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REVIEW ON THE CURRENT CHALLENGES IN VACCINE DEVELOPMENT

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Abstract:

Global health has been greatly impacted by vaccines. Smallpox, rinderpest, and several other major infections have been eradicated. A variety of infectious diseases of childhood have been significantly improved by whom in the past decade. As polio has been virtually eradicated, and measles has been controlled successfully, it may also be eradicated soon. Vaccines can prevent infections such as pneumonia and diarrhoea which cause 6.6 million deaths each year. Due to new pneumococcal conjugate vaccines and rotavirus vaccines, childhood mortality is expected to decline further. As of now, malaria, tuberculosis, and HIV vaccines have had modest success. Vaccinations that stimulate different immune systems and it may be the most effective way to prevent these infections. Reverse and structural vaccinology have revealed novel antigen candidates and molecular immunology has led to the formulation of promising adjuvants. Gene expression profiles and immune parameters in patients, vaccinees and healthy controls have formed the basis for biosignatures that will provide guidelines for future vaccine design. On a long-term basis, vaccines may prevent or modulate diseases other than infectious diseases. It is already possible to develop cancer vaccines, and in the future it will be possible to develop vaccines for addictions, diabetes, hypertension, and Alzheimer's disease as well.

KEYWORDS: *Vaccine. Technology, Immunity, Challenges, Regulatory.*

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1.INTRODUCTION:

The most difficult technological hurdle is turning a vaccine-making system developed in a basic research center into a process that can be amplified & controlled in a manufacturing environment to produce many lakhs of doses annually. The ability to design and develop innovative vaccine candidates, which is the earliest and most important stage in the vaccine creation phase, is possessed by numerous university and government research organizations, as well as start-up biotechnology firms. This is simply the start of a round of intense combat that will demand a high level of expertise, cutting-edge gear, perseverance, and patience.Vaccination is frequently mentioned as the largest human intervention outside of access to clean water and sanitary facilities. Between the end of the nineteenth century and the present, infectious diseases have considerably and steadily decreased in industrialized nations due to a fall in infectious disease mortality before the creation and use of vaccinations. In addition, improvements in sanitation, nutrition, and housing were linked to increases in health. Vaccination has clearly improved both human and animal health, particularly in underdeveloped nations. Smallpox and measles caused about half of the population to perish during outbreaks. Only significantly fewer people died from measles than from smallpox. It outlines some of the main achievements of vaccination, the widespread use of vaccinations now, and how vaccination may benefit global health in the future[1].

1.1. CONVENTIONAL VACCINES

Live wild-type organisms were used as the first vaccinations. Despite the fact that attenuated or dead organisms have mostly taken their place, some of these are still in use. Attenuation is typically accomplished by growing the pathogens in a "unnatural" host (passage); less frequently, viruses are made temperature sensitive or are "cold-adapted" to grow at temperatures below normal. The pathogens are either fixed with substances like methanol (formaldehyde), f3-propiolactone, or, more recently, an imine, for inactivation, or they are autoclaved for inactivation. Despite the lack of a clear scientific foundation, these methods have produced some remarkably effective vaccinations. However, these immunizations frequently have unacceptably damaging side effects for the hosts. Even with products like the smallpox and attenuated poliovirus vaccines, which have had great success, there are a tiny but considerable number of post-vaccination occurrences. The possibility that some pathogenic microorganisms may survive the inactivation procedure makes killed vaccinations potentially problematic. The use of subunit vaccinations, which make an effort to enhance the active components through standard biochemical purification, can help to mitigate some of these hazards of virulence and contamination[2].

1.2. THE NEW VACCINES

The use of recombinant DNA, monoclonal antibodies, the idiotype network hypothesis, and the idea of immune response genes are some of the most significant and far-reaching advancements in biological sciences in general and immunology in particular over the previous ten years. These have a significant impact on how we understand the pathophysiology of infectious diseases and serve as the basis for innovative vaccination techniques. The next sections cover the present and upcoming vaccination advancements based on these findings. Using recombinant DNA technology, subunit vaccines Gene cloning, a collection of recombinant DNA methods for inserting and retaining new genetic material in bacteria, yeasts, or mammalian cells, is currently a potent tool for the production of protein materials, including peptide hormones, cytokines, and subunit vaccines. Numerous papers and reviews have been written about this fascinating technology. Finding the gene, putting it onto a plasmid or other suitable carrier, putting the complex into bacteria, yeast, or mammalian host cells, and then expressing and purifying the needed material are the general steps of the technique. In practice, this can be a difficult undertaking, especially if the protein of interest is only present in trace amounts and can only be discovered by a time-consuming bioassay[3].

