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Cross-Sectoral Perspectives of Market Implementation of the MVA Platform for Influenza Vaccines: Regulatory, Industry and Academia

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Abstract

This study provides a quantitative multidisciplinary approach to identify and prioritize the main implementation challenges of the MVA platform for novel influenza vaccines using a tailor-made prioritization process. Influential key opinion leaders (KOL's) in the field of vaccine research, development, and manufacturing were approached to participate in this study. Semi-structured interviews were performed with 32 KOL's representing the regulatory, industry, and academia fields.

The opinions were analyzed quantitatively, through various ranking methods that were integrated and adapted to fit the purpose of this study, identifying 6 implementation challenges main categories, 21 implementation challenges categories, and 39 implementation challenges underlying causes. The most significant barriers are associated with "production & speed" category whereas the least significant are associated with "regulatory" category.

Perspectives among the KOL's proved to be divergent with regard to implementation challenges for the MVA platform. Through comparing these perspectives, useful information on current and potential future implementation challenges of novel platforms in general may be expected. Providing an overview and assessment to reveal these challenges may lead to a more substantial situation for all stakeholders involved, given that such an overview allows for the recognition of various implementation challenges from a multidisciplinary perspective, making it possible to identify underlying causes that contribute to the successful implementation of the MVA platform. Remarkably, analysis of implementation challenges resulted in core challenges that resemble similarities between the three perspectives.

Keywords: MVA platform; Market implementation; Novel technologies; Novel platforms; Vaccine industry; Interdisciplinary perspectives; Influenza vaccines

Introduction

Despite the success of vaccines in disease prevention and control [1], vaccination still has the potential to make an even greater contribution to public health on a global scale [2]. Introduction of recent advances and novel approaches in the influenza vaccine field provide new opportunities that emphasize the need for adapting/improving state-of-the-art technologies.

With a global annual attack rate estimated at 5%-10% in adults and 20%-30% in children, influenza viruses continue to emerge and re-emerge causing approximately 3 to 5 million cases of severe illness, and 250 000 to 500 000 deaths annually [3]. Immunization remains the most effective way to prevent or mitigate influenza [4].

Although current annual influenza vaccines are relatively effective against epidemic influenza infections, these vaccines don't provide protection against pandemic and emerging influenza viruses [5]. Moreover, ensuring an adequate and timely supply of vaccines remains challenging due to, inter alia, the limitations of current technologies [4,6-9]. For the production of influenza vaccines, egg-based and egg-independent technologies are being used [10]. Even though many benefits arrive from egg-based influenza vaccine production, there are several essential disadvantages. Up scaling of production to meet the global demand is limited by embryonated chicken egg supplying mechanisms. This can also be affected by the virulence of pandemic strain since these viruses can be lethal to embryonated chicken eggs [4]. Moreover, an increased surge in vaccine demand during a pandemic will generate at least 5-10 fold of the current global seasonal influenza vaccine production demand [10].

Egg-independent pandemic influenza vaccine approaches include, but are not limited to, cell-derived whole or detergent split, recombinant proteins, virus-like particles, DNA/RNA vaccines, and viral vector vaccines [10-13]. While all these technologies have inherent potential to improve influenza vaccines by increasing production capability and providing shorter production time, many are limited by efficacy and safety concerns. Recent research shows the promise of using viral vector vaccines with certain additional assets, including ability to induce balanced humoral and cellular immune responses and feasibility for large-scale deployment in a short period of time without the safety concerns associated with the production of pathogenic viruses [4,10,14-17].

In recent decades recombinant poxviruses have shown potential as platforms for the development of vaccines that induce protective

immunity against various infectious and neoplastic conditions of humans and animals with a good safety profile [18,19]. The latter is probably due to their replication, which is largely restricted to avian cells. Despite the availability of a series of attenuated poxviral vaccine vectors with a good safety profile, modified vaccinia virus Ankara (MVA) is among the most advanced and widely used attenuated vectors in clinical trials [20,21].

In our previous study, we have quantified the strengths, weaknesses, opportunities, and threats that come with the modified vaccinia virus Ankara (MVA) platform [7]. Here we present implementation challenges of this platform. Furthermore, although different vaccinia virus vectors are being used in many clinical trials against various diseases, such as HIV [22-24], hepatitis [25], influenza [26], malaria [27,28], tuberculosis (TB) [29], and cancer [30,31], MVA vectors have proven to be relatively safe as compared to other vaccinia virus strains [32,33].

