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Market implementation of the MVA platform for pre-pandemic and pandemic influenza vaccines: A quantitative key opinion leader analysis

Bahar Ramezanpour[a,c,*], Esther S. Pronker[b], Joost H.C.M. Kreijtz[a], Albert D.M.E. Osterhaus[a,d], E. Claassen[a,c,d]

[a] Erasmus Medical Centre Rotterdam, Viroscience Lab, 's Gravendijkwal 230, 3015 CE Rotterdam, The Netherlands
[b] Viroclinics Biosciences BV., Rotterdam Science Tower, Marconistraat 16, 3029 AK Rotterdam, The Netherlands
[c] Vrije Universiteit Amsterdam, Athena Institute, De Boelelaan 1085, 1081 HV Amsterdam, The Netherlands
[d] Artemis One Health Research Foundation, Androclus Building, Uithof Yalelaan 1, 3584 CL Utrecht, The Netherlands

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ABSTRACT

A quantitative method is presented to rank strengths, weaknesses, opportunities, and threats (SWOT) of modified vaccinia virus Ankara (MVA) as a platform for pre-pandemic and pandemic influenza vaccines. Analytic hierarchy process (AHP) was applied to achieve pairwise comparisons among SWOT factors in order to prioritize them. Key opinion leaders (KOLs) in the influenza vaccine field were interviewed to collect a unique dataset to evaluate the market potential of this platform.

The purpose of this study, to evaluate commercial potential of the MVA platform for the development of novel generation pandemic influenza vaccines, is accomplished by using a SWOT and AHP combined analytic method. Application of the SWOT–AHP model indicates that its strengths are considered more important by KOLs than its weaknesses, opportunities, and threats. Particularly, the inherent immunogenicity capability of MVA without the requirement of an adjuvant is the most important factor to increase commercial attractiveness of this platform. Concerns regarding vector vaccines and anti-vector immunity are considered its most important weakness, which might lower public health value of this platform. Furthermore, evaluation of the results of this study emphasizes equally important role that threats and opportunities of this platform play.

This study further highlights unmet needs in the influenza vaccine market, which could be addressed by the implementation of the MVA platform. Broad use of MVA in clinical trials shows great promise for this vector as vaccine platform for pre-pandemic and pandemic influenza and threats by other respiratory viruses. Moreover, from the results of the clinical trials seem that MVA is particularly attractive for development of vaccines against pathogens for which no, or only insufficiently effective vaccines, are available.

1. Introduction

Vaccines are the most cost-effective tools for controlling the spread and impact of infectious diseases in both humans and animals [1]. Vaccines generally work by harnessing the host's adaptive immune system against infectious pathogens, by exposing it to an inactivated, live-attenuated, sub-unit or recombinant version of the wild-type pathogen or parts thereof [2,3]. Furthermore, appropriately managed vaccination campaigns have completely eradicated two devastating infectious diseases of humans and animals: smallpox and rinderpest, respectively. This accomplishment has not been equalled by any other medical or veterinary interventions [4–6]. Unfortunately, interventions for most viral diseases still represent a significant unmet medical need. Reasons include, but are not limited to absence of safe and effective vaccines, lack of vaccine availability, accessibility, and affordability [2]. State-of-the-art technologies may be used to overcome at least some of these limitations. This paper largely focuses on the issue of vaccine availability to combat human pandemic influenza.

* Corresponding author at: Marconistraat 16, 3029 AK Rotterdam, The Netherlands. Tel.: +31 611957039.
E-mail addresses: baharramezanpour@yahoo.com (B. Ramezanpour), e.s.pronker@gmail.com (E.S. Pronker), joostkreijtz@hotmail.com (J.H.C.M. Kreijtz), a.osterhaus@erasmusmc.nl (A.D.M.E. Osterhaus), prof.eric.claassen@gmail.com (E. Claassen).

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Expression systems may be used to express genes encoding immunogens of pathogens in order to directly induce protective immune responses in the human or animal host [7,8]. Vectors applied for this type of vaccine delivery include plasmid DNA, RNA, viral and bacterial vectors [7]. Several viral vector-based vaccine platforms exist, such as adeno-, pox-, parainfluenza-, and alphavirus-based expression systems. Those and the others allow the establishment of vaccines for heterologous pathogens [2,7,9] and all have their inherent advantages and disadvantages.

In the recent decades recombinant poxviruses of mammals and birds have shown potential as platforms for the development of vaccines that induce protective immunity against various infectious and neoplastic conditions of humans and animals [1,10,11]. Despite these supportive data and the apparent potential of poxvirus-based platforms and their current use in animal vaccines, there is still no recombinant poxvirus based vaccine registered for use in humans [12]. Nevertheless, several incremental improvements, such as techniques allowing for better quantitative and qualitative target antigen expression characteristics, prime-boost regimens, as well as viral vector manufacturing and purification technology, justify the expectation that several poxvirus vector-based vaccine candidates for humans are approaching their final stages of development [1,13,12].

Modified vaccinia virus Ankara (MVA) is among the most advanced and well-characterized recombinant vaccine vectors currently in human clinical trials [14]. MVA is a highly attenuated strain of vaccinia virus, originating from chorioallantois membrane produced vaccinia virus Ankara after more than 570 serial passages in primary chicken embryo fibroblasts (CEF). This serial passaging of MVA resulted in a loss of virulence and immune evasion genes as well as its ability to replicate in most mammalian cells [15,16]. Currently, European Medicine Agency (EMA) has approved a vaccine against smallpox containing a non-replicating live form of the MVA virus, which implies effectiveness and safety of this vaccine platform technology as an entity suitable for addressing a wide variety of infectious diseases [17,18].

Altenburg et al. elaborate on the advantages and disadvantages of MVA as viral vector platform for vaccines against influenza and other viral respiratory diseases in their reviews. They describe unique properties of MVA as viral vector vaccine including its biological safety profile, relative easy production process for large-scale manufacturing, and potential to efficiently express a plethora of foreign genes either alone or in combination enabling the use of MVA as a versatile and multivalent vaccine [11,17,19]. Moreover, MVA has immunostimulatory capacities to induce protective immune responses against many infectious agents. In particular targeting the innate in addition to the adaptive immune system obviates the use of an adjuvant [11]. Replication deficiency of MVA is confirmed in various in vivo mammalian models including animals with severe immunodeficiencies [17]. Furthermore, recombinant MVA viruses can be used under conditions of biosafety level 1 in most countries. These features provide advantages compared to replication competent poxvirus vectors and other viral vectors [17].

Pre-existing anti-vector immunity may hamper the effectiveness of vectored vaccines. Nonetheless, also in the presence of pre-existing anti-vector immunity, protective immunity against for instance influenza could be induced [10,11,17]. Although several influenza virus proteins have been shown to induce different levels of protective immunity, in the current study we took the approach that an MVA based vaccine against pandemic influenza should primarily express the hemagglutinin (HA) gene [20–24].