2. COSTS, PROFITS AND MARKETS

It must be acknowledged that pharmaceutical companies are responsible for developing and commercializing vaccines, despite the fact that much of the fundamental vaccine research is carried out in academic institutions or non-profit organizations. Therefore, the market cannot be disregarded while thinking about vaccine development. The fact that demand often does not match the capacity to pay presents a challenge for pharmaceutical corporations. For instance, it is not surprising that the majority of the market value was predicted to reside in high-income nations and the majority of the demand to reside in low-income countries when analyzing the market and the potential profits to be realized from an HIV-1 vaccine. As a result, tiered pricing for vaccines already created for high-income countries has been proposed as a way to benefit all parties: developing countries receive access to a product that would have been out of reach if the vaccines were offered at a uniform price, producers enjoy increased revenues and profits, and the developed countries enjoy slightly lower prices

than would be the case in the absence of the low-price market[4].

3.FRAMEWORK CONSIDERATIONS FOR VACCINE DEVELOPMENT

The necessity, availability, and cost are the three main driving forces behind the development of vaccinations and treatments for newly emerging infectious illnesses. The number of people affected and the severity of the condition, whether it be acute or chronic, can be used to quantify need, either worldwide or locally. The question of whether certain activities are more likely to be pursued by industry or included in the global public health structure is always driven by the cost of development and the return on investment. A estimated that it would cost US$31–68 million (excluding the cost of a manufacturing facility) to develop a single vaccine candidate through Phase 2a, with a total cost of US$319–469 million (including candidates that don't meet expectations either preclinically or during clinical evaluation) to successfully develop a vaccine through to the end of Phase2a[5].

4. NATURAL IMMUNE CONTROL OF INFECTION

The first line of defense is innate immunity, which is nonspecific, whereas an adaptive immune response is characterized by the development of particular secreted and cellular effectors as well as immunological memory. Specialized antigen presentation cells (APCs) (such as dendritic cells) connect the sequential activation of innate and adaptive components, enabling the integration of an ideal immune response to the particular threat. Local APCs are activated between 4 and 96 hours after an infection by one or more of their pattern recognition receptors (PRRs), which identify various PAMPs and DAMPs (pathogen- or damageassociated molecular patterns). The PAMPs are chemicals that are present in communities of related microorganisms, are critical for their survival, and are not found in association with mammalian cells. Illustrations of PAMPS (sources) and their PRRs, as well as their primary method of action[6].

5.CHALLENGES IN PREPARATION OF VACCINES

A significant amount of protective antibodies are produced by the factor H binding protein (FHbp), a key ingredient of the MenB vaccine. This antigen, however, contains more than 500 different amino acid variants that don't result in crossprotective protection. The ideal candidate antigen would be able to trigger protective antibodies that would be effective against all FHbp allelic variants. The antigen's 3D structure was revealed and protective epitopes were identified in each of the mutations.Structure-based data is being used to logically develop vaccines against viruses. The Respiratory Syncytial Virus F protein can be assembled to produce a fresh F protein with a stable protective antigenic site. High levels of protective antibodies were produced after immunizing mice and monkeys with the consolidated neutralizing component of the F protein. The creation of the trimer, the connections between gp140 and gp41, associations with the CD4 interaction site, and mitigating antibodies in the HIV gp140 trimer crosslinked through a broadly hostile antibody were all revealed by cryoelectron microscopy. This makes it possible to develop HIV vaccinations based on structure[7].