An increasing number of novel development/production approaches including viral vector-based techniques shows its potential added value to develop new vaccines that address an unmet medical need. Nonetheless, lack of proper rules and regulations and stringent regulatory requirements act as obstacles in bringing a vaccine candidate to the clinic [34]. International and national regulatory agencies require stringent experiments to address concerns regarding the introduction of novel vaccines. The present study shows that involvement of regulatory, industry, and academia worlds contributes to streamline and improve required regulations, possible biosafety issues, and MVA-vector-associated risks.

The vaccine licensure process prior to vaccine approvals plays a decisive role for manufacturers to expand their engagement in development and manufacturing of novel vaccines [35]. Although demonstration of added value of novel generation vaccines contributes to their successful registration and implementation on the market, providing convincing clinical data appears to be challenging for manufacturers [4]. Furthermore, dependency on external factors discourages industry to invest in development of novel vaccines.

In the present study, we uncover market implementation challenges of the MVA platform [7] by performing semi-structured interviews with the KOL's representing the golden triad; regulatory, industry, and academia. Quantifying expert's opinions regarding market implementation challenges of the MVA platform through various ranking methods (integrated assessment (IA) approach, perspective method, and rank-frequency and importance frequency methods) provides a unique overview from a multidisciplinary perspective, making it possible to identify foremost underlying causes that contribute to the challenges novel vaccines have to face before successful market implementation.

Methodology

A comprehensive analysis of our previous study indicated the added value of diverse perspectives that exist among the KOL's with different backgrounds [7]. A multidisciplinary approach has been used to represent the most influential stakeholders in the field of vaccine research, development, and manufacturing, namely; regulatory, industry, and academia.

Data collection consisted of a literature study on the topic of this research and interviews with KOL's. Semi-structured qualitative interviews serve as a tool to further identify the main implementation challenges in the field of influenza vaccine [36]. The prioritization process was based on several quantitative ranking methods that were integrated and adapted to fit the purpose of our research; integrated assessment (IA) approach [37-42], perspectives method [43,44], and rank-frequency and importance frequency methods [45,46]. The results from all analyses are integrated to create a RCA tree [47,48] (RCA applied top-down) visualizing all three perspectives (Table 1).

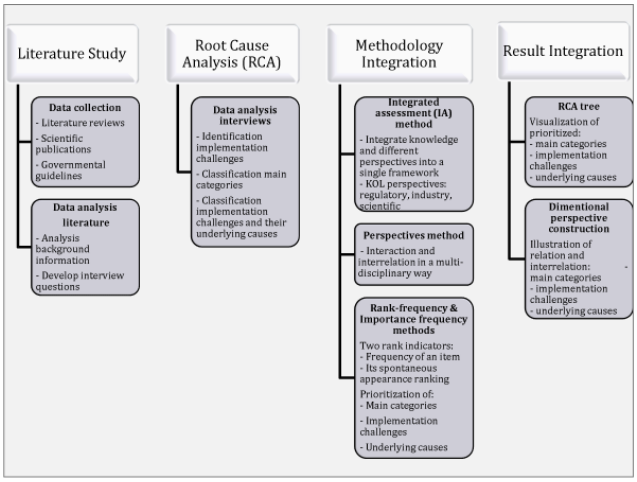

Table 1: Study design.

Descriptive study design

Root cause analysis (RCA): Root cause analysis is an approach designed to identify the underlying causes of events, in this case MVA implementation challenges on the influenza market. Identification of underlying causes enables to reveal different effective options for solutions. The RCA is a four-step process including data collection, causal factor visualization, root cause identification, and generation of the most effective recommendation to overcome the challenges [49,50].

Interviews: The interview candidates were purposively selected using the snowball method [50,51] to provide a diverse and complete overview from the field of influenza. The interviewees were asked a standardized set of questions in order to make the results comparable. The results from the interviews were subsequently used for further analysis (Table 2).

Background	Interviewees	Response rate
Regulatory	9	23%
Industry	18	100%
Academia	5	39%
Total	32	48%

Table 2: Interviewee's background.

Integrated assessment (IA) approach: Integrated assessment (IA) approach provides the opportunity to integrate knowledge and perspectives from several domains into a single framework. This research approach pursues scientific understanding of complex issues based on combining, interpreting, and communicating knowledge

from different disciplines in such way that a cause-effect chain of an issue can be evaluated from different perspectives [37-42]. In contrary to conventional research analysis, IA is very effective in not only unveiling problems and their underlying causes, but at the same time providing relations between these causes. Complex problems have several causes that sometimes interact across multiple domains, consequently, requiring application of inter- and trans-disciplinary approaches.

