Research Article

An interdisciplinary analysis of genetically modified vaccines: from clinical trials to market

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ABSTRACT

Background: Immunization is considered the most effective strategy for infectious disease control and maintaining global health. Conventional vaccines have successfully targeted a broad spectrum of pathogens. However, a large number of untargeted diseases still remain. Introduction of novel Genetically Modified (GM) vaccines allow development of new improved vaccines and immunotherapeutics. Moreover, GM vaccines can also target non-communicable diseases outside the range of infectious diseases, including cancer, autoimmune diseases, and allergies.
Methods: We compiled novel and unique datasets encompassing data from literature, patent documents, clinical trials, and vaccine registers in order to provide a thorough overview of the GM market.
Results: Based on patent data, we found that most patent applications were filed in North America, Asia, and Europe, which coincides with the locations of the largest companies and institutes. Looking at clinical trial data we forecast marketing of two next generation GM vaccines, targeting cancer and malaria. In addition, we calculated phase transition success rates of 82% (phase 1-2) and 76% (phase 2-3).
Conclusions: These findings indicate viable regions for GM vaccine research and development. Phase transition success rates of 82% (phase 1-2) and 76% (phase 2-3) predict a relatively high chance of marketing approval. Increased registrations of GM vaccines complemented by rising numbers of patent applications suggest global growth of the GM vaccine market, which currently holds a proportion of nearly 20% of the total vaccine market.

Keywords: Clinical trials, Genetic modification, Novel vaccine technology, Patents, Phase transition success rate, Registered vaccines

INTRODUCTION

Immunization has been an important factor in providing protection and maintaining and improving global health, but its full potential has not yet been reached.[1,2] Vaccination endeavours have resulted in successful accomplishments, including eradication of smallpox and 99% decrease in polio incidence.[3] In addition to eradication of some communicable diseases, inter alia, a significant reduction of communicable diseases and a further annual prevention of an estimated 6 million deaths worldwide has been realized.[4,5] Although, vaccines have been targeting a broad repertoire of infectious diseases, a

large number of untargeted diseases remains undeniable, including the "big three"; malaria, tuberculosis, and HIV/AIDS.[6] In addition to infectious diseases, a variety of disorders and non-communicable diseases emphasize the necessity for new and/or improved vaccines.[6,7] Conventional vaccines have proven their success, nonetheless, in order to meet the demand of new vaccines, deployment of novel technologies is required. Novel technologies are not only desired for improvements in medical i.e. immunological or clinical outcomes, their contribution to societal outcomes are of great value as well.[5,8] Contributions to society will, for example, consist of health-care cost savings, extending

life expectancy, improved quality of life, and equity enhancement.[5]

Advanced developments in bioengineering including recombinant technology, sequencing, and cell and tissue culturing techniques contributed to vaccine development and provide many yet unexplored possibilities in vaccine development against virtually all pathogens.[9,10] Recombinant technology allows the production of tailor made Genetically Modified (GM) vaccines and enables targeting diseases such as cancer, autoimmune diseases, allergies, and addictions.[6] GM vaccines allow for both relatively efficient production and selected increased immunogenic properties in vaccines. The first recombinant human vaccine, Recombivax HB® was approved in 1986 and was followed by Flumist®, Flublok®, and IMOJEV®.[11-14] Additionally, a landmark in cancer immunotherapy was the FDA approval of Dendreon's prostate cancer vaccine Provenge® in 2010.[15]

Previous studies described changes and trends in the biopharmaceutical and vaccine market, for instance the dramatic decrease in the number of companies that produce vaccines.[16] It should be noted that the GM vaccine market has not been described in detail and prior studies in the field do not provide insights in its current state of global research and development. Furthermore, multiple concerns regarding the vaccine market are expressed in literature, including limited viable markets, intellectual property complications, and the restrictive aspects of rules and regulations.[17-19] Results from our previous research on one of the most advanced GM techniques, namely Modified Vaccinia virus Ankara (MVA) platform, stress the same concerns regarding the total vaccine market.[20]

Considering the changes, developments, and concerns in the field of vaccines, a thorough overview of the current GM vaccine market and a description of its prospects for future growth was needed. In order to achieve this, we developed new and unique datasets for an interdisciplinary analysis of the current GM vaccine market. The unique datasets include data from literature, patent documents, clinical trials, and registered vaccines. Here we present an overview of the global GM vaccine market, revealing trends in patent applications, vaccine approvals, and additionally next generation GM vaccine forecasts.

METHODS

The methods applied in this study were performed in different stages to provide a thorough and complete overview of the Genetically Modified (GM) vaccine market. First a literature study was conducted to obtain search-specific-terminology on GM vaccine publications. Subsequently, patents, clinical trials, and registered vaccines were explored and three separate datasets were compiled for the purpose of in-depth analysis.