Limitations associated with other production platforms also apply to MVA viral vectored vaccine candidates. Considering that MVA has the potential to express multiple foreign antigens of interest, each new recombinant MVA virus is considered a new biological entity and thus requires proper quality assessment. Furthermore, heterologous prime-boost vaccination strategies will complicate the regulatory approval process [17]. These issues need to be addressed prior to successful implementation of this platform for use against pre-pandemic and pandemic influenza and other new emerging pathogens. More data on efficacy in humans would also contribute to success of this platform.

In the present study we have evaluated the commercial potential of MVA vector-based vaccine technology for pre-pandemic and pandemic influenza by approaching key opinion leaders (KOLs) in the field of influenza vaccine development, in order to obtain a balanced view on its strengths, weaknesses, opportunities, and threats using the SWOT–AHP combined analytic method [25–27]. Application of AHP method helps construct a multi-criteria decision-making process, identify decision-making factors, and determine the reciprocal importance of these factors [28]. AHP method provides the possibility to quantify and prioritized subjective, qualitative, and intangible factors into numeric values. Moreover, this approach is an effective decision-making method especially when subjectivity might exist [26].

In doing so we provide an empirically validated contemporary industry view of MVA as a vaccine technology platform. We demonstrate that MVA is considered a suitable platform for vaccine development, and argue that there is a future for MVA based vector platforms to develop not only preventive, but also therapeutic vaccines to address unmet public health needs in the field of infectious diseases.

2. Methodology

The methodology used is built-up into three data collection moments. First, collecting background information from the literature, which subsequently enabled us to develop a balanced set of interview questions. Next, quantification of the qualitative data generated from interviews with KOLs by means of SWOT–AHP application. Finally, drawing conclusions by integrating the two previous steps (Table 1).

2.1. Literature reviews and interviews

A literature study was conducted to gain more insight into the MVA platform and its potential for influenza vaccine development, learn more about the industrial players in the market, and develop a validated set of interview questions. Market potential of a new production platform for influenza vaccine development, such as MVA, is best evaluated by KOLs specialized in the field of influenza

Table 1
Study design. SWOT: strengths, weaknesses, opportunities and threats.

STEP 1	STEP 2	STEP 3
Literature review and interview • Relevant background information • Insights into market competition	**SWOT–AHP application** • Interviews	**Conclusion, data integration** • Results from previous steps are integrated and illustrated in a SWOT matrix
Data analysis • Develop set of interview questions	**Data analysis** • Determine SWOT main groups and factors • Application SWOT–AHP analysis method • Calculating priorities of main groups and each factor within SWOT • Overall factor weight, quantified and ranked	**Visualization** • Influence of SWOT groups are identified and visualized

intervention strategies. In order to determine SWOT of the MVA platform for influenza vaccines, semi-structured interviews with KOLs were performed.

Fifty out of a total number of sixty-two (80%) articles that were selected based on topic relevance were published after 2010. Only thirteen (20%) did not meet this criterion. This study used a combination of Pubmed, Google Scholar, ScienceDirect, Web of Science, applying relevant search terms on the subject including virus vectored vaccine, modified vaccinia virus Ankara (MVA), influenza virus, pre-pandemic and pandemic vaccine, vaccine technology platform, and vaccine production platform.

2.1.1. Interview participants

KOLs, who include a range of influential individuals with extensive knowledge and experience in the field of influenza (e.g. US Department of Health and Human Services (HHS), CEOs and Senior managers from large companies in the field of influenza, World Health Organization (WHO), National Institute of Infectious Diseases (NIAID)), wish to remain anonymous due to confidentiality concerns. Participants were approached to contribute in interviews representing industry, (non) governmental, and public research institutions. This selection was based on their expertise in the influenza vaccine field. Twenty-four out of ninety KOLs agreed to participate in the study (response rate of approximately 30%). In this research we subdivided them into two groups: industry and non-industry. Eighteen participants from industry and six, non-industry participants contributed in the study.

2.1.2. Exploratory interviews

The participants were contacted, informed about the nature of the study, and invited to take part. Two pilot interview sessions were conducted prior to implementation of 60 min semi-structured interviews.

2.1.3. Interview questions

Interview questions (Appendix 5 (supplementary materials)) were developed focusing on the influenza field, in particular MVA virus vector vaccines, and their implementation potential. In essence, the interviews were designed to gather data on how KOLs perceive the current pandemic vaccine field, possibilities to increase the commercially attractiveness and public health value of influenza vaccines, reciprocal competition in the influenza vaccine market, and SWOT of MVA platform for influenza vaccines.

2.2. SWOT analysis

SWOT analysis is a commonly used business analysis tool to evaluate external and internal environmental factors, which could impact the strategic planning process. The purpose of SWOT application in decision-making is to develop and implement a strategy resulting in a good fit between internal and external factors. Internal factors to the theme are usually classified as strengths and weaknesses, and those external to the theme are classified as opportunities and threats (Fig. 1) [25–27,29].

2.3. AHP analysis

AHP is a multi-criteria decision analysis tool that helps express the general decision process by deconstructing a complicated problem into a multilevel hierarchical structure [28]. Furthermore, AHP method is applied as prioritization mechanism to accomplish pairwise comparison of factors representing the relative importance of the criteria determined by the joint judgments of the experts. The team of experts provides their preferences by comparing two given factors. The question is which of the two factors has a greater value

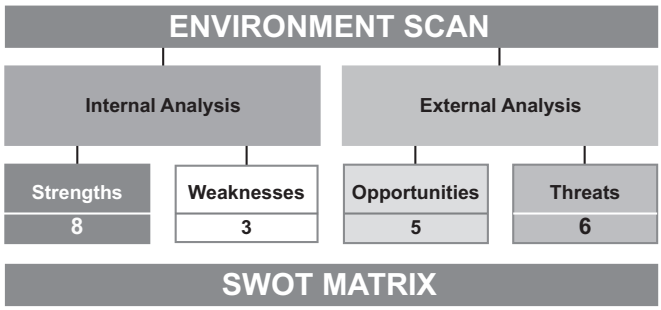


Fig. 1. SWOT analysis framework. Environmental scan provide two different analysis; internal factors and external factors. This study comprises; Internal factors: strengths (8 factors), weaknesses (3 factors); External factors: opportunities (5 factors), threats (6 factors).

and how much. The comparisons are made using a scale of absolute numbers that represents which of the two factors has a greater weight in the choice and how much. In AHP, pairwise comparisons are based on a standardized comparison scale of 1–9 (Table 2). The whole number is entered in its appropriate position and its reciprocal in the transpose position [28,30,31].