Perspective method: Together with the aforementioned approach, the perspectives method focuses on the interaction and interrelation between regulatory, industry, and academia KOL's in a multi-disciplinary way. The perspective method classifies, interprets, and analyses these different perspectives [43,44]. We developed a set of questions and conducted interviews with the KOL's from the field of influenza as part of the perspectives method to analyse the current perspective on the implementation of MVA platform among the experts with different backgrounds. Subsequently, a dimensional perspective construction was created providing insight into differences and similarities between the three stakeholders. This construction plays an essential role in identification of reasons behind discrepancies and demonstrates inherent challenges at different levels.

Rank-frequency and importance-frequency methods: The rank-frequency method cross-tabulates the frequency of an item with its appearance ranking. This method consists of two indicators: the frequency of a factor and its appearance ranking. The importance-frequency method replaces the appearance ranking criterion with an importance ranking criterion [46].

Results

A total of sixty-two peer-reviewed publications, divided in scientific reviews (12), scientific publications (30), and governmental guidelines (3) were evaluated in order to attain more insight into the topic of this study (Table 3).

Policy making on implementation of a vaccine development/production platform involves diverse fields of expertise. To assess the MVA market implementation challenges under different perspectives, 30 KOL's from the vaccine field were interviewed. As a result, three distinctive perspectives on implementation of MVA platform emerged, each led by its own established view in a different discipline and each with a predominant emphasis on specific set of underlying causes (Figure 2). The analysis of interview transcripts reveals 6 main categories of implementation challenge, which subsequently are divided into 21 categories of implementation challenges. These categories are further subdivided into 39 underlying causes.

Reviews	Publications		Governmental Guidelines
Altenburg et al. 2014	Andre et al. 2008	Hanton et al.2002	Kaper et al. 2005
Chan et al. 2013	Baarda et al. 2005	Offermans et al. 2012	WHO et al. 2014
Cherp et al. 2011	Bakari et al. 2011	Osterhaus et al. 2011	WHO et al. 2012
Choi et al. 2013	Bejon et al. 2007	Ramezanpour et al. 2015	
Cottingham et al. 2013	Berthoud et al. 2011	Rotmans et al. 1998	
Krammer et al. 2015	Cavenaugh et al. 2011	Schneider et al. 1997	
Lee et al. 2014	Dany et al. 2015	Sheehy et al. 2012	
Mooney et al. 2013	De Ridder et al. 2007	Smits et al. 2009	
Pandey et al. 2010	Draper et al. 2013	Suter et al. 2009	
Perdue et al. 2011	Edenhofer et al. 2005	Tameris et al. 2013	
Rimmelzwaan et al. 2009	Ferenc et al. 2003	Ulmer et al. 2006	
Rollier et al. 2011	Garcia et al. 2011	Valkering et al. 2009	
	Goodman et al. 1961	Verheust et al. 2012	
	Gomez et al. 2011	Verschuren et al. 2010	
	Greenwood et al. 2011	Zeng et al. 2014	

Table 3: List of total evaluated reviews, publications, and governmental guidelines.

Dimensional perspective construction; three perspectives, their similarities and differences

Mapping the implementation challenges in a dimensional perspective construction visualizes differences and similarities between KOL's responses (Figure 1). This figure illustrates the core implementation concerns associated with each perspective. According to the KOL's multidisciplinary perspectives, following implementation categories are ranked as top three and thus are essential: challenging to provide convincing clinical data, external dependency, and need for new production platforms/facilities. Furthermore, analysis of the obtained data made it possible to identify several other important categories by KOL's perspectives: flexibility requirements, regulatory construct, licensable vaccines, and challenging to demonstrated efficacy, respectively (Figure 1).

From the regulatory, industry, and academia perspective, it is challenging to demonstrate efficacy in clinical trials and therefore difficult to provide compelling data. According to the KOL's, external dependency on factors such as strain reference and reagents emphases the necessity for new production platforms/facilities, which consequently contribute to a more rapid production process and hopefully translating to faster market entry. Flexibility is a prerequisite in every step of the process in order to eventually produce licensable vaccines and acquire regulatory approval.

According to the KOL's from the regulatory authorities and industry, influenza market is viable, large, and complex. Industry emphasizes the importance of demonstrating added value of a product in comparison to other competitive products. Providing compelling data is necessary to validate this added value and make a product more appealing to the eyes of different stakeholders. Moreover, an extensive intellectual property (IP) profile is a requirement in this field.

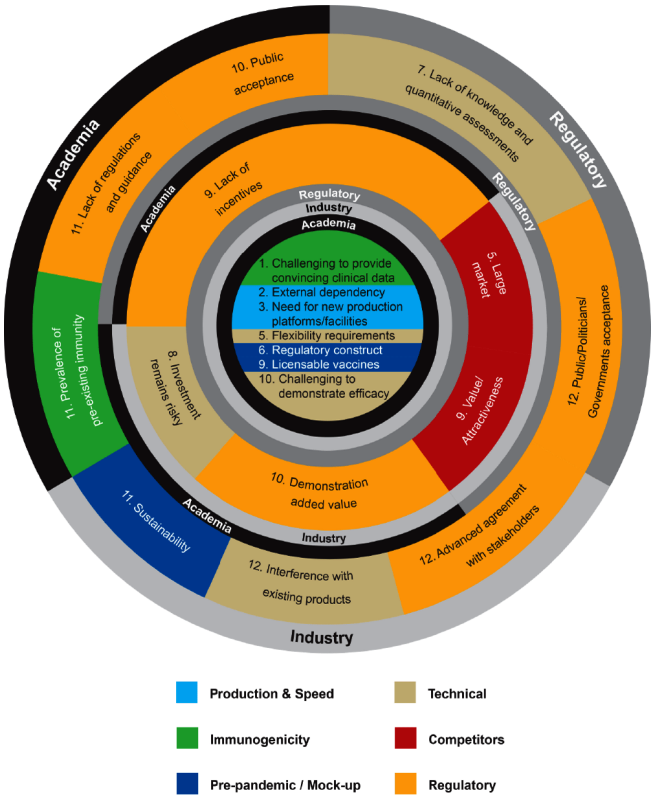

Figure 1: Dimensional perspective construction. Three perspectives on MVA platform implementation have their roots in separate disciplines; regulatory, industry, and academia. They differ with respect to their focus on various domains. The implementation-challenge-categories are situated in the centre of the diagram address the concerns of all three perspectives. Each additional layer represents a different perspective illustrated by colour. And each colour represents a separate main category of implementation challenges. The outer shell represents the main KOL's perspective.

According to the regulatory authorities, providing knowledge and quantitative assessments might be one of the most essential compelling factors helping the acceptance of MVA platform by various stakeholders including public, politicians, and governments. From the academia perspective, the effects of pre-existing immunity against vaccine vectors in the human population may represent a barrier in successful implementation of such platforms. Furthermore, public acceptance towards vector-based vaccines is one of the profound challenges in successful market implementation of MVA.

Both regulatory and academia KOL's indicate that the industry needs to be incentivized to make further investments in the development of novel technologies. Complex territorial regulations and requirements complicate translating vaccine candidates into actual vaccines. Furthermore, implementation of MVA platform might interfere with ongoing projects in the pipeline. A good business model is required to ensure application sustainability of this platform, from an industry perspective. Application of an advance-purchase-agreement can support sustainability and helps risk sharing for development of pandemic vaccines.

RCA tree

Implementation challenges of the MVA platform are assigned to six main categories: production and speed, technical, immunogenicity, competitors, pre-pandemic/ mock-up, and regulatory. These categories are further classified and ranked according to their importance into 21 implementation challenges categories. Underlying causes, a total of 39, related to each challenge are also illustrated in Figure 2.

Production and speed: Comparing to other implementation main categories, the main category "production & speed" has the highest overall score. External dependency challenges, posed predominantly by industry KOL's, are a predominant implementation challenge of the MVA platform. The foremost underlying causes for delay in the production process are unpredictable global demands, external factor including reagents and reference strains provided by the WHO, and rules & regulations. Moreover, advanced production platforms and proper facilities are required to speed-up the process of market entry and validation.

Technical: The main category "technical" is ranked to possess the second highest scores. Within this category flexibility requirements to match antigenic changes in circulating viruses are ought to be essential. Nevertheless, lack of knowledge to provide quantitative assessments regarding cross-reactivity and required protection immunity remains a challenge. Consequently, technical challenges and unpredictable market dynamics and demands are considered to be of high risk to manufacturers when deciding to invest in novel technologies.

Immunogenicity: Within this main category, challenges related to provide convincing clinical data are the foremost mentioned challenge, in particular from a regulatory perspective. The main underlying causes are the lack of clinical data on immunogenicity, cross-protection, safety, and efficacy. Additionally, comparison to the current standard of care raises the bar even higher (Figure 2).

Competitors: Due to the large and complex nature of the influenza market and many comparable competitive products available in late stage development, demonstrating added value assures competitive advantages in gaining market share and public acceptance. Furthermore, the public needs to be educated on the value of vaccinating with a virus, MVA, against another virus, influenza.

Pandemic/Mock-up: Mock-up dossiers are regulatory constructs to make advance-purchase-agreements with governments due to unattractive nature of pandemic vaccines during peacetime. Moreover, mock-up vaccines facilitate and increase the chance of getting proof of concept vaccines into clinical trials. This business strategy will ensure sustainability and therefore increase the chance for development of licensable vaccines by the industry.

Regulatory: According to the regulatory authorities, lack of incentives for vaccine manufacturers and complex requirements and regulations for novel vaccines complicates the translation of pandemic candidates into actual vaccines.

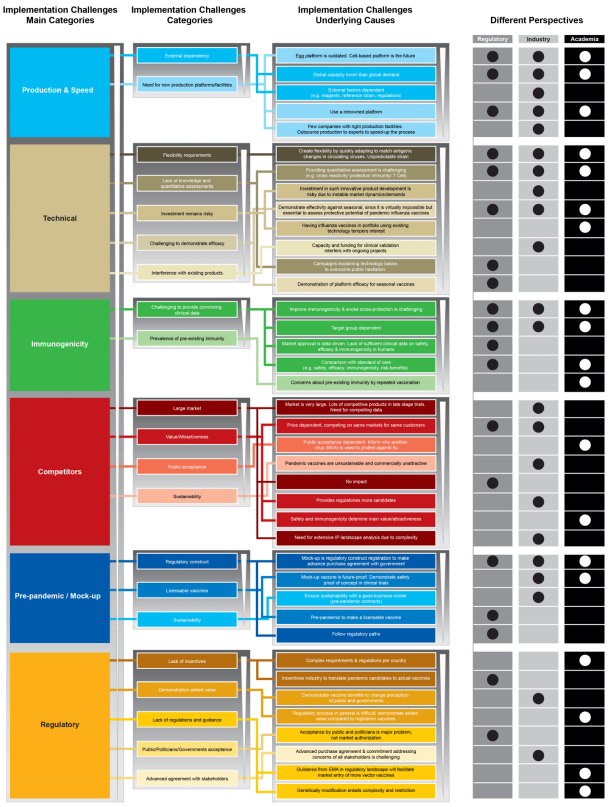

Figure 2: RCA tree. Integration of the overall results: root-cause analysis (RCA), rank-frequency method, integrated assessment (IA) approach, and perspectives method of MVA platform implementation.

Importance frequency

Results presented here indicate the most important implementation challenges, main categories/ categories/ underlying causes, ranked according to each perspective (Figure 3).

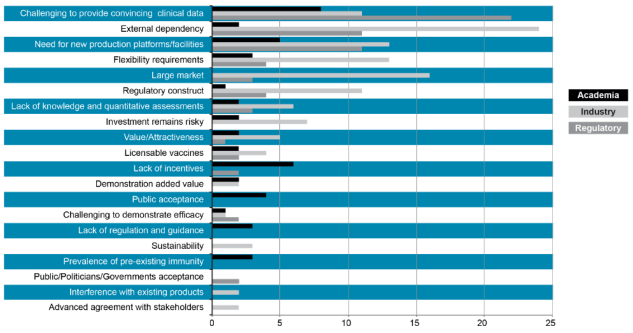

Figure 3: Importance frequency, ordered according to all results of implementation challenges categories from the regulatory, industry, and academia perspective.

From the perspective of the regulatory authority and academia KOL's, providing convincing clinical data with the purpose of vaccine approval remains the most challenging factor for the implementation process of MVA platform. External dependency is experienced as the most essential implementation barrier that the industry has to face in order to get the MVA vaccine development/production platform on the market. All three perspectives consider these challenges as predominant barriers, however with variable importance degrees depending on their backgrounds.

There are also some implementation-challenge-categories solely mentioned by one perspective. Regulatory authorities indicate public/politicians/governments acceptance to play an essential role in the future after implementation of this platform. According to the industry KOL's, sustainability of such platform with respect to time-bound properties of these pandemic vaccines and importance of having a solid business strategy to remain successful is going to be a profound challenge. From the perspective of the academia KOL's, public acceptance of such platform must also be taken into consideration while discussing the challenges.

Discussion/Conclusion

The current study evaluates the market implementation potential of MVA platform to generate next-generation influenza vaccines, which will provide superior immunogenicity, safety profile, and shorter production time. Our study reveals that implementation barriers of the MVA platform can be grouped into six main categories (ranked according to importance): "production & speed"; "technical"; "immunogenicity"; "competitors"; "pre-pandemic/mock-up" and "regulatory". It is noteworthy that the top three categories when ranked according to the rank-frequency as well as that importance frequency coincides with the top three categories shared by all three perspectives. Approaching KOL's representing industry, regulatory, and academia shows how complex the acceptance of an MVA based influenza vaccine production platform can be.

Visualization of integrated results shows that dependency on external factors such as reagents and reference strains requires immediate attention based on the fact that this category is related to the most important main category, "production & speed". Regulatory and academia commonly recommend making less complex and more streamlined regulations that consequently will, inter alia, incentivize the manufacturers to develop vaccines instead of vaccine candidates (Figure 2). Therefore, it is noteworthy that the main category "regulatory" is not as highly ranked as it is generally assumed to be [51]. This state of discrepancy between KOL's perspectives highlights ambiguity regarding novel vaccines regulations and stresses the need for custom-made rules, regulations, and guidelines.

At present, many of the core implementation challenges overlap between the three perspectives with a remarkably high level of resemblance on required immediate attention for the top two challenges. This not only reveals that the solution to these challenges must be an integrated effort, but it also emphasizes the importance of breaking the barriers by working together. This new way of collaboration between various stakeholders will eventually redefine their relationship.

High level of urgency for new production platforms/facilities requires speeding up the search for novel platforms that meet the requirements. Consideration of combining novel technologies with conventional production platforms and vaccine formulations is

necessary to speed up the production of vaccines and reduce time gap between the emergence of new influenza viruses and vaccine availability.

Successful introduction and registration of a new vaccine (platform) is based on and influenced by various factors including provision of sufficient information to decision makers, demonstration of added value comparing to existing products, increased public acceptance of the vaccines by demonstrating safety, efficacy, sustainability, and cost-effective.

Industry KOL's indicate establishing a sustainable business model as a prerequisite to turn a relative commercially unattractive platform into a success. Depending on market dynamics and uncertainties, manufacturers can be confronted with various unexpected events, such as technological/developmental failures and technological/logistical and regulatory challenges, which all contribute to the risks manufacturers have to face in order to realize developing novel pandemic vaccines [8]. Nevertheless, this study indicates that data-driven decision-making for vaccine development approaches will provide a dominating competitive advantage in this large and viable market.

Providing compelling data representing added value of novel technologies and demonstrating competitive edge to many existing products on the market is deemed very important both by regulatory and industry KOL's. Hence, it is essential to explore application of this platform for both seasonal and pandemic influenza as well as other infectious diseases [7]. Moreover, alternative route of immunization such as oral, needle-free skin delivery, nasal, and sublingual must be considered as well [8].

Furthermore, integration of different perceptions and collaboration of different stakeholders working with different paradigms offering different insights contribute in beneficial decision making and helps reaching consensus when interactive complexity plays a predominant role. First and foremost the clinical data on safety and efficacy must be beyond doubt but public opinion can also be a barrier. Therefore, public attitude and public acceptance towards vector-based vaccines such as MVA is another challenge that must be surmounted aided by the application of clear guidance and regulations by relevant authorities. Moreover, the public needs to be educated on the value of vaccinating with a virus, MVA, against another virus, influenza.

Finally, practical challenges of establishing MVA platform on the market and ensuring effective long-term sustainability of this platform require collaboration from different stakeholders. Our study indicates that once regulatory, industry, and academia fields understand each other's perspective and come to the realization that they jointly can anticipate market implementation barriers in a collaborative manner that will lead to a strategic dialogue and consequently increased chance of reaching a consensus. This will be beneficial for each and every party involved and will further make an enormous contribution not only to public health but also to the economy.

The future of vaccines is unpredictable due to, inter alia, high complexity, uncertainty, and ambiguity of its market dynamics. In such an uncertain situation, the threats such as regulatory and political fluctuations, innovative and disruptive technologies, and unforeseeable economical and social consequences could be simultaneously barriers and advantages. Identifying, analyzing, quantifying, prioritizing of implementation challenges from different perspectives provide the opportunity to explore different views, evaluate various options, minimize inherently uncertain risks and barriers, consequently anticipate future challenges and be prepared for future threats.

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Conflict of Interest

All authors state having no conflict of interest for the conduction of this study.

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