Literature search

To confirm the current knowledge concerning GM vaccines we grouped review papers in multiple online search engines, including Embase, Medline, Cochrane, Web-of-science, PubMed, and Google scholar. Searches were restricted to English language publications. Medical subject headings (MeSH) combined with Boolean Operators search strategy was employed as the initial basis for syntax development.[21,22] The final strategy and results were quality controlled by an independent Biomedical Information Specialist from Erasmus Medical Centre medical library. Appendix A provides supplemental information on coding of the search terms for different search engines. An integration of findings from these search engines resulted in 1756 articles. Subsequently, 511 duplicates were removed. Subsequent selection from 1245 remaining papers was done based on the following criteria:

- Only review articles that described vaccine technologies.

- Only studies in the time frame 2009-2014.

- Only review articles that described novel vaccine technologies.

After deduplicating the obtained data and excluding non-relevant studies 87 literature reviews remained for further analysis (1).

Table 1: Literature study databases, results, and adopted selection criteria within GM study scope.

Database	Hits	Hits after removal duplicate	Remaining	Selection criteria	Final database
Embase.com	945	940		No description of vaccine technology	
Medline (OvidSP)	364	97			
Web-of-science	323	123	**1245**	Time frame 2009-2014	**87**
PubMed publisher	8	4			
Cochrane DARE	7	2		No description of novel vaccine technology	
Google scholar	100	79			
Total	**1756**	**1245**			
Region	**Worldwide**				

Terminology

Although the terms "conventional vaccine" and "GM vaccine" are often used in the vaccinology field, these terms are used inconsistent and interchangeable. We have drafted the following delineation of GM vaccine definitions to enable proper selection and interpretation of relevant data (Table 3).

Conventional vaccines can be defined as vaccines based on the wild type pathogen or a part thereof, be it live-attenuated, inactivated or a single purified antigen.[23] Genetically modified vaccines are categorised based on following definition: vaccines produced and/or developed using genetic modification. For examples: recombinant antigen(s), (self-amplifying) DNA/RNA, and vaccines that consist of genetically modified organisms.[2]

Patent analysis

Data on patents concerning GM vaccines was retrieved from Espacenet, an all-inclusive worldwide database providing access to more than 90 million patent documents. Since patents are classified into various technological classes according to the Cooperative Patent Classification (CPC) system, a selected group of three CPC codes was used to focus on GM vaccines (Table 2). In order to focus on vaccines, a CPC code indicating "medicinal preparations containing antigens or antibodies" was used, (A61K39/xx). The focus on GM criteria was obtained by using two CPC codes indicating genetic engineering, subsequently including relevant genetically modified vaccines regarding gene therapy (C12N15/xx and A61K48/xx). Search criteria included CPC codes combined with the search terms vaccin* and genetic* OR modif* (Boolean operator). In the search of patent literature all regular subclasses including higher series and relevant subclasses were taken into account to ensure the completeness of patent data. Higher series and subclasses delineate aspects of the regular classes, e.g. technologies, functional features etc.

Table 2: Predominant CPC groups in GM patent literature.

#	CPC code	Groups
1	1A61K39/xx	Medical preparations containing antigens or antibodies (A61K39/xx) AND vaccin*
2	C12N15/xx	Mutation or genetic engineering; DNA or RNA concerning genetic engineering, vectors, e.g. plasmids, or their isolation, preparation or purification; Use of hosts therefore (C12N15/xx) AND genetic* or modif*
3	A61K48/xx	Medicinal preparations containing genetic material which is inserted into cells of the living body to treat genetic diseases; Gene therapy (A61K48) AND vaccin*

Accuracy in patent analysis was assured by comparing patent priority numbers and deduplicating patents originating from the same patent family. Documents were classified as priority documents based on the oldest application and publication data and were then categorised as mother patents. Application of this methodology resulted in 40.308 unique mother patents worldwide.

For the purpose of investigating market anticipation of companies and institutes, only patents published in or after 2005 were included and all published documents were extracted from Espacenet, resulting in 15.977 relevant patent documents. Completeness of data was achieved by the iterative methods used in data extraction. CPC codes from key-word-extracted documents were fed back into the database resulting in new hits which were then deduplicated.

The final dataset was quality controlled by an independent biomedical intellectual property specialist from The Netherlands Enterprise Agency (RVO), a part of the Ministry of Economic Affairs.

Subsequently, these 15.977 patent documents were merged based on their geographical location of application. The dataset obtained contained information on patent applicants, date of application, and country codes indicating where patent applications were filed. Finally, identification of all published documents was done based on their publication number and kind codes. Kind codes function as patent descriptor, to distinguish the patent status and indicate the number of times a document was published. Countries were then categorised based on the region they belong to, resulting in the total number of applied and granted patens in the following continents: North America, South America, Europe, Africa, Russia, Asia, and Oceania. The results of this analysis are shown in Figure 1, representing continental patent density including both applied and granted patents, and the top 15 companies and institutes that own the most GM vaccine related patents. The colour gradient in Figure 1 was based on the total number of patents that were filed in each continent.

GM patent filing rates were explored by adopting the same patent data search criteria that were used to make Figure 1, as described above. The year 1970 was selected as starting point and patent filing dates were grouped per year. The resulting number of patent documents per year was plotted and the timeline is shown in Figure 3.

To analyse only the relevant GM vaccine indications that are described in patent literature the search for relevant documents was narrowed by only using CPC code A61K39/xx and C12N15/xx (number 1 and 2 in Table 2), and only patent documents filed in or after 2005 were included (Table 4). The GM vaccine indications of patent documents were categorised in infectious disease, cancer, allergy and immune system, genetically related disease,

and multi-purpose, based on their CPC codes and in ambiguous cases the patent descriptions. Hereafter, an analysis was conducted to show which companies and institutes are involved per indication, based on the number of patents they possess, shown in Figure 4. Finally a distinction was made between companies and institutes in order to explore what indications they are currently aiming on, and to explore future indications in the development pipeline. In addition, this analysis was done to illustrate the relatively young nature and growth of the GM vaccine market.

Clinical trial analysis

Clinical trials were analysed in this study to provide an overview of the current development state of GM vaccine technologies and their indications in the different phases of clinical development. Subsequently, clinical trial data collected from clinical trial databases was used as future prediction tool, and enabled us to predict possible future vaccines. This prediction was made based on frequency of indications in each phase combined with the current phase transition success rates of clinical trial phases.

Data on clinical trials for this study were obtained from the WHO International Clinical Trials Registry Platform, which provides a complete overview of registered clinical trials worldwide.[24] The WHO International Clinical Trials Registry Platform provides data on exclusively active and on-going medical studies, which was used for dataset compilation. Specific search terms on the topic were used in combination with the term 'vaccine' to create a dataset related to GM vaccines (Table 3) which resulted in 1146 clinical trial records. The clinical trial dataset obtained contains information on starting dates, development phases, indications and specific targets.

Data analysis was conducted on the clinical trial pipeline (phase 1 to 4) for GM vaccine technologies, therapies and treatments registered between November 1st, 1999 and March 5th 2014. The number of clinical trials per development phase was counted and the top five most frequent indications per phase were selected for further analysis. To illustrate a total overview, marketed GM vaccines that proceed testing in phase four were included, and are described in the next part of this methodology. The results of these analyses are shown in Figure 2.

Table 3: Clinical trial search terms, results, and dataset variables.

Database	Search terms combined with "Vaccine"	# Total vaccines	Variables
WHO International Clinical Trials Registry Platform	Vector	1146	Technology class
	DNA		
	RNA		Type of organism
	Recombinant Protein		
	Chimeric		Indication
	Recombinant		
	Generically Modified		Specific target
	Genetically Engineered		
	Modified		Expression system
	Live-attenuated		
	Attenuated NOT Live-attenuated		Production system
	VLP		
	Virosome		Development phase (1,2,3,4)
	Engineered		
	Genetic		
	Live		
Region	**Worldwide**		

Table 4: Registered vaccine databases and results.

County	Database	Results
US	U.S. Food and Drug Administration (FDA)	100
EU	European Medicines Agency (EA)	41
Brazil	Oswaldo Cruz Foundation known as Fiocruz	9
India	Central drugs standard control	218
China	China Food and Drug Administration (CFDA)	317
South Africa	South African vaccination and immunization centre (SAVIC)	37
Australia	Government Department of Health, Register of Therapeutic goods	75
Japan	Pharmaceuticals and Medical Devices Agency	24
Total		**821**
Region	**India was not included in dataset used for timeline construction**	

Registered vaccines

Data on all currently registered vaccines for human use were primarily gathered from various governmental databases (Table 4). Registered vaccines for human use were obtained from the following regions: USA, EU, BRICS countries, Japan, and Australia. Data from India and Russia were excluded from this analysis due to a lack of information on approval dates and the general inaccessibility of Russian registers. The data search resulted in 821 registered vaccines, approved between 1937 and 2013. According to the dataset the first GM

vaccine approval was granted after 1988, consequently selected as starting point for Figure 3.

After deduplication the remaining 797 registered vaccines were categorised in two groups 'conventional vaccines' and 'GM vaccines' based on the information provided by the manufacturers. This categorization was conducted in order to illustrate difference in approval timelines of both groups and possible increase of GM vaccines approval.