5.1. CHALLENGES ENCOUNTERED IN DEVELOPING VACCINES AND CURRENT PROGRESS.

5.1.1..EFFICACY AND SAFETY

The creation of effective and safe vaccines is urgently required to stop the present pandemic, and more than 100 vaccines are now being produced in numerous nations. Postmarketing surveillance will be crucial in identifying any new adverse reactions to the vaccination in post-authorisation safety studies (PASS) and real-world evidence reporting when clinical trials and evaluation of vaccine efficacy by vaccine dossiers are accelerated. The BNT162b2 mRNA-based vaccine now causes headaches, exhaustion, and soreness at the injection site, while there have been several instances of patients experiencing anaphylactic reactions after getting the vaccination. As a result, the BNT162b2 mRNA-based vaccination should not be given to anyone with a history of immediate onset anaphylaxis to a vaccine, medication, or food, according to the Medicines and Healthcare products Regulatory Agency (MHRA) recommendations[8].

5.1.2. EMERGENCE OF CORONAVIRUS VARIANTS

Recently, coronavirus variations have been found as a result of the virus's adaptation and mutation to increase its survival. One of the many versions, B.1.1.7 (or VUI 202012/01), had a substantially higher transmission rate than the original virus and the other variants, at 71% (95% CI: 0.67 to 0.75). Due to spontaneous and frequent structural changes in the spike protein that increase transmissibility, B.1.1.7, the main variety in the United Kingdom, is thought to be linked to a higher risk of death than other variants. Similar to this, the S protein RBD of the P.1 variety developed three mutations at K417T, E484K, and N501Y. By

interfering with the production of antibodies following an earlier natural infection or by vaccination, these alterations are discovered to have an impact on the antigenic profile and transmissibility[8].

5.1.3. VACCINE DISTRIBUTION CHALLENGES

The BNT162b2 mRNA-based vaccine candidate from Pfizer and BioNTech is the frontrunner in late-stage vaccine development, with reported interim analysis results indicating that the vaccination is 95% effective in preventing COVID-19. The vaccine must be kept at 70 degrees Celsius during the whole distribution process from the manufacturer's warehouse to its final destination.This implies that towns or regions without access to ultracold storage systems will have to wait longer for other vaccine candidates that are kept in more hospitable environments[14].

5.1.4. SCIENTIFIC COMPLEXITY

Understanding the disease-causing microorganism in great detail is the first step in creating a vaccine. Researchers must locate particular proteins or antigens on the pathogen's 4. Scientific Complexity: Research on the disease-causing pathogen is the first step in creating a vaccine. Specific antigens or proteins on the surface of the pathogen that can activate a defending immune response must be found by researchers. Due to the virus's capacity for fast mutation, this has proven to be particularly difficult for some infections, such as HIV[10].

5.2 CURRENT PROGRESS IN VACCINE DEVELOPMENT (AS OF 2021):

5.2.1..COVID-19 VACCINES

The development of the COVID-19 immunizations marked a significant turning point in vaccine research and development. Many vaccines, including those produced by PfizerBioNTech, Moderna, Johnson & Johnson, AstraZeneca, and other companies, quickly received full or emergency use authorization in a number of countries. Several technologies, including viral and mRNA vector platforms, were used to create these vaccines[11].

5.2.2.MRNA TECHNOLOGY

The effectiveness of COVID-19 vaccinations based on mRNA showed this technology's promise. By encoding particular antigens, it enables the quick production of vaccinations against a variety of infections. Since then, mRNA vaccines for other infectious diseases like influenza and Zika have been researched[12].

5.2.3. VECTOR VACCINES

The potential of vector-based vaccinations, like the adenovirus vector used in the COVID-19 vaccines developed by Johnson & Johnson and AstraZeneca, has been demonstrated for infectious diseases like Ebola.

5.2.4..IMPROVED MANUFACTURING

creation efficiency has improved thanks to developments in vaccine manufacturing, including the creation of recombinant proteins and cell-based vaccines. These methods shorten the time needed for manufacturing scale-up and can be customized for various vaccinations[13].

5.2.5. AI AND BIOINFORMATICS

Bioinformatics and artificial intelligence are being used more and more to hasten vaccine development. These technologies aid in the early identification of potential problems, the optimization of vaccination candidates, and the prediction of prospective antigens[14].

