WILL THERE BE SUFFICIENT VACCINES TO CONTROL EMERGING AND GLOBALIZING INFECTIOUS DISEASES? – A REVIEW

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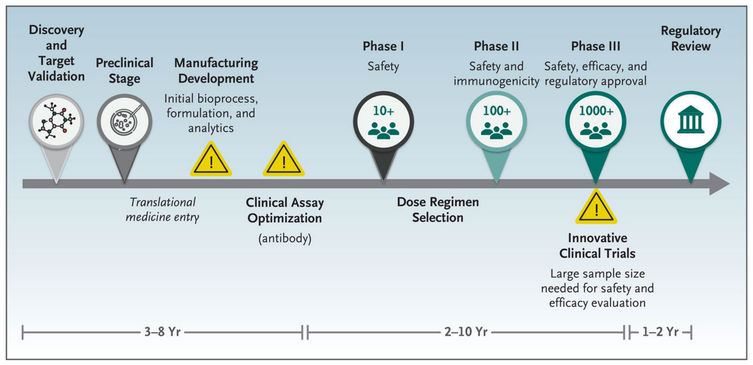
Introduction

Our review assesses the status of vaccine technology in the context of the globalization and emergence of infectious diseases. We looked at current vaccine technology, the development of vaccines for 23 infectious diseases (6 presented in poster), and methods of assessing effectiveness and duration of vaccine immunity. This review is intended to give an overview of the strengths and weaknesses of current vaccine development against future changes in infectious disease threats.

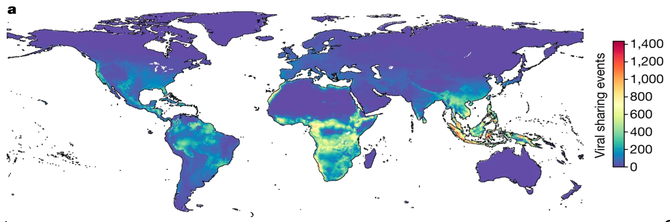


Contrary to the pervious timeline of vaccine development that could take up to 20 years, COVID-19 vaccine development illustrated advancement in the speed of the process to less than 18 months.

Globalizing & Emerging Disease

An estimated 10,000 viral species have the ability to infect humans and most of those are circulating unnoticed among the planet's mammalian wildlife. In the next 70 years, intermingling of previously separate species will result in the transfer of pathogens into human populations (Ref. 69). This is based on scientific modeling of phylogenetic similarities, species' territorial ranges, species populations, expected territorial expansions, and on the individual species' unique dispersal capabilities.

These evolutionary changes will occur at areas of densely populated wildlife, at the edges of the climate change zones such as Indonesia, India, and Africa's Sahel region (Sudan, Niger, Nigeria, Mauritania, Chad, Mali, Burkina Faso, and Eritrea) (Ref. 68).



"Climate change will drive novel viral sharing among mammal species" (Ref. 69)

The 23 diseases for review were chosen from CDC, WHO, and IDSA databases, looking at their importance for vaccine development relative to their global morbidity, recent emergence, globalization trends, and evolving resistance to antimicrobials.

Advancing Vaccine Technology

The mRNA technology came to fruition with the science of packaging in liposomes to allow the mRNA to reach intracellular ribosomes without degradation. Scientists can control how much protein is produced and for how long, which cells express the protein, and whether the mRNA creates a precise activation or suppression of the immune system. The inclusion of modified nucleosides lowered inflammatory response and could increase the amount of protein that mRNA could make by 10- to 1,000-fold. (Ref 66)

The modern tools for sequencing genomes add tremendous speed to identifying an antigen target. This is particularly true for viral vaccines where the genome is very limited, between 2 kb up to 1 Mb.

The establishment of immunological surrogate endpoints is aimed at finding relevant indicators of vaccine protection through animal or human challenge experiments to obtain the relationship between immune protection indicators and clinical protection. Neutralizing antibody levels are generally used as the primary surrogate endpoint of the immunological protection of viral vaccines.

Other than mRNA, recombinant DNA technology is the mainstay of vaccine development. Pathogen antigens are inserted into the DNA of other bacterial or mammalian cells, which are then used as factories for production of large quantities of the antigen. The vaccine is simply a delivery solution with the antigen suspended in the solution

Although T cell immunity is a critical component of vaccine induced protection, its measurement is currently limited. Though many options exist, such as CTL, most are cost prohibited and not standardized at this time.

Spreading Disease: Monkeypox

Two vaccines exist for monkeypox: JYNNEOS (also known as Imvamune or Imvanex) and ACAM2000. JYNNEOS is the preferred vaccine since it is a nonreplicating virus vaccine. ACAM2000 is a live virus vaccine which has risks for the immunosuppressed, people with atopic dermatitis or other extensive dermatoses, and frail populations such as those with heart failure and cardiomyopathies. These populations would be at high risk of complications if infected with monkeypox.