RESULTS

Patent literature

In total 15.977 patent documents were included in this study, all filed in or after 2005. Patent documents were indexed by country code and subsequently grouped. Figure 1 illustrates that over the past 10 years most patents were filed in North America, Asia, and Europe, reflected by colour gradient. Patent documents filed under country code WO (World Intellectual Property Organization; WIPO) and EA (Eurasian Patent Organization; EAPO) are not included in this figure, since they are spread over multiple countries in various regions. WO and EA country codes account for 2713 and 153 numbers of patents, respectively.

The illustrated companies and institutes were identified by analysing information on patent applicants, and were included based on the total number of GM vaccine patents they own, regardless of where the documents are registered. The cut-off point for inclusion was determined to be 99+ patents and resulted in 17 top companies and institutes. Numbers indicate the share of patents in percentage of the total number of patents filed in or after 2005. We identified GSK (4.9%), Novartis (4.5%) and Merial (2.2%) to be the top 3 companies.
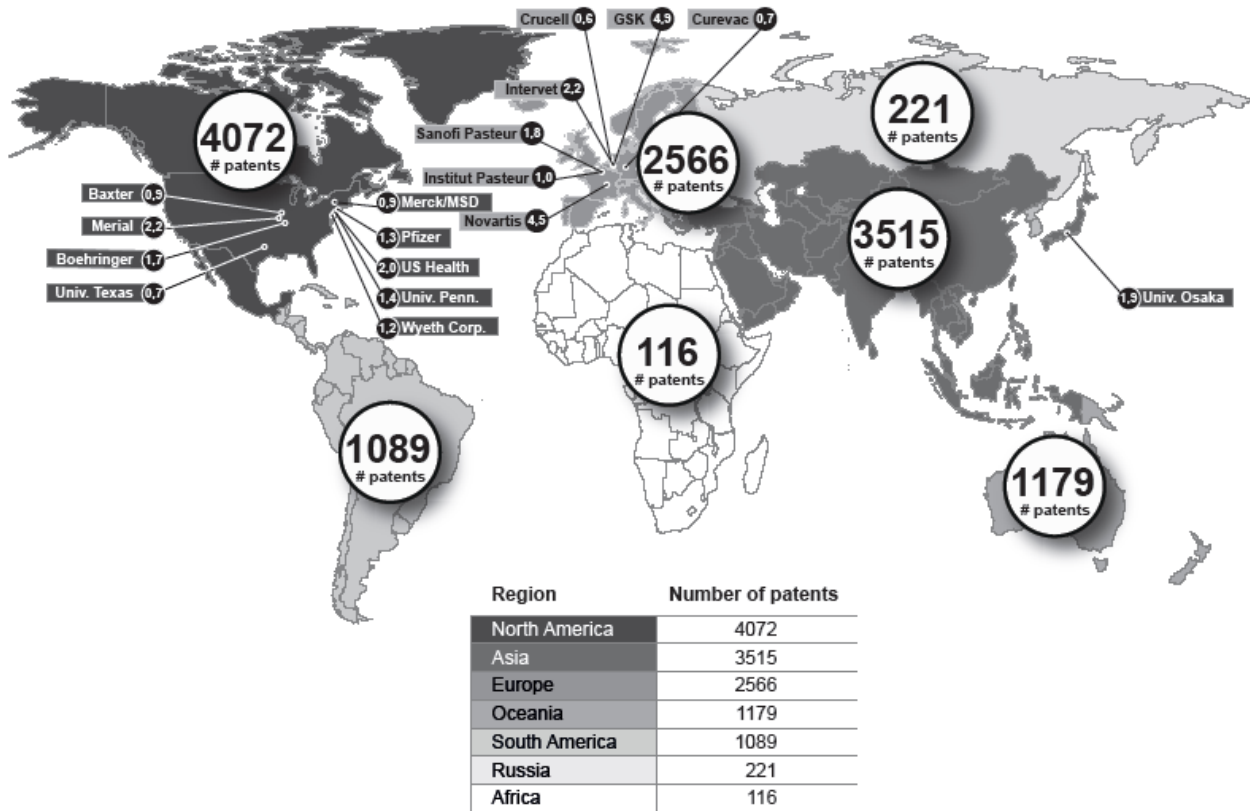
Figure 1: Patent density based on the number of patents filed in each region, illustrated by gradient. Geographic location of the top 17 companies and institutes worldwide based on the number of patents they own (inclusion cut-off: 99+ patents in possession) and the correlating percentage of the total 15.977 patent documents that were included. Numbers behind companies and institutes indicate the share of patents they possess in percentage of the total number of patents.

Accompanying Figure 1, the top companies and institutes per indication group are shown in Figure 4. Indications mentioned in patents were categorized in five groups, based on the information provided in the patent descriptions. Only patent documents filed in or after 2009 were included, and the search terms were narrowed, using only the first two CPC codes (Table 2). The ranking is based on the number of patents the companies and institutes own. In this figure, purple circles indicate companies and the green circles represent institutes.

Figure 4: Top companies and institutes per indication group, based on the number of patents they own. Purple circles indicate companies, green circles indicate institutes.

Clinical trials

A total of 1146 clinical trials were included in this study. Figure 2 shows the number of active GM vaccine clinical trials per phase. The number of trials is gradually decreasing towards phase 4. Snapshot phase transition success rates are calculated between phase 1, 2 and 3, indicating the percentage of clinical trials that proceed testing in the next phase. Phase 1 counts 438 clinical trials, and a percentage of 82% is expected to proceed testing in phase 2. Of 358 clinical trials in phase 2, 76% is expected to proceed testing in phase 3. The 'registered' column represents the number of registered GM vaccines that are currently available on the market. Currently, 78 of 124 registered vaccines are testing in phase 4.

Per clinical trial phase the top 5 most frequent GM vaccine indications were identified and are visualised in phase specific pie charts. Cancer indications were present in the top most frequent GM vaccine indications of phase 1 (n=90) and phase 2 (n=106). Malaria indications (n=19) were found to be part of the most frequent GM vaccine indications of phase 1.

Figure 2: Number of active GM vaccine clinical trials per phase, accompanied with the number of currently registered GM vaccines. Pie charts illustrate the five most frequent indications per phase. Phase transition success rates are indicated between phase 1-phase 2 (82%), and phase 2-phase 3 (76%).

Registered vaccines and patents

Vaccine registration data between 1988 and 2013 and patent filing data between 1970 and 2015 were included in this study. In total 797 registered vaccines were analysed (conventional and GM) and a timeline shows an upward trend in vaccine approvals starting in 2000 (Figure 3A). The same trend occurs in both GM vaccine approval and GM vaccine patent filing, respectively (Figure 3B and 3C). GM vaccines were found to represent nearly 20% of the total number of registered vaccines in the year 2013.

In total 40.308 unique patents were included to explore the rate of GM vaccine patent filing worldwide. Figure 3c illustrates a rising trend, significantly increasing in the year 2000, which correlates with figure 3b. Figure 3 illustrates the general growth of the GM vaccine market.

Figure 3: 3A, Timeline demonstrates the total number of registered-, conventional-and GM vaccines. Additionally, a percentage of the total number of GM vaccines in relation to the total number of vaccines is illustrated. 3B shows an upward trend of GM vaccine approvals between

2000 and 2013. 3C, patent application timeline between 1970 and 2015, illustrating an upward trend based on the number of yearly filed GM vaccine patents.

Region	Number of patents
North America	4072
Asia	3515
Europe	2566
Oceania	1179
South America	1089
Russia	221
Africa	116

Figure 1: Patent density based on the number of patents filed in each region, illustrated by gradient. Geographic location of the top 17 companies and institutes worldwide based on the number of patents they own (inclusion cut-off: 99+ patents in possession) and the correlating percentage of the total 15.977 patent documents that were included. Numbers behind companies and institutes indicate the share of patents they possess in percentage of the total number of patents.
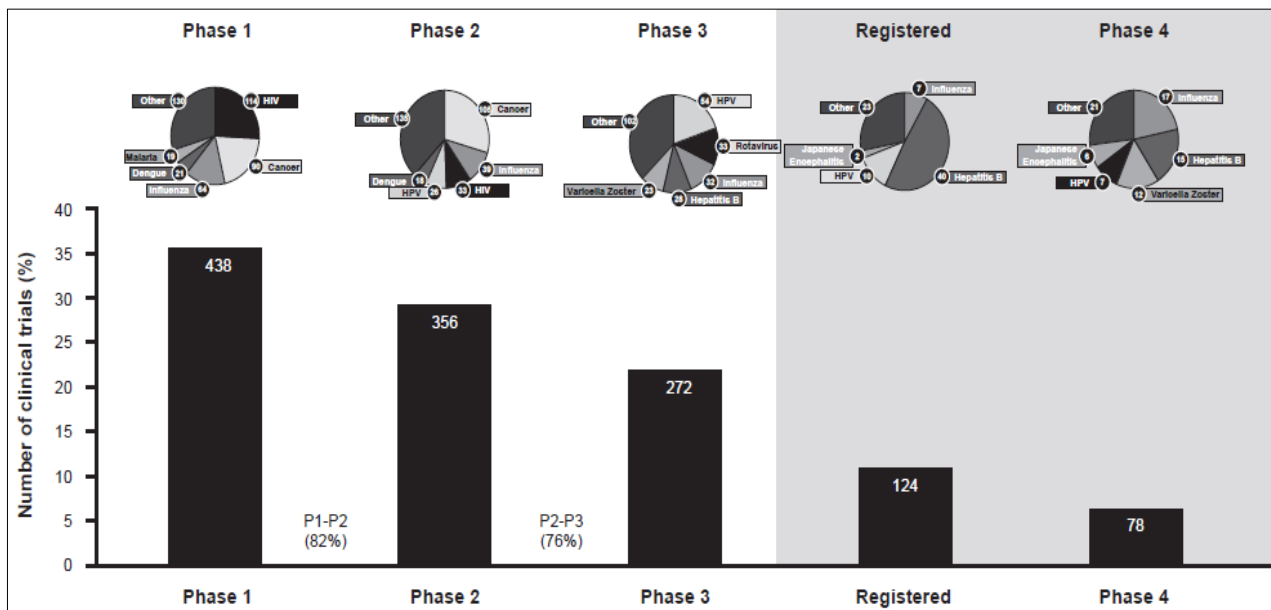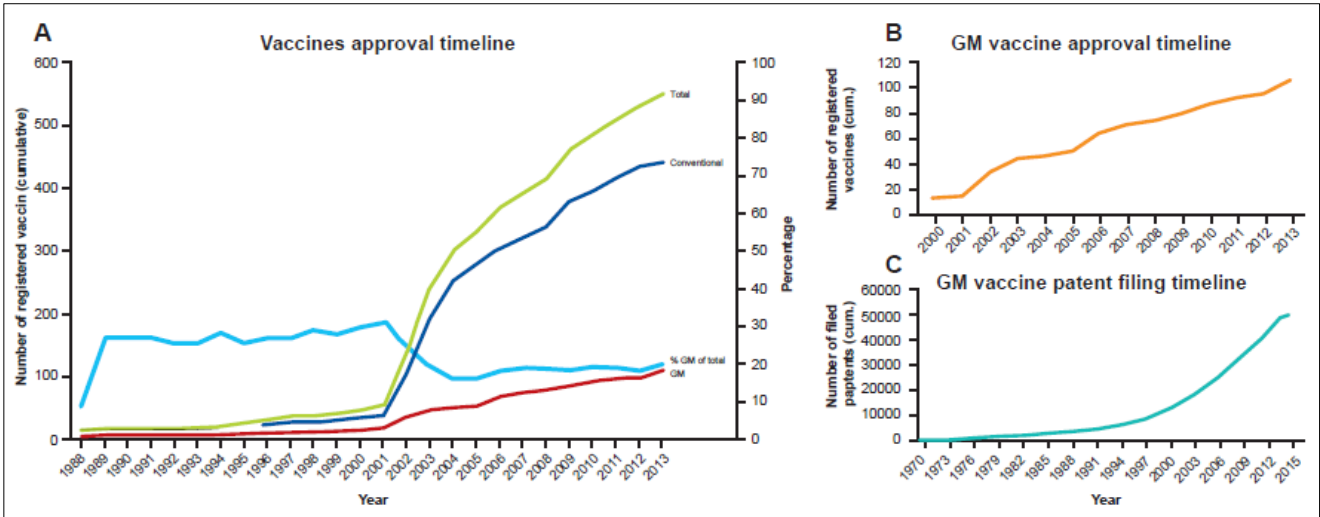

Figure 2: Number of active GM vaccine clinical trials per phase, accompanied with the number of currently registered GM vaccines. Pie charts illustrate the five most frequent indications per phase. Phase transition success rates are indicated between phase 1-phase 2 (82%), and phase 2-phase 3 (76%).

Figure 3: 3A, Timeline demonstrates the total number of registered-, conventional-and GM vaccines. Additionally, a percentage of the total number of GM vaccines in relation to the total number of vaccines is illustrated. 3B shows an upward trend of GM vaccine approvals between 2000 and 2013. 3C, patent application timeline between 1970 and 2015, illustrating an upward trend based on the number of yearly filed GM vaccine patents.

Figure 4: Top companies and institutes per indication group, based on the number of patents they own. Purple circles indicate companies, green circles indicate institutes.

DISCUSSION

This study provides an interdisciplinary overview of the GM vaccine pipeline, reaching from patents to registered vaccines. Here we demonstrate unexpected high phase transition success rates of GM vaccines in clinical trials, 82% (P1-P2) and 76% (P2-P3). This study also indicates a significant increase of global GM vaccine market share (20%), supported by rising trends in patent applications and vaccine registrations. Most viable regions for GM vaccine markets are North America, Asia, and Europe.

