Viral Vaccine Strategies

Noorulhuda F. khalaf

Affiliation: Tropical Biological Research Unit / College of Science / University of Baghdad

* Correspondence: nooralaubadie@gmail.com

Received: 25/5/2022

Accepted :15/8/2022

Published: 8/12/2022

Abstract

Background: Lately, many viruses emerged or re-emerged from the obscurity and became considerable threats to the global health, raising alarms concerning their constant epidemic transmissions. A very important public health concern of those viruses is the continuous circulation amongst the population of the immunologically naive, susceptible hosts. With each one of the new viral emergences or re-emergences, there appears a call for a fast development of a vaccination and induction of a protective immunity thus could be one of the most powerful tools for the prevention of that concern through conferring the protection to the endangered population.

Vaccinations have been considered one of the crucial components of disease preventions towards the emerging virus infections due to the fact that, often, other options for the medical solutions are non-existent or limited. Whereas the conventional methods for developing a vaccination remain amenable to the emerging viruses, advents of the newest technologies in the molecular methods have a profound influence on the understanding of the biology of the viruses, as well as immune responses and methods of vaccination that are based upon attenuated, replicating, and non-replicating virus vector methods became beneficial platforms for vaccination.

Conclusion: In combination with a continuous understanding in biology of the newly appearing viral illnesses, a many different recent strategies of vaccination have been developed for protecting from the re-emerging and new viruses could become possible. It was found that the biggest challenge in all strategies used in the preparation of viral vaccines is to find vaccines that have a low cost, are highly specialized, and have high efficiency for the purpose of confronting emerging viral diseases. In this paper we focus on different viral vaccines strategies.

Keywords: vaccine, strategies, virus, DNA.

Introduction

The vaccinations had led to the transformation of the public health, in particular, from the moment when the national immunization programs have first become established and coordinated properly in 1960's. In the nations that have high coverage of the vaccination program, several diseases which have been responsible earlier for most childhood deaths had basically disappeared(1).World Health Organization (WHO) had estimated that 2 to 3 million lives are saved yearly due to the current programs of immunization, which contribute to considerable decrease of mortality rates of children who are younger than 5 years of age all over the world, from 93 death cases per 1000 live births in the year of 1990 to 39 death cases per 1000 live births in the year of 2018(2) .The vaccinations have exploited extraordinary capability of highly developed immune system of the humans for responding to, and remembering, encounters with the pathogen anti-gens (3).

There's a high necessity for the better understanding of immunological bases for the vaccinations for developing vaccines to face the hard-to-target pathogen types that antigenically variable pathogens like human immunodeficiency viruses (4),controlling the outbreaks threatening the worldwide health security (like Ebola or COVID-19) (5,6) and for working out the way for the revival of the immune responses in aging immune systems for the protection of growing populations of the older adults from various infectious illnesses(7).

The antigens could as well result in the induction of the protective immune responses and represent a base of the vaccinations, which were advanced for the prevention of a number of the viral infections, since the end of the 1980's (8).

The protection that has been conferred by vaccination has been evaluated in the clinical trials, relating the immune responses to vaccination antigen to the clinical endpoints (like preventing the infections, a disease severity reduction or reduced hospitalization rates) (9).In this review we highlighted recent development and conventional of viral vaccine strategies.

There are numbers of biotechnologies which use for making viral vaccines and we illustrate these techologies by started from recent to traditional one:

1- Viral vector vaccines:

The viral vectors have been considered to be possible vaccination tools. Their utilities are based upon the viruses' capability for infecting the cells. Generally, the benefits of the viral vectors can be summarized as: (i) highly efficient transduction of genes; (ii) highly specific gene delivery to the targeted cells; (iii) inducing robust immune responses, besides increased cellular immunities (10).