Pairwise comparisons are separately made for each SWOT group. In the next step relative weights of factors are calculated where W_1, W_2,..., W_n are the weights obtained by the comparisons. Subsequently, multiply together the elements in each row of the matrix, and then take the nth root of that product. "W" is called an "eigenvector" of order n. The sum of the nth roots is used to normalize the eigenvectors to add to 1 (Table 5).

$$\begin{matrix} \frac{W_1}{W_1} & \frac{W_1}{W_2} & \cdots & \frac{W_1}{W_n} \\ \frac{W_2}{W_1} & \frac{W_2}{W_2} & & \frac{W_2}{W_n} \\ \vdots & \vdots & & \vdots \\ \frac{W_n}{W_1} & \frac{W_n}{W_2} & \cdots & \frac{W_n}{W_n} \end{matrix}$$

Each eigenvector is normalized by multiplying the matrix of judgments by eigenvectors of each element, providing a new vector. Relative importance values are obtained by using the eigenvalue techniques to obtain "λ". "λ" is called an "eigenvalue". λ is calculated by dividing each new vector by the corresponding eigenvector element. The mean of these values is the estimated λ_{max}. If the pairwise comparisons are consistent, $\lambda_{max} = n$.

Table 2
AHP scale. Pairwise comparison scale.

Intensity of importance	Definition	Explanation
1	Equal importance	Two activities contribute equally to the objective
3	Moderate importance	Experience and judgement slightly favour one activity over another
5	Essential importance	Experience and judgement strongly favour one activity over another
7	Very strong importance	An activity is favoured very strongly over another; its dominance demonstrated in practice
9	Extreme importance	The evidence favouring one activity over another is of the highest possible order of affirmation
2, 4, 6, 8	Intermediate values	When compromise is needed between two

Table 3
Random Index.

n:	1	2	3	4	5	6	7	8	9	10
RI	0.00	0.00	0.58	0.90	1.12	1.24	1.32	1.41	1.45	1.49

The quality of the AHP is related to the consistency of the pairwise comparison judgments. Therefore, it is important to judge the consistency of the decision-making. The Consistency Index (CI) is calculated using the following equation:

$$\mathrm{CI} = \frac{\lambda_{\max} - n}{n - 1}$$

Consistency Ratio (CR) can conclude whether the evaluations are sufficiently consistent.

According to Random Index (RI), if the number of CR exceeds the value of 0.1, the evaluation procedure has to be repeated to improve consistency (Table 3). A CR of 0.1 or less is generally stated to be acceptable. The AHP method applied in this study is based on research method developed by Saaty [28,30] and used by Görener, Lee, and Kahraman [26,27,32].

$$\mathrm{CR} = \frac{\mathrm{CI}}{\mathrm{RI}}$$

2.4. SWOT–AHP analysis model

Here, we provide quantitative means for SWOT analysis. One of the main limitations of the classical SWOT analysis is that the importance of each factor cannot be quantified. Therefore, it is difficult to assess the mutual effect on factors and each factor on the decision [26]. In order to circumvent this inadequacy, the SWOT framework is designed into a hierarchic structure and the model is integrated and analyzed using the AHP.

In this study SWOT factors are identified by KOLs from industry, (non) governmental, and public research institutions. All pairwise comparisons are accomplished by the joint judgement of a team of experts representing the relative importance of the criteria. Expert team is constituted from four members with expertise in the field of influenza and analysis skills [26].

Quantification of the SWOT frame via AHP provides the opportunity to calculate priorities for the groups and factors analyzed. The inconsistency ratios represent whether the experts are consistent with themselves while assigning the scores in the pairwise comparison matrixes. This method is used to determine relative priorities on absolute scales from both discrete and continuous paired comparisons in multilevel hierarchic structures. Furthermore, AHP is an effective decision-making method especially when subjectivity might exist [26].

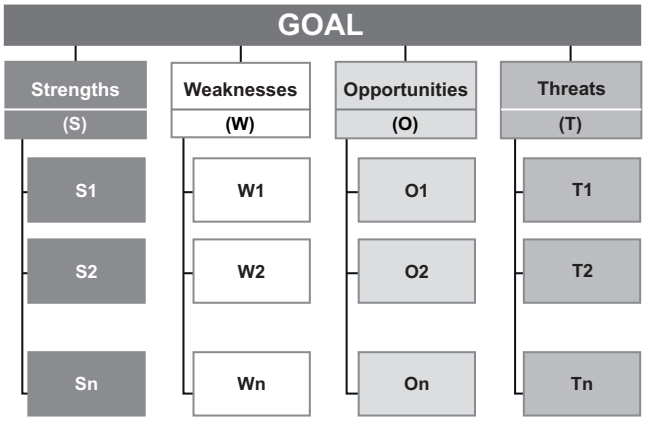


Fig. 2. Hierarchical structure of the SWOT matrix.

In this study, the result of the AHP–SWOT model application was divided into three parts: goal, the SWOT groups and the factors included within each SWOT group (Fig. 2). The goal of this study is identification and quantification of MVA's strengths, weaknesses, market opportunities, and potential threats to provide insight into the potential and critical issues that impact the overall success of implementation of this novel platform.

3. Results

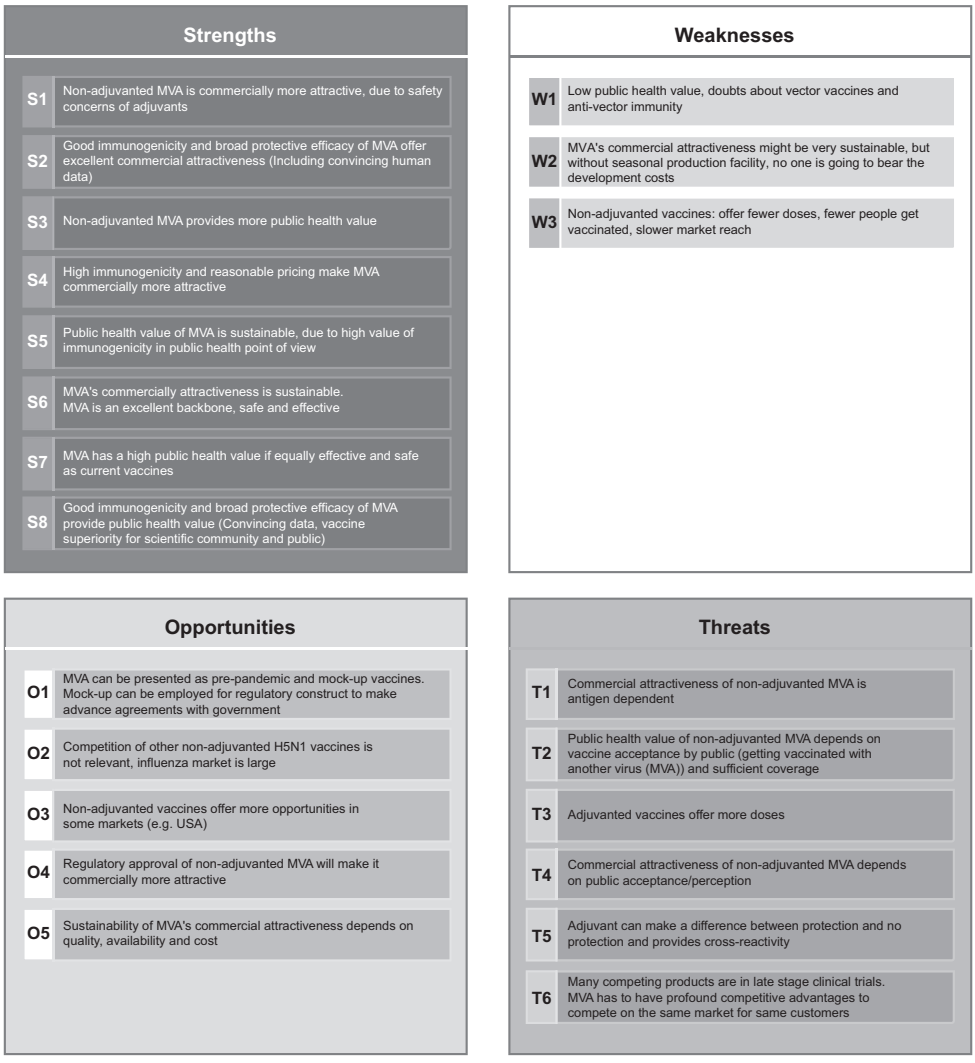
Results of the literature study on the MVA platform and its potential for influenza vaccine development in comparison to alternative influenza pandemic vaccine production methods are presented in Table 4.