Prior to this study, no comprehensive research was conducted to investigate the current state of GM vaccine field. Therefore, this study was designed to provide a thorough overview of the current state of Research and Development (R&D) with respect to medical studies, intellectual property protection, and vaccine registrations.

Remarkable high phase transition success rates are revealed from the analysis of clinical trial phases. Comparing to previous studies on biopharmaceuticals, the snapshot phase transition success rates that we present here are relatively high, P1-P2 82% and P2-P3 76%.[25,26] The stakeholders that are willing to invest in biopharmaceuticals will assess the likelihood of success before making huge investments. Therefore we postulate that the observed high phase transition success rates will create momentum and provide versatile opportunities in GM vaccine R&D and eventually in vaccine field. Consequently, high rates of market approval may contribute to solving unmet medical needs, which eventually leads to societal benefits.

A significant increase of GM vaccine approvals was observed in the period of 1988 to 2013. GM vaccines currently take up 20% of the global vaccine market. Vaccine approval timelines illustrates an upward trend in the number of registered GM vaccines, which is accompanied by an upward trend in GM vaccine patent filing. These upward trends indicate the occurrence of several influential changes within the GM vaccine field with a starting point of 2000-2001. Literature provides several reasons behind this instant increase, for example, announcement of the Global Fund project by WHO in the beginning of the year 2002, which has resulted in significant increases in funding.[27] Furthermore, the Immunization Vision and Strategy (GIVS) developed by WHO and UNICEF and Bill & Melinda Gates Foundation awards in 2001 to develop drugs and vaccines through public-private partnerships, which led to increased spending on vaccines worldwide.[28,29] A decline in GM vaccine share was observed in the period 2000-2001 (Figure 3A), which is caused by the exponential increase in conventional vaccine registrations in that same period. The total number of registered vaccines inflated, which consequently resulted in a smaller GM vaccine share. Overall, the continuous growth of GM vaccine market within the vaccine field indicates an increase in GM vaccine market share.

The most viable GM vaccine markets are located in North America, Asia, and Europe. The regions were compiled of separate countries that emerged from our data (Figure 1) and chosen based on the most frequent discussed continental pharmaceutical markets. This could be explained by the fact that the most knowledge and resources are to be found in these regions.[30] North America is the leading region in patent possession; most GM vaccine related patents are filed here, which may be due to the size and capacity of the current pharmaceutical market in the US.[31] Rules and regulations in Russia and

Africa make it difficult to file a patent in these regions, which results in a lower number of observed patent applications. Moreover, combined with unfavorable rules and regulations, a trailing pharmaceutical market could explain the cause for lower numbers of patent applications.[19,32] Subsequently, the number of patents identified the leading companies and institutes in the field of GM vaccines. GlaxoSmithKline (4.9%), Novartis (4.5%), and Merial (2.2%) were identified as largest stakeholders based on the number of patents they own. Jointly, they are responsible for 11.6% of the total number of GM vaccine related patents, regardless of where patents were applied. Our analysis reveals that most companies and institutes reside in the United States (Figure 1). The involvement of Big Pharma companies shows the viability and domineering nature of the GM vaccine market.[33] Companies are found to dominate the indication groups "infectious disease" and "allergy and immune system" (Figure 4). Institutes and universities seem to dominate the newer indication groups "cancer", "genetically related disease" and "multi-purpose".

Considering the GM vaccine markets' viability and growth, we predict the registration of GM vaccines targeting cancer and malaria in the coming years. The clinical trial analysis was performed in bulk, which enabled us to accurately forecast future GM vaccines. We assume that a large group of clinical trials targeting a single disease is more likely to receive one or several marketing approvals.[26] New indications, cancer and malaria, were only present among the group of most frequent indications of phase 1 and phase 2.

The findings of this study should be interpreted in the light of several limitations. First, due to the fact that the field of GM vaccines has not been investigated prior to this study, a clear definition/delineation of what should be considered a GM vaccine is lacking. Therefore we designed clear search criteria in this study, based on different definitions of GM vaccines found in literature, in order to reduce terminology and definition confusion. The search criteria were used to delineate the topic of our study, but might have led to the exclusion of relevant data or studies. To validate our data, multiple certified independent professionals have checked our methodology and the datasets created for this study.

Second, patent documents were retrieved from Espacenet by adopting the use of several CPC codes related to GM vaccines. We chose these CPC codes based on the terminology of GM vaccines that is described in literature. We cannot claim completeness of data because we could only apply our search criteria on the public domain of information. Since this concerns a patent database, the more recent patent documents were not included in our dataset because they only become public 18 months after filing. Additionally, patent literature is often written in a broad context to avoid being bound to specific technologies or indications. The lack of clear indication descriptions led to narrowing the search

criteria in order to compile a smaller specific dataset that was used for construction of Figure 4. Only CPC code A61K39/xx and C12N15/xx (Table 2) were included, and a period of 5 years was selected.