These vaccines have utility as post-exposure prophylaxis. They are most effective in preventing onset of disease if given within 4 days from date of exposure. If given between 4 and 14 days of exposure, vaccination may reduce symptoms, but not prevent disease (Ref. 1).

As of Sept 16 2022, there are 61,282 cases worldwide, 23,499 cases in the United States, and 2,017 cases in Texas.

The CDC's vaccination is only targeting high risk populations, such as men who have sex with men.

Spreading Disease: Ebola

There has been extensive development of multiple vaccines since an outbreak in the US in 2014-2016. The vesicular stomatitis virus (VSV) - Zaire Ebola virus vaccine has been a major resource with 130,000 people vaccinated in Africa in its 2019 outbreak.

Ervebo (rVSV-ZEBOV) is the current predominant Ebola vaccine. It is a live attenuated replication competent vesicular stomatitis virus (VSV) vaccine genetically engineered to express an Ebola virus glycoprotein. It is given as a single dose and is estimated to have 97.5% effectiveness in preventing disease. In the US, it may be used to protect health care workers in Ebola virus response teams. In Africa, it is used to vaccinate contacts around index cases, but has also been used in the population during large outbreaks. Antibodies to Ebola persist for at least 2 years. Other Ebola vaccines include Zabdeno (AD26.ZEBOV), which is a two dose recombinant adenovirus vaccine and Mvebea (MVA-BN-Filo), which is a modified vaccinia vaccine.

Emerging Disease: Zika Virus

13 vaccine clinical trials are now underway for Zika virus. These include trials for DNA vaccines, mRNA vaccines, and purified inactivated virus (PIV) vaccines.

A phase I clinical trial assessed the safety and immunogenicity of a synthetic DNA vaccine targeting ZIKV pre-membrane and envelope genes (prM-ENV). 40 participants were injected with either a 1mg dose or 2mg dose of the vaccine at baseline, 4 weeks, and 12 weeks. Electroporation at the inoculation site followed injection to increase immunogenicity of the vaccine. At week 14, ZIKV-specific binding antibodies developed in all participants. Moreover, immune serum drawn from vaccinated participants prevented ZIKV infection in cellular models and prevented death in a mouse model, indicating that vaccine-induced antibodies can prevent infection and disease in vivo.

Phase I/II trials are underway for an mRNA vaccine that successfully produced high levels neutralizing antibodies against ZIKV infection in monkey and mouse models. This vaccine also prevented fetal demise in mouse pregnancy models.

Three ZIKV purified inactivated virus vaccine phase I trials are underway after PIV vaccines reduced viremia in mice that were infected with ZIKV.

Emerging Disease: West Nile Virus

Human West Nile virus vaccines may not be available for several years, as no phase three trials are currently underway. Still, there is preliminary data on several potential vaccines (Ref. 8).

ChimeriVax-WN02 is a live, attenuated recombinant yellow fever 17D virus-based vaccine that was well tolerated and showed development of neutralizing antibodies after a single dose. A DNA vaccine encoding pre-membrane and envelope glycoproteins is another candidate. It was well tolerated and all subjects in a small trial developed neutralizing antibodies. Another live attenuated chimeric virus vaccine has shown to be safe, well tolerated, and immunogenic.

Spreading Disease: Dengue

In the US, dengue is seen most often in Puerto Rico, Samoa, and the Virgin Islands. It is also occasionally seen in Texas and Florida and with climate change may continue to increase in prevalence in these states (Ref. 6).

There are four dengue viruses. An effective vaccine must target all four dengue viruses because there is concern that a vaccine specific for one virus will create antibodies that may enhance the severity of illness from another dengue virus.

A current candidate is CYD-TDV (Dengvaxia). It has been licensed in Latin America and Southeast Asia as of 2015, in Europe as of 2018, and in the US by the FDA as of 2019. Still, it can only be used in children who have had previous dengue infection documented by serology, which is a narrow indication.

Emerging Disease: Lyme

There is no current vaccine being used for protection against Lyme disease. A previously available vaccine, LYMERix®, was discontinued in 2002 because of insufficient demand. Those who received this vaccine, now over 20 years ago, are no longer protected.

There have been efforts again to develop active and passive immunization for Lyme disease. Pfizer has a vaccine, VLA15, in phase 2 human trials. It is a multivalent, protein subunit vaccine to an outer surface protein of Borrelia, which is designed to prevent infection with strains that cause disease in North America and Europe. The University of Massachusetts Medical School's MassBiologics has produced a monoclonal human antibody that can be used for pre-exposure prophylaxis and passive immunization aimed at seasonal protection (Ref. 42).

Conclusion

There has been a myriad of emerging and spreading virulent diseases. We looked at the following diseases as representative of potential infectious disease challenges: HIV, Ebola, COVID-19, Monkeypox, Influenza, West Nile Virus, