK21) formulated with an oil or aqueous adjuvant. The WOAH *Manual of Diagnostic Tests and Vaccines for Terrestrial Animals* (*Terrestrial Manual*) describes procedures that should be adopted to ensure the homologous potency of the product, and FAO and WOAH have produced guidelines for vaccine selection and vaccination monitoring [33] (Fig. 2). Nevertheless, the market is complex, with regional differences in prevailing viruses, approaches to vaccination and governance systems for vaccine quality control and authorisation. In many countries there is no standardisation of vaccine strains, and different vaccine manufacturers supply FMD vaccines derived from a wide range of different master-seed strains. Furthermore, the quality of FMD vaccines (defined by potency, antigenic relevance, antigen payload and purity) is highly variable, and the selection of an appropriate vaccine needs to consider heterologous responses elicited by the formulated product against the target viral lineages likely to be encountered in the field [34] (Fig. 2).

Where markets are supplied by diverse vaccine producers, FMD vaccine selection may be informed by a tender that sets out the vaccine specifications required by the customer. However, interpretation of the information supplied by producers is not always straightforward, and the European Commission for the Control of Foot-and-Mouth Disease (EuFMD) has therefore initiated a system of FMD vaccine prequalification [35].

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This entails expert review of information provided by manufacturers to determine whether their products meet the minimum standards set out in the *Terrestrial Manual*. Independent assessment of vaccines is extremely important. Failure to do this has contributed to poor trust in FMD vaccine quality and a lack of investment in FMD vaccines.

Effective vaccines elicit strong neutralising antibody responses that target epitopes presented on the exterior of the FMDV capsid. Advances in B-cell antibody sequencing help researchers dissect the host polyclonal responses to these epitopes and identify conformational and conserved structures that contribute antigenicity [36]. Furthermore, 146S-specific immunoassays offer the potential to directly assess vaccine antigen content without the requirement to vaccinate animals [37,38]. However, the ability to assess whether vaccinated individuals are protected after vaccination is still largely reliant upon serological methods such as the virus neutralisation test. Unfortunately, recent studies have shown that there is no universally recognised heterologous antibody titre that defines a 'protective' response in vaccinated animals across different serotypes and strains [39], and alternative immunoassays that assess the avidity of antibody responses (such as IgG1 in cattle) are now being evaluated for use [40,41,42].

New FMD vaccine platforms under development exploit knowledge of structural and molecular properties of FMDV gained over the past 50 years. The two leading candidate technologies are FMD vaccine viruses with an attenuating deletion of the leader protease (Lpro) [43,44,45] and stabilised virus-like particles (VLPs) expressed as recombinant proteins [46,47,48,49]. Handling of Lpro deleted viruses has been approved at BSL-2 in the United States, providing a pathway to produce inactivated vaccines independent of expensive high-containment facilities. Furthermore, these vaccine viruses contain specific antigenic markers in the viral 3B and 3D proteins to facilitate a surveillance strategy that can reliably differentiate infected from vaccinated animals [44]. Similarly, VLP-derived vaccines are produced outside of high containment, thereby reducing infrastructure costs and biosafety concerns associated with the current inactivated vaccines. These VLP vaccines can be engineered to accommodate artificial mutations within the recombinant capsids to make them more thermostable and reduce the reliance upon the cold chain [50]. Together, these technologies offer the potential to, within the next five to ten years, supply high numbers of vaccine doses on a cost-effective basis into a market where there is an under-supply of good-quality vaccines.

An important limitation of all existing and candidate technologies that utilise inactivated or recombinant viral capsids is that they elicit only a short duration of protection and

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regular re-vaccination is required. Although vaccines with these characteristics have successfully controlled FMD in Europe and most of South America, there are different challenges in controlling FMD in Africa and Asia, where livestock populations are more mobile and resources for livestock identification and recording of vaccination are usually lacking. In these settings, the use of live-attenuated vaccines is sometimes discussed [51], since this type of vaccine should generate a longer-lasting immune response after a lower vaccine dose. Viruses can be rationally attenuated to maintain immunogenicity despite loss of virulence, but there are significant challenges to deploy safe live-attenuated vaccines for FMD, particularly in endemic regions where reversion to virulence via recombination with field viruses needs to be carefully considered.

The importance of a clear vaccination strategy

There is a wealth of published material debating the value and challenges of emergency vaccination to control incursions in formerly FMD free countries or zones [52], as well as on the application of mass prophylactic vaccination for FMD control and eradication [53,54]. However, good-quality FMD vaccines are expensive to produce, and for endemic countries that seek to manage the impacts of FMD without the capacity for eradication by means of animal movement controls and mass vaccination, the Progressive Control Pathway for FMD (PCP-FMD) recommends risk-based vaccination strategies. Such strategies employ targeted vaccination that may include emergency ring vaccination around outbreaks and prophylactic vaccination of the most valuable and severely affected animals (often dairy cattle) and/or those most likely to spread infection (e.g. prior to movement). There is also interest in vaccinated compartments in support of animal or meat exports to other non-free countries. However, implementation of these approaches in resource-constrained circumstances is often difficult and rarely monitored, so there are few publications on their effectiveness and costs/benefits [55].

Progress on foot and mouth disease control

A 15-year programme (the Global FMD Control Strategy) to promote and accelerate the control and ultimate eradication of FMD was launched by FAO and WOAH in 2012 [56]. At its heart is the PCP-FMD, which provides a framework for stepwise control for countries to advance from a situation of limited understanding of the FMD situation in the country and *ad hoc* control efforts to eventually meet the international standards required for official recognition of freedom from FMD. There is a strong focus on monitoring progress and providing evidence that control measures achieve the desired impact, as well as weighing the costs and benefits, which is often missing [57]. In the Global FMD

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Control Strategy, the PCP-FMD is complemented by activities to strengthen Veterinary Services and the control of other transboundary livestock diseases.

An external review of the implementation of the strategy was completed in October 2023 [58]. It concluded that for the countries engaged in the PCP-FMD, progress has been made, albeit unevenly in different parts of the world and less than anticipated (Fig. 3). Common gaps and challenges noted included insufficient levels of resources, regional coordination, surveillance capacity, vaccination coverage, livestock movement controls and awareness about the negative socio-economic impacts of FMD and the benefits of control. Measures to improve resource mobilisation are perhaps the most critical.

Specific issues that pose a challenge to effectively control FMD include: i) the comprehensive menu of useful activities provided by the PCP-FMD to resource-constrained countries at an early stage of FMD control, which may promote the adoption of insufficiently focused and unrealistic national control plans; ii) governments choosing to control the supply of FMD vaccine as a public good, constraining private schemes of supply and purchase but failing to meet requirements for vaccine quantity or quality; iii) the lack of an evidence base for the cost-effectiveness of risk-based FMD impact controls (i.e. PCP-FMD Stage 2 measures); and iv) the extreme challenge for countries seeking to progress from risk-based control (Stage 2) to virus elimination (Stage 3) when there is insufficient control of livestock movements and/or lack of potential to develop a lucrative export market in livestock products, for example in countries that do not have surplus production.

Addressing these issues requires a multidisciplinary approach, with increased attention to develop the evidence base required to advocate for effective long-term investment in FMD control. Notably, many of the challenges identified (such as insufficient regional coordination, surveillance capacity and movement controls) are not specific to FMD but also pertain to other transboundary animal diseases (TADs). Therefore, an integrated, holistic approach to mitigate TADs risk should be considered, including establishing effective and sustainable animal health systems in the national Veterinary Services, particularly at a time of significant spread of other diseases affecting some of the same hosts as FMD, such as African swine fever and lumpy skin disease [59,60].

Sharing best practices and updates on new approaches to all aspects of FMD investigation and control is vital, and a notable achievement in recent years has been the development of training materials and especially online courses and sources of information, spearheaded by EuFMD [61]. An early focus was on field training of

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European vets in countries where FMD is endemic, but this has broadened to cover many aspects of FMD management, and to date the virtual learning platform has over 28,000 worldwide users. Moreover, since September 2019, more than 8,600 veterinarian learners have completed EuFMD virtual learning courses.

In the last 30 years, perhaps one of the greatest changes in the management of infectious diseases has been the development of, use of and growing reliance upon simulation modelling of their spread and of the impact of different constraints and interventions. This has been fuelled by technological advances, such as increases in the availability of detailed datasets, including whole-genome sequences available in real time during epidemics, and in computational power [62]. The approach had a dominant effect on decision-making during the 2001 FMD epidemic in the United Kingdom [63] and more recently in the management of SARS-CoV-2 [64]. Challenges for further developing and applying the approach to FMD control include the paucity of epidemics from which detailed host and disease data are available (consisting mainly of incursions into FMD free areas) and the lack of demographic data for endemic settings [65].

Arguably, the most important impact of FMD is the loss of access to lucrative livestock export markets. Over the last 20 years, significant changes have been made to the FMD chapter of the WOAH *Terrestrial Animal Health Code* (*Terrestrial Code*) to clarify the requirements for safe trade in FMD-susceptible animals and their products and to reduce the burden on exporters without increasing the risks to importers. Notable changes have included the introduction of containment zones and FMD free compartments and a reduction in the waiting period for status recovery when an emergency vaccinate-to-live strategy is combined with the stamping out of infected animals. An attempt to evaluate the consequent changes in trade, risk and risk mitigation costs has been made [66].

Commodity-based trade (CBT) offers an alternative to compartmental, zonal or national FMD freedom to obtain market access for animal products from regions where FMD is present. There are provisions for this in the *Terrestrial Code*, notably the articles on trade in deboned beef and setting out the ways in which FMDV can be inactivated in different products. CBT has been promoted for beef exports from southern Africa, where FMDV-infected African buffalo (*Syncerus caffer*) make eradication of FMD difficult [67]. It involves management of FMD risk along value chains to enable assurance that the final products are free of FMDV and therefore can be traded with negligible risk of infection transmission, irrespective of the FMD status of the locality of production. Cost–benefit analysis of different trade safeguards, including CBT, has been modelled [68]. The trade in animal products between FMD-infected countries should require less stringent

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mitigation, but differences in circulating serotypes and strains of FMDV must be taken into account. The lack of internationally accepted standards for such trade means that the terms of bilateral agreements must be debated individually.

It has been reported that the number of countries or zones recognised by WOAH to be sufficiently disease-free to engage in international trade in live animals has risen steadily since 2001, as has the volume of goods traded by those countries, aided by the application of a compartmental approach to disease management [66]. WOAH-recognised FMD free countries strive to maintain this status in the face of increasing global movement of people and products that can spread the infection [68]. Cabezas *et al.* [69] reported that between 1996 and 2020, 163 territories were granted official FMD free status, but there were also 45 FMD free status suspensions. Africa and the Americas accounted for over 50% of FMD free status suspensions, while over 70% of these occurred in formerly FMD free territories where vaccination was not practised.

Conclusions

FMD remains an important disease 100 years after the creation of WOAH. Over this time, advances in the ability to control FMD have been partly offset by a tremendous increase in global connectivity through travel and trade, which has facilitated transboundary spread of the disease. Although several countries have succeeded in eliminating FMD with the existing tools, FMD has stubbornly persisted in many lower- and middle-income countries where it is difficult to enforce strict controls on animal movements and the costs to implement effective vaccination are often prohibitive. Recent developments in tools to support surveillance and control have the potential to improve the situation, particularly if they are strategically deployed within the framework of the PCP-FMD and are accompanied by evidence to demonstrate their benefits and investment to enable their application.

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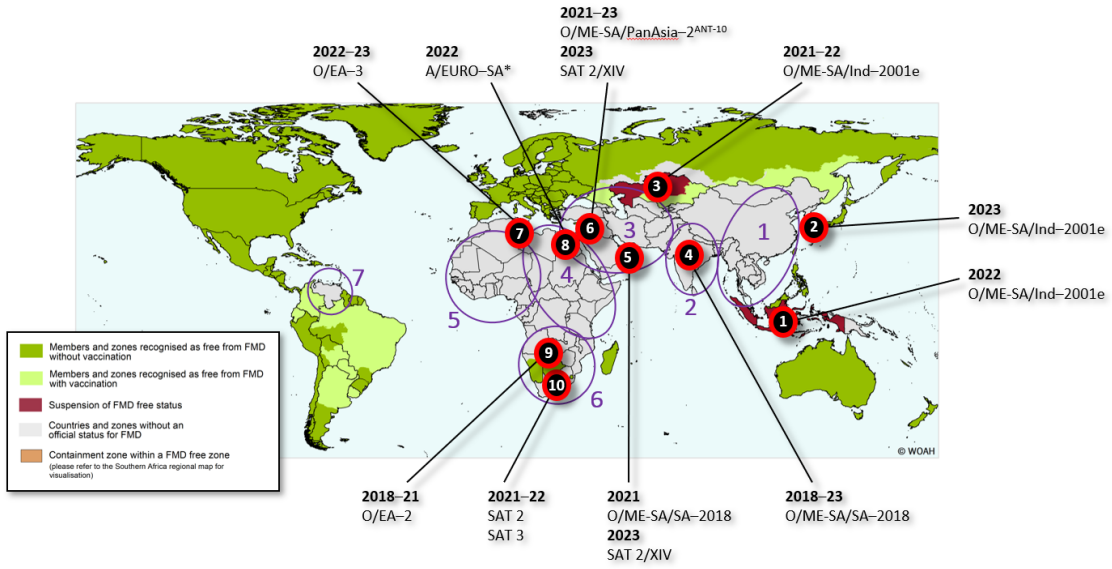

FMD: foot and mouth disease

SAT: Southern African Territories

Figure 1

Global status and distribution of foot and mouth disease

The figure highlights ten recent epidemiological events that have occurred within, or at the margins, of the seven endemic pools (numbered ovals). These include the dominance in Pool 1 of the O/ME-SA/Ind-2001e lineage, which has caused outbreaks in Indonesian archipelago (1), South Korea (2) and Southern Russia/Kazakhstan (3); the emergence in Pool 2 countries of the O/ME-SA/SA-2018 lineage (4), which has recently also been detected in Oman and the United Arab Emirates (5); the spread of a new clade of the O/ME-SA/PanAsia-2^{ANT-10} sub-lineage into the Eastern Mediterranean (Jordan, Israel and Palestine) [6]; new cases due to SAT 2/XIV in the Middle East, which originate from East Africa (5,6); continued incursions of the O/EA-3 topotype in North Africa (7); the unexpected detection of South American viruses in Egypt (8); the southerly movement of the O/EA-2 topotype into Pool 6 (9); and outbreaks due to SAT 2 and SAT 3 in South Africa (10)

*In addition to official reports of cases due to A/EURO-SA, published data also indicate that O/EURO-SA has caused field cases in Egypt (11)

Map background uses **WOAH official FMD status** [1]

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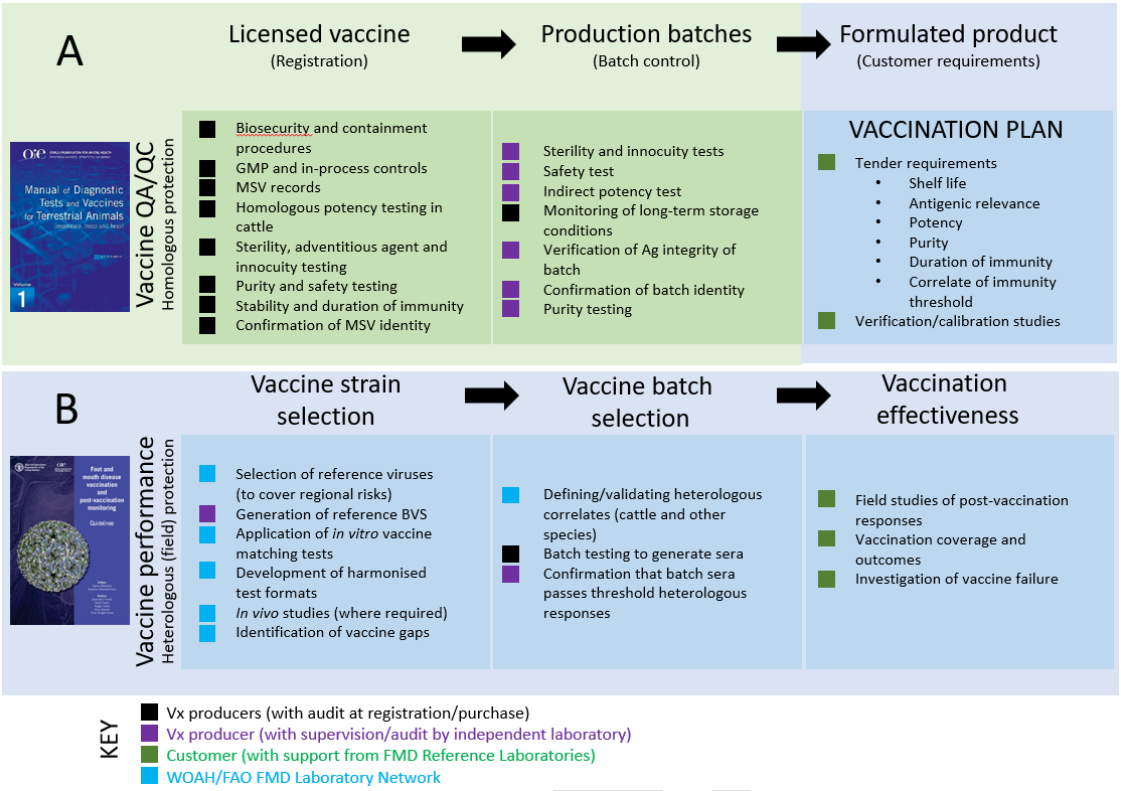

QA: quality assurance

QC: quality control

GMP: Good Manufacturing Practice

MSV: master seed virus

Ag: antigen

BVS: bovine vaccine serum

Vx: vaccine

FMD: foot and mouth disease

WOAH/FAO FMD Lab Network: World Organisation for Animal Health/Food and Agriculture Organization of the United Nations Foot-and-Mouth Disease Laboratory Network

Figure 2

The quality control of foot and mouth disease vaccines, highlighting the separate steps involved, the main actors involved in this process and their responsibilities

These parallel processes cover (A) the production of a foot and mouth disease vaccine that can elicit homologous responses that conform to World Organisation for Animal Health standards and (B) selection and deployment of a formulated food and mouth disease vaccine that is well-matched to the foot and mouth disease virus threats in the population targeted for vaccination

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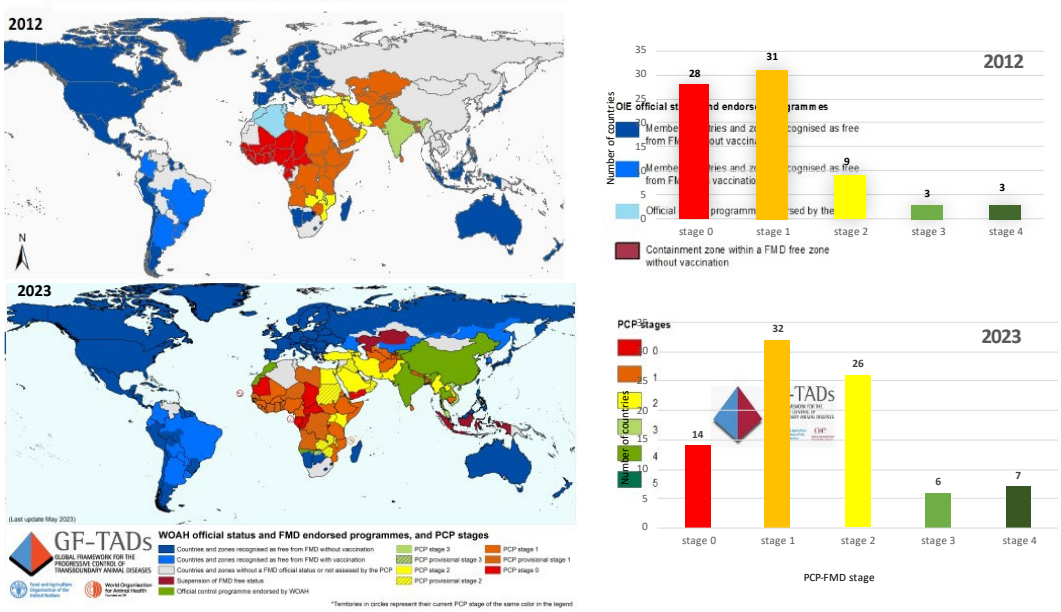

Figure 3

Evolution of progress along the Progressive Control Pathway for Foot and Mouth Disease and World Organisation for Animal Health official foot and mouth disease status between 2012 and 2023

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