The idea of the viral vector vaccinations differs from concept of the sub-unit vaccinations, due to the fact that the latter are helpful in the prevention of the infectious diseases through eliciting humoral responses (5).The recombinant viral vectors have the possibility for the therapeutic uses, due to the fact that they have the ability of enabling the intra-cellular antigen expression and inducing robust cytotoxic T lymphocyte (CTL) responses, which result in eliminating virus-infected cells (11).In spite of their efficiency, the viral vectors pose considerable issues which require being addressed. In the foreseeable future, the viral vector-based vaccinations could be utilized increasingly used for fighting major illnesses, like the malaria and HIV-1. In some of the vectors, the stable expressions of interesting gene have been accomplished through the mechanisms of the viral integrations. Integration into the genome of the host may result in causing cancer (12).An additional obstacle to clinical uses of the viral vectors is presence of preexisting immunity towards the vector. Which results from earlier exposures to the virus and producing neutralizing anti-bodies which result in reducing the effectiveness of the vaccination? (13).

Viral vector development needs high levels of the biological safety for the purpose of gaining acceptance by the public. Which is why, the low- (or non-) pathogenic viruses are usually chosen. In the majority of the cases, the viruses are engineered genetically to eliminate or decrease the pathogenicity (14).In addition to that, the majority of the viral vectors are replication-defective. For instance, in the adenovirus-based vectors, both early areas (E1B and E1A) of encoding regions, required for the replication in the infected cells, are deleted and substituted with target gene (15).

In the case of the utilization of viral vector, there is an importance in assessing the possible implications through comprehending virological and epidemiological properties.

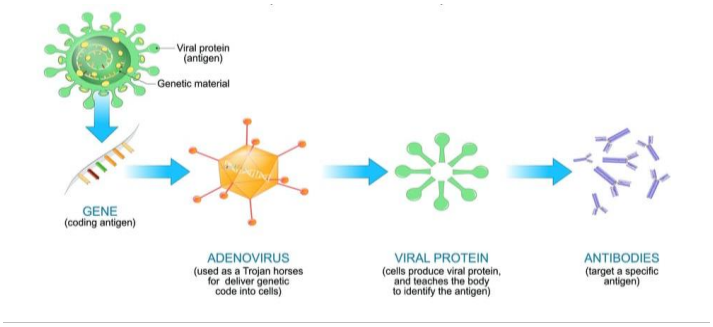


Figure (1): key mechanism action of viral vector vaccine (16).

2- Recombinant DNA or Protein vaccines:

The recombinant DNA technology provides the ability to combine the DNA from 2sources or more. Humanpapilloma-virus (HPV), Hepatitis B virus (HBV), and influenza (i.e. Flublok brand) vaccinations have been created through inserting a segment of respective viral gene to the virus or yeast cell gene (17,18).The modified virus or yeast cell results in the production of HPV capsid protein, pure hepatitis B surface anti-gen, or influenza hemagglutinin when growing (9).

The majority of the investigated vaccinations in the present day have been based upon high-purity recombinant proteins or sub-units of the pathogens The conventional recombinant protein vaccine example that is presently used in the humans is vaccination from HBV infections, which is one of the chronic liver diseases that occur all over the world (19).This virus causes a considerable tropism for the human liver cells, partly as a result a certain receptor, which expressed on the infected cell surfaces. The present day vaccinations are created through the expression of hepatitis B surface antigen (HBs-Ag) in the yeast cells. The HBs Ag accumulates to virus-like particles (VLP) that are quite highly immunogenic, which makes HBV vaccination a highly effective vaccination (20).The system of yeast expression could secrete anti-gen into culture supernatant which has the ability of facilitating its purification. In addition to that, the yeast cells present some eukaryotic cellular machinery that is responsible for post-translation protein modification, which have the ability to render the glycosylated proteins (21).The technology of HBV vaccination production was transferred to a number of the manufacturers and prices had been reduced, as a result of competition that had resulted in making this vaccination affordable to the majority of the developing nations.

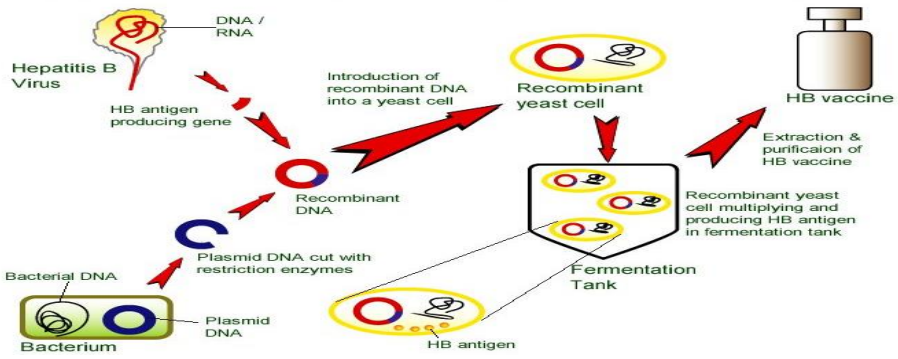


Figure (2): Steps of Hepatitis B virus vaccine production. (22)

3- DNA vaccination:

Directly injecting naked DNA plasmid in the muscle as vaccination system with capability for inducing immune responses and protection after challenge is well established now, due to the fact that this method was utilized for expressing many antigens from a variety of the pathogens that present promising result (23, 24). DNA vaccination (also referred to as genetic vaccination) includes plasmid that contains: a) 1*E.coli* replication origin, for plasmid amplification; b) strong promoter, in general, from the cytomegalo-virus; c) several sites of cloning, where one could insert the gene that needs being expressed, d) antibiotic as a marker of selection**.** (24,25). The concept behind a system of DNA vaccination is that an antigen may be directly expressed by host cells in a similar way to the one which occurs throughout the viral infections. Therefore, the anti-gens may be processed in a form of proteins that are synthesized within cytoplasm, and fragmented peptides that have been presented to immune system by the class I MHC molecules. Moreover, in the case of the exporting or secretion of the protein, it may be processed by the MHC molecules of class II and, thus, mount certain anti-body response**.**(23,24).The DNA vaccinations have a number of the characteristics, which may represent benefits over other processes of the immunization: there is no infection risks, in contrast to the attenuated vaccinations; they result in the humoral as well as cell-mediated immunity, in addition to that, they have the ability to induce the long-lived immune responses as well as an increase in the cytotoxic T-cell responses. Moreover, the DNA vaccinations avoid issues that are related to the production of the recombinant protein vaccinations, like the inadequate folding of the target molecules or high costs for purifying recombinant protein types (26).The optimal examples on DNA vaccine s will be tested on human are herpes and influenza.

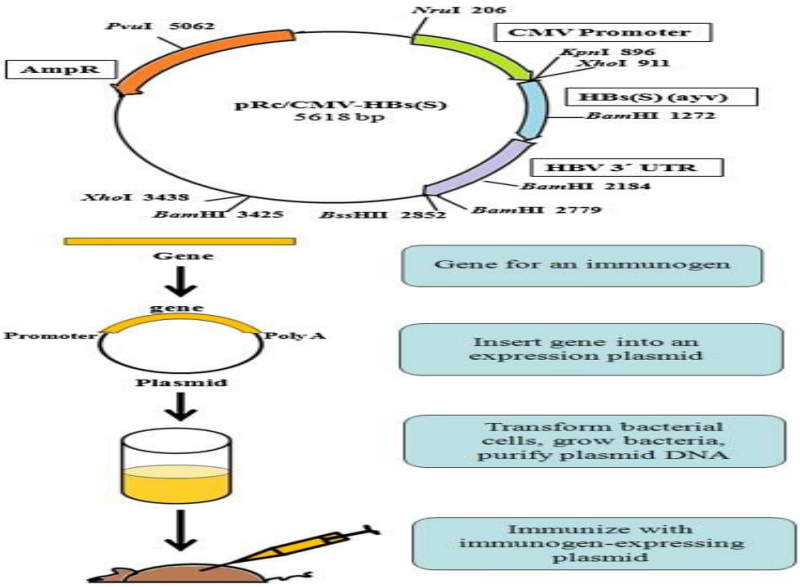


Figure (3): DNA vaccine preparation method. (27)

4- Inactivated virus vaccines:

This type of vaccination is typically made through the exposure of the virulent virus to the physical or chemical agents, for instance, formalin or β-propiolactone, for the purpose of destroying the infectivity at the same time as maintaining the immunogenicity. At first, the virus for those purposes has been usually obtained from the infected animal sources, for instance, mouse brains, none-the-less, the infected cell cultures present cleaner starting materials (28).

The necessity for using large antigen amounts for eliciting sufficient anti-body response is one of the major disadvantages (29).In general, with those types of the vaccines, the main course of the vaccination includes 2 or 3 injections; in addition to that, the "booster" dosages could be needed at intervals for maintaining the protective immunity (30).The physical or chemical treatments that are utilized for the elimination of the inactivated virus vaccines' infectivity could be rather damaging to modify the immunogenicity, particularly of the antigens that are required for eliciting cell-mediated immune responses.

This results in immune response that is narrower in the spectrum and shorter in duration for the viral antigens, weaker mucosal and cell-mediated immune response, and potentially less efficient in the prevention of the viral entry.

The most widely utilized inactivating agent, formalin, has been known to result in the induction of the irreversible changes in a wide range of the viral anti-gens; its continuous utilization is a result of conservative behavior of the vaccine manufacturers and the regulatory agencies and a rareness of the researches that are focused on this subject (31).Using β-propiolactone in manufacturing some human rabies vaccinations has benefits in the fact that the proteins aren't damaged and inactivating agent is hydrolyzed entirely in hours to the non-toxic products (32).

The non-ionic detergents like poly-oxylene ethers can be utilized in cases of the enveloped viruses to the solubilize virions and release glycol-protein peplomers as well as other envelope proteins.

The differential centrifugation or the ultra-filtration is utilized for semi-purifying solubilized glycoproteins before formulation for utilization as what is known as "split" vaccinations. Some widely-utilized influenza vaccinations are created with the use of this process (33).

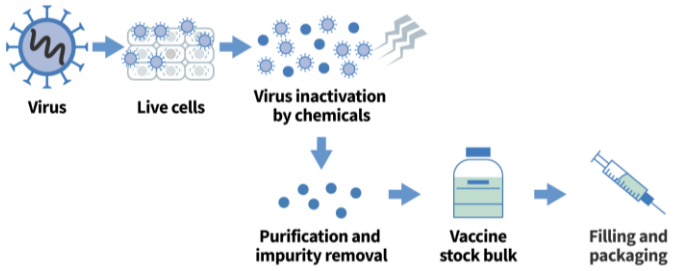
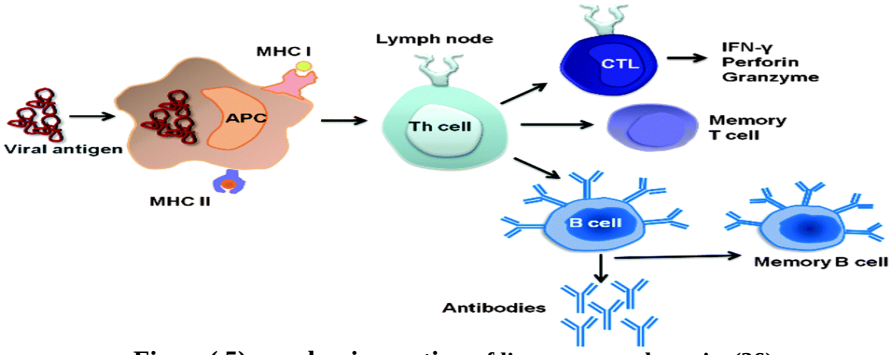


Figure (4): manufacturing process of inactivated vaccine. (34).

5- Live Vaccinations:

The live vaccinations include live attenuated micro-organisms that still have the ability to replicate inside the host. Micro-organisms are 'weakened', which means that they lost the majority of their capacity to cause disease, however, remain to have their immunogenic characteristics. In the majority of the situations, the live vaccine shows a considerably higher immunogenicity compared to the inactivated vaccinations, due to the fact that natural infection is nearly perfectly imitated through eliciting wider variety of the immunological responses, the humoral (i.e. B cells) as well as the cellular (i.e. $CD8^+$ and $CD4^+$ T cells)(35).One vaccination administration is typically enough for the induction of long-term, and in some of the cases even life-long, protection.



Figure(5): mechanism action of live attenuated vaccine(36).

On the other hand, the most significant drawbacks of those vaccinations are the safety concerns: particularly, older live vaccines like the oral polio vaccine (OPV) which carries risks of the reversion to the natural virulence through the attenuated organism's back-mutations and a potential of resulting in symptomatic affections that are similar to the wild-virus infections in recipient or in the unprotected contact (such as, vaccination-related paralytic poliomyelitis after the OPV) (37).

Conclusion

It has been observed in this study that preventing important infectious illnesses, like the HIV, HBV and, amongst other illnesses, keeps being challenging for the area of the vaccinology in the present day.

None-the-less, important improvements in molecular biology, immunology, microbiology, recombinant DNA, bio-informatics, genomics, and associated areas presented new information for helping to elucidate significant pathogenic mechanisms that are involved in those diseases and in the pathogen interactions with hosts.

It is clear now that integrated method is highly important for fostering the continuous progression in the area of the immunology, potentially constituting the limiting factor for developing novel vaccinations.

There is a high importance as well realizing that vaccine development challenges aren't limited to discovering effective and safe antigens, delivery systems and adjuvant.

The balancing between the costs, advantages and risks must definitely is assessed prior to the translation of candidate of vaccination to clinic.

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استراتيجيات اللقاحات الفايروسية

نور الهدى فخري العبيدي

وحدة الابحاث البايولوجية للمناطق الحارة / كلية العلوم / جامعة بغداد

* Correspondence: nooralaubadie@gmail.com

الملخص

المقدمة: في الاونه الاخيرة ظهرت العديد من الفايروسات او عادت للظهور بدون سبب واضح واصبحت تشكل تهديدات على الصحة العالمية ، مماثار الانذارات بشان انتقالها الى وباء مستمر.وقد وجد ان من اهم هذة التهديدات هي الانتقال هذة الفايروسات بين العوائل التي تفتقر الى التثقيف المناعي والمعرضة الى الاصابة .لهذا ظهرت حاجة ملحة لتطوير سريع للتطعيم وتحريض مناعة وقائية ، وبالتالي يمكن أن يكون أحد أقوى الأدوات للوقاية من هذا القلق من خلال منح الحماية إلى السكان المعرضين للخطر.

تم اعتبار التطعيمات أحد المكونات الأساسية للوقاية من المرض تجاه العدوى الفيروسية الناشئة لكون الحلول الطبية في كثير من الأحيان غير موجودة أو محدودة. إن ظهور أحدث التقنيات في الطرق الجزيئية له تأثير عميق على فهم بيولوجيا الفيروسات ، وكذلك الاستجابات المناعية وطرق التطعيم القائمة وبذلك أصبحت طرق ناقلات الفيروس الموهنة والمتضاعفة وغير المتكاثرة منصات مفيدة للتحصين. بالاقتران مع الفهم المستمر في علم الأحياء للأمراض الفيروسية التي ظهرت حديثًا ، تم تطوير العديد من الاستراتيجيات الحديثة المختلفة للتلقيح ، للحماية من عودة ظهور الفيروسات مرة اخرى.

الهدف: تسليط الضوء على مختلف الاستراتيجات المستخدمة في تحضير اللقاحات الفايروسية ولقد وجد ان التحدي الاكبر في تصيع هذة اللقاحات هي الموازنة مابين الكلفه وكفاءة وتخصص هذة اللقاحات في الحد من الانتشار او عودة ظهور الفايروسات القديمة والتي ممكن ان تتحول الى وباء بدون معرفة الاسباب لذلك.

الكلمات المفتاحية : فايروسات ، تطعيمات ، الطرق الجزيئية ، استراتيجيات.