Finally, clinical trials ought to be removed from the WHO ICTRP database after termination or completion, which is done on a weekly or monthly basis (varies per country). Since the dataset that was used for clinical trial analysis is a snapshot dataset, there is a probability that erroneous clinical trial data has been included in relatively limited amounts.

In conclusion, this study provides evidence on the growth of worldwide GM vaccine market.[34,35] Advances in research and development and the next generation of GM vaccines can be anticipated in the coming years. We forecast the market entry of cancer vaccines and the targeting of malaria by GM vaccines. Additionally, this study identified viable markets for both big pharmaceutical companies and pioneering institutes. The results of this study point out a compelling need of a clear definition of GM vaccines, and future research on GM vaccine production platforms is recommended.

ACKNOWLEDGMENTS

Appendix A. Literature search syntax

Embase.com   945

('genetic immunization'/de OR 'DNA vaccine'/de OR 'live vaccine'/de OR 'virosome vaccine'/de OR 'recombinant vaccine'/de OR 'virus like particle vaccine'/de OR (((gene* OR live OR protein*) NEAR/3 (vaccin* OR immuni*)) OR ('virus like' NEXT/1 particle*)):ab,ti OR (('DNA modification'/de OR dna/exp OR rna/exp OR 'genetic recombination'/exp OR 'recombinant protein'/exp OR 'virus vector'/exp OR 'bacterial vector'/de OR virosome/de OR (genetic* OR attenuat* OR enigneer* OR modif* OR DNA OR rna OR vector* OR recombin* OR chimeric* OR virosom*):ab,ti) AND (vaccine/exp OR Vaccination/exp OR immunization/exp OR (vaccin* OR immuni*):ab,ti))) AND ('systematic review'/de OR 'meta analysis'/de OR ((systematic NEAR/3 review*) OR (meta NEXT/1 analy*)):ab,ti)

Medline (OvidSP)   364

(exp "Vaccines, Synthetic"/ OR "Vaccines, Attenuated"/ OR "Vaccines, Virosome"/ OR (((gene* OR live OR protein*) ADJ3 (vaccin* OR immuni*)) OR ("virus like" ADJ particle*)).ab,ti. OR ((exp dna/ OR exp rna/ OR exp "Recombination, Genetic"/ OR exp "Recombinant Proteins"/ OR exp "Genetic Vectors"/ OR Virosomes/ OR (genetic* OR attenuat* OR enigneer* OR modif* OR DNA OR rna OR vector* OR recombin* OR chimeric* OR virosom*).ab,ti.) AND (exp vaccines/ OR exp Vaccination/ OR exp immunization/ OR (vaccin* OR immuni*).ab,ti.))) AND ("meta analysis".pt. OR ((systematic ADJ3 review*) OR (meta ADJ analy*)).ab,ti.)

Cochrane DARE   7

(((((gene* OR live OR protein*) NEAR/3 (vaccin* OR immuni*)) OR ('virus like' NEXT/1 particle*)):ab,ti OR (((genetic* OR attenuat* OR enigneer* OR modif* OR DNA OR rna OR vector* OR recombin* OR chimeric* OR virosom*):ab,ti) AND ((vaccin* OR immuni*):ab,ti)))

Web-of-science   323

TS=((((((gene* OR live OR protein*) NEAR/3 (vaccin* OR immuni*)) OR ("virus like" NEAR/1 particle*)) OR (((genetic* OR attenuat* OR enigneer* OR modif* OR DNA OR rna OR vector* OR recombin* OR chimeric* OR virosom*)) AND ((vaccin* OR immuni*)))) AND ("systematic review*" OR "meta analy*"))

PubMed publisher 8

(((((gene*[tiab] OR live[tiab] OR protein*[tiab]) AND (vaccin*[tiab] OR immuni*[tiab])) OR (virus like particle*[tiab])) OR (((genetic*[tiab] OR attenuat*[tiab] OR enigneer*[tiab] OR modif*[tiab] OR DNA[tiab] OR rna[tiab] OR vector*[tiab] OR recombin*[tiab] OR chimeric*[tiab] OR virosom*[tiab])) AND ((vaccin*[tiab] OR immuni*[tiab])))) AND (((systematic review*[tiab]) OR (meta analy*[tiab]))) AND publisher[sb]

Google Scholar

"genetic|DNA|live|attenuated|virosome|recombinant|engineered|modified   vaccine|vaccines|immunization|immunisation   "systematic review"|"meta analysis"

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