5.3. CHALLENGES FACED IN DEVELOPMENT OF HUMAN PAPILLOMAVIRUS AND ROTA VIRUS

Recent examples from Merck Research Laboratories for three vaccine product candidates show the numerous challenges involved in turning a basic vaccine concept into a functional vaccine. These projects are well underway and have been in the works for at least seven years. In fact, it is anticipated that they will receive licenses in the US and many other countries in 2005.

5.3.1. HUMAN PAPILLOMAVIRUS

The first one is an immunization against four different strains of the human papillomavirus (HPV). Following extensive animal research using VLPs produced by a process of self-synthesis of the HPV L1 peptide, this artifact entry was approved by Commonwealth Serum Laboratories (Australia) and the University of Queensland. These initial studies provided a strong preclinical "proof of concept," demonstrating that this method has the potential to be developed as a preventive immunization for people. VLP was selected as an antigen because it is naturally non-infectious and because VLP-based hepatitis B vaccinations have a good track record. The HPV vaccination's preclinical to clinical conversion process began in 1993 and took 9 years to complete[15].

5.3.2. ROTAVIRUS

The rotavirus vaccine developed has five different human-bovine virus candidates that have been grown up using VERO cells. It is a live, weakened virus vaccination. The Reovirus genus, which includes Rotavirus, is a member of the Reoviridia virus family. By taking advantage of the rotavirus genes' inherent ability to reassort in cell culture, the final reassorted strains were chosen from each of the five final kinds. The general approach for developing a vaccine would be similar to that for HPV, but the technological obstacles are very different. The production of rotavirus vaccines requires the creation of masterseeds for each of the five rotavirus species as well as the VERO cell bank. The VERO cells are grown to convergence on a surface and then infected with rotavirus. Each reassortant goes through a distinct phase, totaling ive. The ideal approach is oral administration[16].

5.5. CHALLENGES IN VACCINATION'S LONG-TERM FUTURE:

5.5.1. VACCINE HESITANCY

The public must have faith in immunizations. To sustain high immunization rates, it is imperative to address vaccine hesitancy, which is caused by misinformation and mistrust.

5.5.2. EMERGING DISEASES

Researchers will need to react swiftly to create effective vaccinations as new diseases continue to appear. It is difficult to anticipate and prepare for these hazards[17].

5.5.3. GLOBAL EQUITY

It remains difficult to guarantee universal access to immunizations. To stop epidemics and advance international health, disparities in vaccine access and distribution must be addressed.

5.5.4. ANTIGENIC VARIATION

The development of long-lasting vaccines is challenging for some infections, such as HIV and malaria, which show significant levels of antigenic diversity. It will take creative solutions to overcome this obstacle[18].

5.5.5. SAFETY MONITORING

It is vital to keep an eye on long-term safety as new vaccine technologies are developed.

Potential side effects must be evaluated and addressed by researchers.

5.5.6. VACCINE PRODUCTION CAPACITY

It is still difficult to increase vaccine production capacity to fulfill demand on a worldwide scale. When quick scaling is required during pandemics, this is particularly pertinent[19].

6.TECHNOLOGIES AND APPROACHES FOR VACCINE R&D

We identified four technologies and approaches that may enhance vaccine R&D based on information from experts, stakeholders, and related literature.The technology and methods we found can be used at many phases of vaccine research and development.By studying the pathogen's DNA, RNA, proteins, or other biological molecules, omics and reverse vaccinology helps in the early exploration process by enabling researchers to more quickly find antigens that trigger a protective immune response. After that, scientists can use computer simulations to more quickly forecast which possible antigens will trigger an immunological response and which changes to the antigens will strengthen the immune response.