Analyzing the SWOT groups and factors from the interview transcripts resulted in 8 strengths, 3 weaknesses, 5 opportunities, and 6 threats tabulated in a SWOT matrix, as presented in Table 5. Subsequently, quantification of the SWOT group by means of AHP

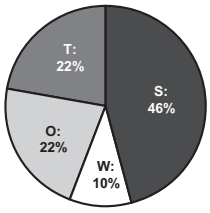
Table 4
Alternative influenza pandemic vaccine production methods beyond phase I. Pro's and con's in relation to the MVA platform. (3. Sub-unit: influenza virus-derived; purified essential antigens (e.g. hemagglutinin (HA) and neuraminidase (NA)) that stimulate immune system, vector-derived; expression system for gene encoding antigens/delivery system for genes/antigens to generate desired immune response.) [33–53].

Alternative production methods		Advantages	Disadvantages	Refs.
1. Whole inactivated virus (WIV)		• Established technology	• Side-effects • High dose/Adjuvant required	[33–36]
2. Split virus		• Established technology • Less side-effects compared to WIV	• High dose/Adjuvant required	[33,37]
3. Sub-unit (HA/NA/...)	Influenza virus derived	• Established well-defined technology • Less side-effects compared to WIV and Split Virus	• High dose/Adjuvant required	[38–40]
	Vector derived (e.g. baculovirus)	• Rapid production • Less side-effects	• High dose/Adjuvant required	[41]
	VLP	• Rapid production • Less side-effects	• Complex technology • High level purification	[42–44]
4. Vectored subunit (e.g. Adenovirus)		• High dose production possibility • Cross-reactive	• Pre-existing interfering immunity	[38,45,46]
5. Live-attenuated		• Established technology • Low/single dose required • Needle free application	• Temperature sensitive	[47,48]
6. DNA vaccines		• No pre-existing interfering immunity	• Limited efficacy	[38,51–53]

Table 5
SWOT matrix; importance degrees within SWOT group. Comparing the importance degrees of the SWOT group, strengths appear to be the most outstanding property of MVA (example; strengths from SWOT group: product of the row; 20, *n*th root; 2.12, sum of all *n*th roots; 4.59, importance degree; 2.12/4.59 = 0.46).



SWOT groups	Strengths	Weakness	Opportunities	Threats	Importance Degrees
Strengths		5.000	2.000	2.000	0.461
Weakness	0.200		0.500	0.500	0.103
Opportunities	0.500	2.000		1.000	0.218
Threats	0.500	2.000	1.000		0.218
CR = 0.002					1.000



offers the possibility to calculate the priorities for each group and factors within these groups. Pairwise comparisons of the SWOT groups are determined by asking the question of which of the two groups has a greater weight in the choice and how much. Each preference is converted into a numeric value based on 1–9 Saaty's AHP scale [28]. All pairwise comparisons were performed by a team of experts in the field. Multiplying the entries in each row of the matrix together and then taking the *n*th root of that product provide the eigenvector (importance degree). Subsequently, the *n*th roots are summed and the sum is used to normalize each eigenvector number to add to 1 (Example strengths from SWOT group (Table 5): product of the row; 20, *n*th root; 2.12, sum of all *n*th roots; 4.59, importance degree; 2.12/4.59 = 0.46.).

Table 5 demonstrates that the strengths far outdistance (46%) the opportunities, threats, and weaknesses of MVA platform, respectively. The strengths are 4.48 times more important than weaknesses (0.461/0.103) and 2.11 times more important than opportunities and threats (0.461/0.218).

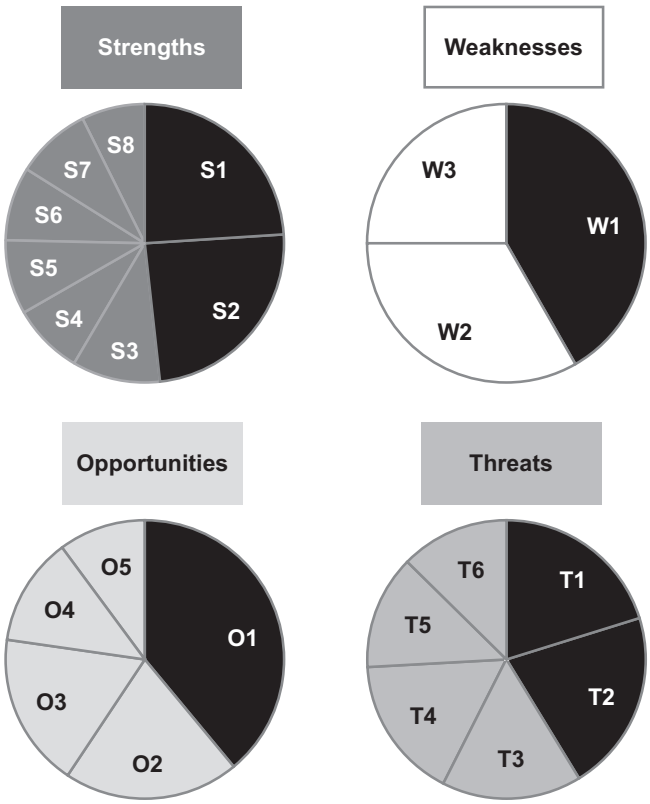


Fig. 3. The priority degree of the categorized factors from strengths, weaknesses, opportunities and threats. S1/S2–W1–O1–T1/T2 are the most influential factors within the SWOT groups.

3.1. Descriptive results, strengths

The eight main strengths are determined as follows:

- *Non-adjuvanted MVA is commercially more attractive.* This is due to safety concerns that adjuvants still raise. The benefits from adjuvants have to be balanced with the risks of adverse reactions.
- *Good immunogenicity and broad protective efficacy of MVA offer excellent commercial attractiveness.* Convincing human clinical trials data have to be provided.
- *Non-adjuvanted MVA provides more public health value.* This is due to safety concerns.
- *High immunogenicity and reasonable pricing make MVA commercially more attractive.* Although the vaccine market is competitive, providing vaccines with high immunogenicity and reasonable pricing creates a competitive advantage in the market.
- *Public health value of MVA is sustainable.* This is due to high value of immunogenicity in a public health point of view.
- *MVA's commercially attractiveness is sustainable.* MVA is an excellent backbone, safe, and effective.
- *MVA has a high public health value.* In case of equal safety and effectiveness as current vaccines.
- *Good immunogenicity and broad protective efficacy of MVA provide public health value*. Convincing data have to be provided on vaccine superiority for scientific community and public.

3.2. Descriptive results, weaknesses

The three main weaknesses are determined as follows:

- *Low public health value.* Doubts are expressed concerning vector vaccines and anti-vector immunity.
- *MVA's commercial attractiveness might be very sustainable, but without seasonal production facility, no one is going to bear the development costs.*
- *Non-adjuvanted vaccines: offer fewer doses, fewer people get vaccinated, slower market reach.*

3.3. Descriptive results, opportunities

The five main opportunities are determined as follows:

- *MVA can be presented as pre-pandemic and mock-up vaccines.* Mock-up can be employed for regulatory construct to make advance agreements with government.
- *Competition of other non-adjuvanted H5N1 vaccines is not relevant.* Influenza market is large. There are still opportunities for entry and growth for vaccines companies.
- *Non-adjuvanted vaccines offer more opportunities in some markets (e.g. USA).* This is due to strict regulations for the human use of adjuvants than those applied for veterinary vaccines.
- *Regulatory approval of non-adjuvanted MVA will make it commercially more attractive.*
- *Sustainability of MVA's commercial attractiveness depends on quality, availability, and cost.*

3.4. Descriptive results, threats

The six main threats are determined as follows:

- Commercial attractiveness of non-adjuvanted MVA is antigen dependent. Dependent on the virulent of emerging pandemic influenza virus.
- *Public health value of non-adjuvanted MVA depends on vaccine acceptance by public and sufficient coverage.* It is challenging to convince people to get vaccinated against influenza virus with another virus (MVA).
- Adjuvanted vaccines offer more doses.
- *Commercial attractiveness of non-adjuvanted MVA depends on public acceptance/perception.*
- *Adjuvant can make a difference between protection and no protection and provides cross-reactivity.*
- *Many competing products are in late stage clinical trials.* MVA has to have profound competitive advantages to compete on the same market for same customers.

Subsequently, AHP was used to perform pairwise comparisons to derive relative importance degrees of the factors within each group. As demonstrated in Table 6, in the comparison matrix the sum of vector is 1, and the vector represents the relative importance among the factors compared. Comparison of various factors within the strengths group illustrates that S1 and S2 are considered to be equally influential in this group. Table 6 exemplifies the comparison matrix applied to determine the importance degrees of each SWOT group. The priority degrees of the SWOT factors within the groups have been visualized in Fig. 3. The most influential factors within the SWOT groups are: S1/S2, W1, O1, T1/T2.

Last, the overall priority scores of the SWOT factors were calculated by multiplying the importance degrees of SWOT groups, as shown in Table 5, by the priority degrees of the factors within the groups as shown in Table 7. The overall priorities of the most influential SWOT factors were: strengths, 0.111 (e.g. $0.461 \times 0.241 = 0.111$); weaknesses, 0.043; opportunities, 0.085; threats, 0.045. The final stage was to calculate the consistency ratio in order to find out how consistent the judgments have been relative to large samples of purely random judgments. The number 0.1 is the accepted upper limit for consistency ratio (CR) [26]. The final CR of all the pairwise comparisons is within the limit.

Table 6
Comparison matrix of strengths. Various factors within this group are being compared. Considering the strengths of MVA, S1 and S2 are equally the most influential factors in this group.

Strengths	S1	S2	S3	S4	S5	S6	S7	S8	Product	nth root	Eigenvector (EV)	Norm. EV	Eigenvalue (λ)
S1		1.000	2.000	3.000	3.000	3.000	3.000	3.000	486.00	2.167	0.241	1.934	8.019
S2	1.000		2.000	3.000	3.000	3.000	3.000	3.000	486.00	2.167	0.241	1.934	8.019
S3	0.500	0.500		1.000	1.000	1.000	1.000	2.000	0.50	0.917	0.102	0.836	8.197
S4	0.333	0.333	1.000		1.000	1.000	1.000	1.000	0.11	0.760	0.085	0.679	8.025
S5	0.333	0.333	1.000	1.000		1.000	1.000	1.000	0.11	0.760	0.085	0.679	8.025
S6	0.333	0.333	1.000	1.000	1.000		1.000	1.000	0.11	0.760	0.085	0.679	8.025
S7	0.333	0.333	1.000	1.000	1.000	1.000		1.000	0.11	0.760	0.085	0.679	8.025
S8	0.333	0.333	0.500	1.000	1.000	1.000	1.000		0.06	0.697	0.078	0.627	8.093
CR = 0.005										8.987	1.000	1.000	8.054

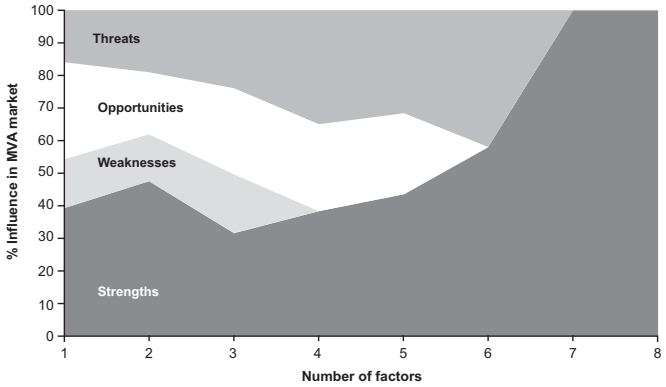


Fig. 4. Illustration of overall priority of SWOT factors per group. Strengths, opportunities, and threats are the three determining group in the MVA market, respectively.

Fig. 4 visualizes the graphical interpretation of overall priority of the SWOT group within the field of MVA according to the KOLs. 46% of the MVA market is assigned to the strengths of this platform. Opportunities, threats, and weaknesses constitute 22%, 22% and 10% of the market, respectively.

4. Discussion

This study provides unique quantitative data to support studies suggesting that MVA meets the unmet needs of the current vaccine platform for pandemic influenza vaccine development [1,10–12,14,15]. The findings show the following ranking of each SWOT group priority: strengths (importance degree (ID), 46.1%), opportunities and threats (ID, 21.8%), and weaknesses (ID, 10.3%). These results indicate that the KOLs evaluated strengths of the MVA platform outweigh weaknesses, opportunities, and threats. This indicates that safety, good immunogenicity, and broad protective efficacy are overall the most important considerations for successful implementation of this vaccine platform. Furthermore, literature describes various (pre) clinical trials and studies demonstrating immunostimulatory capacities that make MVA induce protective immune responses against many infectious agents [11,15,19,20,54,55].