Selected technologies and approaches for vaccine research and development (R&D)

6.1. CHALLENGES AFFECTING THE ADOPTION OF R&D

Name	Description
Omics	Omics refers to the combined analyses of DNA (genomics and epigenomics), RNA (transcriptomics), proteins (proteomics), other small molecules (metabolomics), and other biological components. In vaccine R&D, omics is meant to improve the understanding of pathogens and host immune responses.
Reverse vaccinology	Reverse vaccinology uses computer-based analytics to assess a pathogen's genetic code and identify potential antigens. Reverse vaccinology allows researchers to identify potential vaccine antigen candidates without the need to grow the pathogens and develop vaccines that were previously difficult or impossible to make.
Nextgeneration vaccine platforms	Next-generation vaccine platforms incorporate the genetic information that codes for a pathogen's antigen into a delivery vehicle. A delivery vehicle can be another virus (viral vector), a microparticle, or a lipid nanoparticle. The delivery vehicle protects the genetic information until it is administered into an individual, where the immune response is triggered. The platform may also be able to be used in a plug-and-play fashion to pair a delivery vehicle with different genetic sequences to create new or updated vaccines. Vaccine platforms may have uniform, predictable characteristics, such as safety effects; however, each antigen in a specific platform will have different immune response characteristics[20].

6.2.TECHNOLOGIES AND APPROACHES.

We identified three main obstacles preventing the adoption of technologies and methods for vaccination R&D based on information from experts, stakeholders, and related literature:

- Inherent technological limitations
- Complex, costly instruments
- The need for highly trained personnel

6.2.1. INHERENT TECHNOLOGICAL LIMITATIONS

The following technologies and methods may be employed to varying degrees, depending on their technological capabilities[21].

6.2.1.1. OMICS AND REVERSE VACCINOLOGY

Some antigens, such as those based on sugar (polysaccharides) or fat (lipids and glycolipids) antigens found in bacteria and parasites, cannot be predicted by reverse vaccinology; in these cases, more conventional methods are used. Additionally, despite the use of omics, it may be difficult to pinpoint typical immune responses to antigens because to the considerable variation in immune system responses between individuals.

6.2.1.2. NEXT-GENERATION VACCINE PLATFORMS

Vaccine researchers must carefully analyze the chosen genetic sequences from pathogens that code for antigens to ensure the efficacy of next-generation vaccine platforms. If they don't, the outcome can be vaccination candidates that are useless. A different mRNA vaccine candidate, for instance, was not as effective in clinical testing as the first two mRNA COVID19 vaccines that were approved for emergency use[22].

6.2.1.3. ROUTES OF VACCINATION

Researchers need to make sure the antigen still has the ability to elicit the necessary immune response in order to use non-traditional vaccination methods. It's possible that some antigens can't be administered by unconventional means. For instance, oral vaccination formulations must be created in a way that allows them to endure the challenging gastrointestinal environment. Investing in manufacturing capacity for vaccines that are given through unconventional channels may also be necessary to accommodate new delivery methods.

6.2.1.4. MONOCLONAL ANTIBODIES

In some aspects, monoclonal antibodies are different from vaccinations. They lack the longlasting immunity that vaccines may offer, are made of proteins that can degrade over time, and do not stimulate the immune system in the same way that vaccines do. Additionally, intravenous administration of monoclonal antibodies has been standard practice in a medical setting. However, altering particular portions of these proteins can lengthen the duration of protection and even enable intramuscular or subcutaneous injections as opposed to intravenous delivery[23].

6.2.2. COMPLEX COSTLY INSTRUMENT

The following technologies and methods' level of adoption may also be influenced by how complicated and expensive they are.

6.2.2.1. OMICS AND REVERSE VACCINOLOGY

Some researchers might not be able to use omics-based tools due to their high cost, such as massively parallel sequencing tools and related reagents, and the complexity of the generated data.

6.2.2.2. ROUTES OF VACCINATION

According to one expert we spoke with, creating vaccines for various immunization methods may be costly due to the sophisticated technologies needed in formulation development.

6.2.2.3. MONOCLONAL ANTIBODIES

Monoclonal antibody development and production have historically been difficult, expensive, and time-consuming processes. However, new methods for simpler monoclonal antibody discovery, selection, and optimization have slashed the complexity and length of time for development from years to weeks. Additionally, advancements in manufacturing may result in lower production costs. Lack of defined or lucrative markets, such as for vaccines for viruses with pandemic potential or that largely impact developing nations, may make these potentially high costs and complexity even worse. These financial difficulties can prevent the development of new vaccines[24].

6.2.3.THE NEED FOR HIGHLY TRAINED PERSONNEL

The adoption rate of the ensuing technologies and strategies may also be influenced by the availability of highly skilled personnel to run the intricate machinery and procedures.