This study was designed to explore the commercial potential of the MVA platform for the development of novel generation pandemic influenza vaccines. Results from both literature study and KOL's perspectives helped us understand the current strengths, weaknesses, opportunities, and threats for implementation of this platform. Furthermore, the quantified data helped in assessing the reciprocal effect within each SWOT group and effect of each factor within each group on the strategic planning process.

Since conversion from qualitative to quantitative scales is based on untested assumption, critics argue the existence of possible inconsistency in pairwise comparisons. The use of pairwise comparison, however, simplifies the expert's judgmental tasks to focus each time on a part of the issue. Furthermore, AHP method automatically carries out an inherent inconsistency check by requiring more judgments to be made than it is needed to establish a set of weights [56,57]. Critics have also questioned whether the AHP method can represent KOL's preference given the quantitative representations of these judgments and the mathematical method applied. It is important to realize that deconstructing important factors during decision-making process allows simplifying a complex problem into a multi-criteria decision-making, which consequently contributes to the main purpose of any decision; creating insights and understanding rather than finding the right answer.

Literature has widely acknowledged that MVA has advantages over currently used vaccines and vaccine platforms in development

Table 7
Inconsistency ratio of the SWOT group and priority of the factors within the groups have been illustrated. Overall priority of each factor is resulted from multiplying the priority of the group with priority of the factor within the group.

SWOT factors	Inconsistency Ratio	Priority of the factor within the group	Overall priority of the factor
Strengths			
S1 Non-adjuvanted MVA is commercially more attractive, due to safety concerns of adjuvants	0.005	0.241	0.111
S2 Good immunogenicity and broad protective efficacy of MVA offer excellent commercial attractiveness (Including convincing human data)		0.241	0.111
S3 Non-adjuvanted MVA provides more public health value		0.102	0.047
S4 High immunogenicity and reasonable pricing make MVA commercially more attractive		0.085	0.039
S5 Public health value of MVA is sustainable, due to high value of immunogenicity in public health point of view		0.085	0.039
S6 MVA's commercially attractiveness is sustainable. MVA is an excellent backbone, safe and effective		0.085	0.039
S7 MVA has a high public health value if equally effective and safe as current vaccines		0.085	0.039
S8 Good immunogenicity and broad protective efficacy of MVA provide public health value (Convincing data, vaccine superiority for scientific community and public)		0.078	0.036
Weaknesses			
W1 Low public health value, doubts about vector vaccines and anti-vector immunity	0.046	0.413	0.043
W2 MVA's commercial attractiveness might be very sustainable, but without seasonal production facility, no one is going to bear the development costs		0.327	0.034
W3 Non-adjuvanted vaccines: offer fewer doses, fewer people get vaccinated, slower market reach		0.260	0.027
Opportunities			
O1 MVA can be presented as pre-pandemic and mock-up vaccines. Mock-up can be employed for regulatory construct to make advance agreements with government	0.012	0.388	0.085
O2 Competition of other non-adjuvanted H5N1 vaccines is not relevant, influenza market is large		0.205	0.045
O3 Non-adjuvanted vaccines offer more opportunities in some markets (e.g. USA)		0.179	0.039
O4 Regulatory approval of non-adjuvanted MVA will make it commercially more attractive		0.125	0.027
O5 Sustainability of MVA's commercial attractiveness depends on quality, availability and cost		0.103	0.022
Threats			
T1 Commercial attractiveness of non-adjuvanted MVA is antigen dependent	0.017	0.206	0.045
T2 Public health value of non-adjuvanted MVA depends on vaccine acceptance by public (getting vaccinated with another virus (MVA)) and sufficient coverage		0.206	0.045
T3 Adjuvanted vaccines offer more doses		0.164	0.036
T4 Commercial attractiveness of non-adjuvanted MVA depends on public acceptance/perception		0.164	0.036
T5 Adjuvant can make a difference between protection and no protection and provides cross-reactivity		0.130	0.028
T6 Many competing products are in late stage clinical trials. MVA has to have profound competitive advantages to compete on the same market for same customers		0.130	0.028

[1,15,19,58]. Under the strength group, immunogenicity related factors were rated as the most influential strength to be considered with an approximately 0.5 total priority of factors within this group and a 0.23 as overall priority. Subsequently, immunogenic capabilities of MVA without the need of an adjuvant are the second most influential subject in this group with a 0.34 priority rate within the group and a 0.16 overall priority rate. Finally, factors related to safety and effectiveness of this platform are considered to be important assets of this platform with a priority rate of 0.17 within the groups and an overall priority rate of 0.078. From a KOL's perspective, factors related to immunogenicity and without an adjuvant need, increase the commercial attractiveness and public health value of this platform. Moreover, factors related to immunogenicity and safety and effectiveness of this platform increase its sustainability value in the vaccine market. According to the KOLs, providing human data on MVA's capability to induce enhanced immunogenicity and broad protective efficacy will further increase commercial attractiveness of this platform.

Furthermore, these properties provide the opportunity of getting regulatory approval in particular in some markets where

adjuvants are not being accepted due to safety concerns. Industry representatives indicate that using the MVA platform creates opportunity to invade other as yet unreached markets. Furthermore, the use of mock-up dossiers approved for regulatory authorities may help in negotiating advance agreements with governments, ensuring industries future cash flow. In case of novel vaccines, safety of the vaccine is the first consideration. Safety data from the MVA's clinical trials shows great promise [16]. At the same time, KOLs emphasize the fact that MVA's capability to induce such immunogenicity could be largely dependent on the antigen used. According to the literature, much research is dedicated to emerging novel and alternative vaccine strategies over the last decade. Research in vaccine field emphasizes emergence of the poxviral vaccine platforms as a profound delivery platform [1,11,59].

KOLs indicate that one of the main challenges that MVA-vectored vaccines are facing is the acceptance of this platform by the lay public in the vaccine field. This challenge is contradicted by our literature search results. Application of poxvirus vectors for the expression of foreign genes of interest is becoming more attractive than other viral vectors [16,17]. Despite the fact that there are no licensed poxvirus vector-based human vaccines on the market yet, there is an increasing amount of clinical trials of poxvirus vector vaccine candidates for infectious diseases [12]. This discrepancy might be an indication that there is a perception change towards the vector vaccines. In this context it is important to recognize that MVA, as a modified live form of the vaccinia virus, has already been approved as a backbone vector system in a vaccine against smallpox [60].

A key unmet need of the current influenza vaccines are speed and scalability resulting in production of sufficient vaccine dosages within the required time frame. KOLs indicate the same unmet need as one of the threats MVA might be encountering. Recently, large-scale production of MVA has been shown to be possible for four million doses of non-recombinant MVA-smallpox-vaccine. Moreover, two companies have developed cell lines suitable for MVA manufacturing to avoid the need for embryonated eggs [10]. Non-industry representatives consider issues related to quality, safety, availability, and reasonable pricing of vaccines essential for MVA's commercial sustainability. Moreover, they indicate that public vaccine acceptance will likely be a key factor to simultaneously increase public health value and commercial attractiveness of the MVA platform.

This study indicates that the sustainability of the MVA platform can be assured by exploring this platform for use in both seasonal and pandemic influenza as well as other infectious diseases in particular those caused by newly emerging viruses [10]. Some KOLs stress the challenge of having many competitors in the influenza market fighting for the same costumers. In 2011, the global influenza vaccine market was valued at over three and a half billion dollars and is predicted to grow annually about 6% over the next seven years to reach over five billion dollars in 2018 [61].

The most favourable feature of this platform is its proven immunogenicity, broad protective efficacy without the requirement of an adjuvant, and its relatively easy scalability which make MVA the vaccine platform of choice for many so far unmet vaccine needs. Thus, MVA's specific properties stress the great potential of this platform. Although the public acceptance of such vaccines can be challenging, providing safety data in human trials could result in a change in perception. The influenza market offers sufficient opportunities for MVA to be implemented as a novel vaccine platform with broad protection against seasonal and pandemic influenza viruses. Despite the fact that poxviral vector platform holds a great promise for market implementation, more collaboration is required between academia, vaccine industries, and the regulatory authorities [11].

Conflicts of interest

The authors declare that they have no conflict of interest.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.vaccine.2015.04.086

References

[1] Draper SJ, Cottingham MG, Gilbert SC. Utilizing poxviral vectored vaccines for antibody induction-progress and prospects. Vaccine 2013;31:4223–30.
[2] Wong SS, Webby RJ. Traditional and new influenza vaccines. Clin Microbiol Rev 2013;26:476–92.
[3] TNIoAaID (2013) Types of Vaccines. Vaccinesgov, http://www.vaccines.gov/more_info/types/
[4] Tomori O. From smallpox eradication to the future of global health: innovations, application and lessons for future eradication and control initiatives. Vaccine 2011;29(Suppl. 4):D145–8.
[5] de Swart RL, Duprex WP, Osterhaus AD. Rinderpest eradication: lessons for measles eradication? Curr Opin Virol 2012;2:330–4.
[6] Roth GA, Fee E. Images of health, smallpox: the first vaccine. Am J Public Health 2011;101:1217.
[7] Liu MA. Immunologic basis of vaccine vectors. Immunity 2010;33:504–15.
[8] Tarahomjoo S. Development of vaccine delivery vehicles based on lactic acid bacteria. Mol Biotechnol 2012;51:183–99.
[9] Teigler JE, Phogat S, Franchini G, Hirsch VM, Michael NL, Barouch DH. The canarypox virus vector ALVAC induces distinct cytokine responses compared to the vaccinia virus-based vectors MVA and NYVAC in rhesus monkeys. J Virol 2014;88:1809–14.
[10] Cottingham MG, Carroll MW. Recombinant MVA, vaccines: dispelling the myths. Vaccine 2013;31:4247–51.
[11] Kreijtz JH, Gilbert SC, Sutter G. Poxvirus vectors. Vaccine 2013;31:4217–9.
[12] Rollier CS, Reyes-Sandoval A, Cottingham MG, Ewer K, Hill AV. Viral vectors as vaccine platforms: deployment in sight. Curr Opin Immunol 2011;23:377–82.
[13] Moss B. Reflections on the early development of poxvirus vectors. Vaccine 2013;31:4220–2.
[14] Gomez CE, Najera JL, Krupa M, Perdiguero B, Esteban M. MVA and NYVAC as vaccines against emergent infectious diseases and cancer. Curr Gene Ther 2011;11:189–217.
[15] Volz A, Sutter G. Protective efficacy of modified vaccinia virus Ankara in preclinical studies. Vaccine 2013;31:4235–40.
[16] Gilbert SC. Clinical development of modified vaccinia virus Ankara vaccines. Vaccine 2013;31:4241–6.
[17] Altenburg AF, Kreijtz JHCM, de Vries RD, Song F, Fux R, Rimmelzwaan GF, et al. Modified vaccinia virus Ankara (MVA) as production platform for vaccines against influenza and other viral respiratory diseases. Viruses 2014:6.
[18] EMA. Imvanex, modified vaccinia Ankara virus. EMA Sci Med Health 2013.
[19] Kreijtz JH, Suzer Y, Bodewes R, Schwantes A, van Amerongen G, Verburgh RJ, et al. Evaluation of a modified vaccinia virus Ankara (MVA)-based candidate pandemic influenza A/H1N1 vaccine in the ferret model. J Gen Virol 2010;91:2745–52.
[20] Rimmelzwaan GF, Kreijtz JHCM, Suezer Y, Schwantes A, Osterhaus AD, Sutter G. Preclinical evaluation of influenza vaccines based on replication-deficient poxvirus vector MVA. Procedia Vaccinol 2011:4.
[21] Sutter G, Wyatt LS, Foley PL, Bennink JR, Moss B. A recombinant vector derived from the host range-restricted and highly attenuated MVA strain of vaccinia virus stimulates protective immunity in mice to influenza virus. Vaccine 1994;12:1032–40.
[22] Bender BS, Rowe CA, Taylor SF, Wyatt LS, Moss B, Small Jr PA. Oral immunization with a replication-deficient recombinant vaccinia virus protects mice against influenza. J Virol 1996;70:6418–24.
[23] Berthoud TK, Hamill M, Lillie PJ, Hwenda L, Collins KA, Ewer KJ, et al. Potent CD8+ T-cell immunogenicity in humans of a novel heterosubtypic influenza A vaccine, MVA-NP+M1. Clin Infect Dis 2011;52:1–7.
[24] Powell TJ, Peng Y, Berthoud TK, Blais ME, Lillie PJ, Hill AVS, et al. Examination of influenza specific T cell responses after influenza virus challenge in individuals vaccinated with MVA-NP+M1 vaccine. PLOS ONE 2013;8:e62778.