6.2.3.1. OMICS AND REVERSE VACCINOLOGY

Highly-skilled staff may also be required due to the complexity of the equipment and methods, such as massively parallel sequencing devices and bioinformatics tools, required for omics analysis[25].

6.2.3.2. MONOCLONAL ANTIBODIES

A specialized workforce is needed due to the complexity of the technology and industrial processes used to create and produce monoclonal antibodies. A manufacturing run, for instance, may take up to two weeks and involve as many as 10 different phases.

6.2.3.3. NEXT-GENERATION VACCINE PLATFORMS

According to an expert we spoke with, the intricacy of platform technology necessitates a highly skilled workforce. For platform technologies, uniformity of generated doses depends on how biological processes are carried out[26].

7.CHALLENGES AFFECTING THE ADOPTION OF VACCINE TESTING TECHNOLOGIES AND APPROACHES

We identified four obstacles preventing the adoption of technology and methods for vaccination testing based on data from experts, stakeholders, and the scientific literature:

- Limited technological maturity
- Difficulty protecting patient data
- Ongoing data standards development
- Limited stakeholder collaboration and agreement on common approaches to testing

Clinical trial researchers, vaccine creators, and participants all may be impacted by these difficulties.

7.1. LIMITED TECHNOLOGICAL MATURITY

Depending on their technological maturity or capacity to provide evidence of their validity, the following technologies and techniques will be embraced to varying degrees[27].

7.1.1. ORGAN CHIPS

Organ chips' usefulness is limited since they are not yet developed enough to imitate many of the intricate actions and reactions of the human immune system. Organ chips specifically duplicate the innate immune response, but the ability to duplicate the adaptive immune response is still under development, according to NIH. Organ chips can be utilized for some parts of toxicity assessment, however more development may be necessary to show that they don't result in erroneous negative results.

7.1.2. VIRTUAL TRIALS AND WEARABLE DEVICES

Many businesses will need to create new technology skills in order to conduct entirely virtual trials. They will need to incorporate wearable technology, for instance, and create methods for gathering and analyzing potentially vast amounts of data. For data submitted for vaccine licensure, several wearable technologies that are still in the early stages of research will need to show that they have been analytically and clinically validated[28].

7.2. CHALLENGES PROTECTING PATIENT DATA

Patients who agree to have information from their medical records and other sources included in trials give additional persons access to that data, making data privacy protection more difficult. Clinical trial researchers must abide by all applicable federal privacy rules and regulations, including the Health Insurance Portability and Accountability Act Privacy Rule.The following technologies and methods are directly impacted by the requirement to protect patient data.

7.2.1. ELECTRONIC HEALTH RECORDS (EHR)

The social security numbers, addresses, and medical diagnoses of patients are just a few examples of the sensitive data found in EHRs.

7.2.2.AI AND ML

There are privacy hazards associated with the use of AI and ML systems in clinical settings, and there are worries that the use of more advanced computer algorithms may make it simpler to re-identify data from patient records and other sources.

7.2.3. VIRTUAL TRIALS AND WEARABLE DEVICES

Virtual trials gather information apart from the typical clinical care environment. There is a requirement for security in data transfer. Protections must continue to be upheld for researchers in compliance with the Privacy Rule[29].

7.3. ONGOING DATA STANDARDS DEVELOPMENT

To promote interoperability, which is generally defined as the ability of a system to exchange electronic health information with, and use electronic health information from, other systems, without special effort on the part of the user, the Centers for Medicare & Medicaid Services and the HHS Office of the National Coordinator for Health Information Technology released final rules in 2020 that demand data exchange and data element standards for use in EHRs. This covers the application of technical standards for the transmission of EHR data as well as language requirements for the data's actual content.Researchers' capacity to use EHRs for research, particularly clinical trials, has historically been constrained by a lack of data standards and interoperability. The following issues with using EHRs in clinical trials could be resolved with the aid of the new regulations:

7.3.1. LACK OF CONSISTENCY IN HEALTH RECORD DATA

Standards either haven't been created for various types of clinical data or haven't been widely accepted. The capacity to apply criteria to identify qualified patients and analyze data from EHRs has been hampered by this discrepancy[30].

7.3.2. LACK OF EHR INTEROPERABILITY

EHR data have always been based on various data standards that are difficult to interchange. The transmission of data between EHRs and electronic data capture systems, which researchers employ to gather and manage clinical trial data, has been hampered by a lack of universally accepted data standards.

8. CHALLENGES AFFECTING THE ADOPTION OF VACCINE MANUFACTURING TECHNOLOGIES

We identified three main obstacles that prevent the adoption of technology for vaccine manufacturing by using information from experts, stakeholders, and the scientific literature:

- Inherent technological limitations
- High costs and the need for highly trained personnel
- Business risk

8.1. INHERENT TECHNOLOGICAL LIMITATIONS

The limitations of certain technology and methods will determine how far they are used in the manufacture of vaccines.

8.1.1. SINGLE-USE SYSTEMS

Disposable bioreactor bags may leak, and some plastic components used in single-use systems may leach undesired compounds into the process.Additionally, a specialist we spoke to said that scaling out is preferable to scale up due to constraints in disposable bioreactor scale. In addition, there are worries regarding the effects of recycled plastics used in single-use systems after they are disposed of.

8.1.2. CELL-FREE SYNTHESIS

Some proteins, including sugar-based (polysaccharide) antigens, may be difficult for cell-free systems to manufacture in the right folding or state.

8.1.3. CONTINUOUS MANUFACTURING

Not all vaccination kinds can be manufactured continuously. Continuous manufacturing procedures,

for instance, cannot be used for vaccines made in eggs, such as the majority of seasonal influenza vaccinations. Additionally, some vaccines cannot be produced continuously because the molecular mechanisms by which cells manufacture the antigens are poorly understood, and this limits the capacity to manage the manufacturing process.In order to ensure that the safety and efficacy of the vaccine have not been adversely affected, vaccine companies may be required to seek and obtain FDA approval of manufacturing changes prior to vaccine distribution. This presents challenges when switching from batch to continuous manufacturing.The price of certain technologies and methods as well as the requirement for specialist staff will influence how widely they are used. For instance, these technologies require manufacturers to make up-front financial investments that may be prohibitively expensive. Additionally, firms could be hesitant to replace machinery for which they have already incurred sizable capital expenses[31].

8.1.4. SINGLE-USE AND MODULAR BIOPROCESSING SYSTEMS

The implementation of modular bioprocessing systems may require high capital costs. Single-use and modular bioprocessing systems, though, might result in operating cost savings and improved productivity after implementation, offsetting initial expenditures. Additionally, constructing an integrated modular facility takes more technical construction know-how and qualified, experienced employees to get a facility up and running.

8.1.5. CONTINUOUS BIOPROCESSING

The expense of creating new infrastructure, adding additional machinery, and automating for continuous processing could deter people from using this technology.Furthermore, compared to traditional batch processing, continuous flow processes demand a different skill set and set of skills for design, development, validation, and operation. How a new method of producing vaccines might impact its ability to make money. It frequently makes business sense for a manufacturer to use more conventional technology for the product if introducing an innovative technology might result in additional activities, costs, and time to support product approval, according to a National Academies of Sciences, Engineering, and Medicine report that was sponsored by the FDA. Manufacturers who want to sell a product globally face additional difficulties due to various requirements in other nations. One expert we spoke to indicated that while the National Academies of Sciences[32].

8.2. BUSINESS RISK

The level of adoption of certain technologies and methodologies may also be influenced by how manufacturers view the business risk. Manufacturers might be concerned about the regulators' assessment of a new vaccine manufacturing technique and how it might impact the technology's potential to make money. It frequently makes business sense for a manufacturer to use more conventional technology for the product if introducing an innovative technology might result in additional activities, costs, and time to support product approval, according to a National Academies of Sciences, Engineering, and Medicine report that was sponsored by the FDA. Manufacturers who want to sell a product globally face additional difficulties due to various requirements in other nations. One expert we spoke to indicated that while the National Academies of Sciences, Engineering, and Medicine paper concentrated on pharmaceutical manufacturing, the same principles apply to manufacturing for vaccines[33].

9.CHALLENGES AFFECTING SCALING UP MANUFACTURING TO MEET SURGES IN DEMAND

The capacity to meet spikes in vaccination demand, including spikes brought on by epidemics or worldwide pandemics, is impacted by two major problems. The ability of manufacturers in the private sector to meet additional demand without adversely affecting their capacity to produce other approved vaccines is the first factor. The second is the federal government's capacity to guarantee that manufacturing capacity to combat pandemics is accessible and functional[31].Because they don't build extra, unused capacity for emergency situations, vaccine manufacturers, according to the experts we spoke with, are unable to fully address novel threats from various categories of pathogens. Additionally, using existing infrastructure to produce pandemic vaccines could have a negative impact on the production of current vaccines for diseases like measles, mumps, and rubella.There aren't many people who are adequately trained. Consider the issue of COVID19 vaccination cross-contamination. There aren't many people who are adequately trained. Consider the issue of COVID-19 vaccination cross contamination. • Flexibility- and productivity-enhancing technologies and methods are not supported. For instance, during the pandemic rather than beforehand, facility retrofitting and technical transfer of new manufacturing procedures for COVID-19 vaccinations required for the Texas and Maryland sites were completed[34].

9.1. MARKET FAILURES AND OTHER CHALLENGES RESULT IN FEWER VACCINES

Market failures happen when interactions in the market produce results that are less favorable for society. Due to market failures, vaccine producers create fewer vaccinations than would have been most advantageous to society, providing less protection from infectious diseases. Markets that offer no or negative returns on investment, the high expense, and the poor likelihood of success in creating vaccines are further obstacles that limit vaccine investment.

9.1.1. POSITIVE EXTERNALITIES

We concentrated on two distinct vaccine development market failures. The first relates to the composition of vaccines. This circumstance is referred to as a positive externality in economics. Developers cannot price their products based on this added benefit because this protection is built into every vaccination, therefore they are not paid for stopping the spread of the disease. Therefore, even though society would benefit from having more vaccinations available, developers frequently underinvest in vaccines.

9.1.2. IMPERFECT INFORMATION

The second kind of market failure results from product developers' incapacity, because of incomplete knowledge, to properly account for the illness risk in the price of the product. However, the creator is aware that a patient is likely to seek therapy after they contract the ailment. 71 This information can be used by developers to charge treatments far greater fees than they would for vaccinations. As a result, vaccines typically have a lower return on investment than treatments. Vaccine sales worldwide account for just around 1.5% of total pharmaceutical sales due to price incentives that are skewed away from medicines and toward vaccinations[35].

9.1.3. CHALLENGING MARKETS DUE TO UNCERTAIN DEMAND

Some markets present difficulties for vaccine developers because they offer low, no, or negative returns on investment. These markets include those for vaccines created for infectious illnesses that only exist in undeveloped nations, are given low priority, or have the potential to become pandemics in the future but are not currently a concern. According to experts, developers of these vaccines have little financial incentive to invest in them because of the low returns or market uncertainties. Negative 61% of the results indicated that the private sector is unlikely to meet this need without public-sector action.

CONCLUSION:

This thorough analysis has carefully navigated through the various problems, remarkable advancements, and optimistic prospects in the dynamic field of vaccine development, where science meets society's health requirements. In addition to highlighting the significance of vaccinations as a cornerstone of public health, the critical analysis of these themes also emphasizes the obligation of the global community to address the intricate concerns that surround them. We acknowledge that the route to vaccine development is paved with obstacles, from choosing the appropriate antigens to getting through regulatory barriers, as we reflect on the challenges encountered in developing vaccines and the current state of the field. The quick creation of vaccinations during crucial junctures like the COVID-19 pandemic is an example of how researchers' tenacity and innovation have produced extraordinary accomplishments. Financial Expenditure for the Development of New Vaccines is a topic that was discussed, and it highlights the importance of maintaining a steady financial stream for vaccine development. The importance of funding science, invention, and fair access to vaccinations cannot be overstated, particularly in light of the continuous war against infectious illnesses.

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Disclouse of conflict of interest

The authors have no conflict of interest to declare.

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