[25] Kangas J, Kurttila M, Kajanus M, Kangas A. Evaluating the management strategies of a forestland estate–the S-O-S approach. J Environ Manage 2003;69:349–58.
[26] Görener A, Toker K, Uluçay K. Application of combined SWOT and AHP: a case study for a manufacturing firm. Procedia Soc Behav Sci 2012;58:1525–34.
[27] Kahraman C, Demirel NC, Demirel T. Prioritization of e-government strategies using a SWOT–AHP analysis: the case of Turkey. Eur J Inf Syst 2007;16:284–98.
[28] Saaty TL. The analytic hierarchy process. New York: McGraw-Hill; 1980.
[29] Hill T, Westbrook R. SWOT analysis: its time for a product recall. Long Range Plan 1997;30:46–52.
[30] Saaty TL. Decision making for leaders: the analytical hierarchy process for decisions in a complex world. Anal Hierarchy Process Ser 1982;2:71–4.
[31] Saaty TL. Decision making with the analytic hierarchy process. Int J Serv Sci 2008;1:83–98.
[32] Lee S, Walsh P. SWOT and AHP hybrid model for sport marketing outsourcing using a case of intercollegiate sport. Sport Manag Rev 2011;14:361–9.
[33] Hampson AW. Vaccines for pandemic influenza, the history of our current vaccines, their limitations and the requirements to deal with a pandemic threat. Ann Acad Med Singap 2008;37:510–7.
[34] Plosker GL. A/H5N1 prepandemic influenza vaccine (whole virion, vero cell-derived, inactivated) [Vepacel(R)]. Drugs 2012;72:1543–57.
[35] Keating GM, Plosker GL, Lyseng-Williamson KA. A/H5N1 prepandemic influenza vaccine (Vepacel(R)): a guide to its use. BioDrugs 2012;26:425–30.
[36] Vajo Z, Tamas F, Sinka L, Jankovics I. Safety and immunogenicity of a 2009 pandemic influenza A H1N1 vaccine when administered alone or simultaneously with the seasonal influenza vaccine for the 2009-10 influenza season: a multicentre, randomised controlled trial. Lancet 2010;375:49–55.
[37] EMA. Adjupanrix (previously Pandemic influenza vaccine (H5N1)) (split virion, inactivated, adjuvanted); 2009. EMA http://www.ema.europa.eu/ema/index.jsp?curl=pages/medicines/human/medicines/001206/human_med_001214.jsp&mid=WC0b01ac058001d124
[38] Sedova ES, Shcherbinin DN, Migunov AI, Smirnov Iu A, Logunov D, Shmarov MM, et al. Recombinant influenza vaccines. Acta Nat 2012;4:17–27.
[39] Couch RB, Patel SM, Wade-Bowers CL, Nino D. A randomized clinical trial of an inactivated avian influenza A (H7N7) vaccine. PLoS ONE 2012;7:e49704.
[40] EMA. Focetria, influenza vaccine (H1N1) (surface antigen, inactivated, adjuvanted); 2009. EMA http://www.ema.europa.eu/ema/index.jsp?curl=pages/medicines/human/medicines/000710/human_med_000796.jsp&mid=WC0b01ac058001d124
[41] Cox MM. Recombinant protein vaccines produced in insect cells. Vaccine 2012;30:1759–66.
[42] Lopez-Macias C. Virus-like particle (VLP)-based vaccines for pandemic influenza: performance of a VLP vaccine during the 2009 influenza pandemic. Hum Vaccin Immunother 2012;8:411–4.
[43] Tang XC, Lu HR, Ross TM. Baculovirus-produced influenza virus-like particles in mammalian cells protect mice from lethal influenza challenge. Viral Immunol 2011;24:311–9.
[44] Lopez-Macias C, Ferat-Osorio E, Tenorio-Calvo A, Isibasi A, Talavera J, Arteaga-Ruiz O, et al. Safety and immunogenicity of a virus-like particle pandemic influenza A (H1N1) 2009 vaccine in a blinded, randomized, placebo-controlled trial of adults in Mexico. Vaccine 2011;29:7826–34.
[45] Nair H, Lau E, Brooks W, Seong A, Theodoratou E, Zgaga L, et al. An evaluation of the emerging vaccines against influenza in children. BMC Public Health 2013;13 Suppl(3):S14.
[46] Tripp RA, Tompkins SM. Virus-vectored influenza virus vaccines. Viruses 2014;6:3055–79.
[47] Rudenko L, van den Bosch H, Kiseleva I, Mironov A, Naikhin A, Larionova N, et al. Live attenuated pandemic influenza vaccine: clinical studies on A/17/California/2009/38 (H1N1) and licensing of the Russian-developed technology to WHO for pandemic influenza preparedness in developing countries. Vaccine 2011;29 Suppl 1:A40–4.
[48] Carter NJ, Curran MP. Live attenuated influenza vaccine (FluMist(R); Fluenz): a review of its use in the prevention of seasonal influenza in children and adults. Drugs 2011;71:1591–622.
[49] Khurana S, Chearwae W, Castellino F, Manischewitz J, King LR, Honorkiewicz A, et al. Vaccines with MF59 adjuvant expand the antibody repertoire to target protective sites of pandemic avian H5N1 influenza virus. Sci Transl Med 2010;2:15ra15.
[50] Liang XF, Wang HQ, Wang JZ, Fang HH, Wu J, Zhu FC, et al. Safety and immunogenicity of 2009 pandemic influenza A H1N1 vaccines in China: a multicentre, double-blind, randomised, placebo-controlled trial. Lancet 2010;375:56–66.
[51] Ferraro B, Morrow MP, Hutnick NA, Shin TH, Lucke CE, Weiner DB. Clinical applications of DNA vaccines: current progress. Clin Infect Dis 2011;53:296–302.
[52] Ledgerwood JE, Hu Z, Gordon IJ, Yamshchikov G, Enama ME, Plummer S, et al. Influenza virus h5 DNA vaccination is immunogenic by intramuscular and intradermal routes in humans. Clin Vaccine Immunol 2012;19:1792–7.
[53] Smith LR, Wloch MK, Ye M, Reyes LR, Boutsaboualoy S, Dunne CE, et al. Phase 1 clinical trials of the safety and immunogenicity of adjuvanted plasmid DNA vaccines encoding influenza A virus H5 hemagglutinin. Vaccine 2010;28:2565–72.
[54] Kreijtz JH, Goeijenbier M, Moesker FM, van den Dries L, Goeijenbier S, De Gruyter HLM, et al. Safety and immunogenicity of a modified-vaccinia-virus-Ankara-based influenza A H5N1 vaccine: a randomised, double-blind phase 1/2a clinical trial. Lancet Infect Dis 2014;14:1196–207.
[55] Clegg CH, Rininger JA, Baldwin SL. Clinical vaccine development for H5N1 influenza. Expert Rev Vacci 2013;12:767–77.
[56] Barfod MB, Leleur S. Alternative procedures for deriving value functions based on point scales and AHP. Technical note, Centre for Traffic and Transport. Technical University of Denmark; 2007.
[57] Goodwin P, Wright G. Decision Analysis for Management Judgment. Wiley; 1998.
[58] Price PJ, Torres-Dominguez LE, Brandmuller C, Sutter G, Lehmann MH. Modified Vaccinia virus Ankara: innate immune activation and induction of cellular signalling. Vaccine 2013;31:4231–4.
[59] Draper SJ, Heeney JL. Viruses as vaccine vectors for infectious diseases and cancer. Nat Rev Microbiol 2010;8:62–73.
[60] EMA. Imvanex, modified vaccinia Ankara virus; 2013. EMA http://www.ema.europa.eu/ema/index.jsp?curl=pages/medicines/human/medicines/002596/human_med_001666.jsp&mid=WC0b01ac058001d124
[61] GlobalData. Influenza vaccines therapeutics – pipeline assessment and market forecast to 2018; 2011. Research and Markets Abstract available at http://www.researchandmarkets.com/research/67d93b/influenza_vaccines
[62] Osterhaus ADME. ARCAS: Analysis of the route to commercialisation of MVA based influenza vaccines. ARCAS. Erasmus Universitair Medisch Centrum: European Research Council; 2012.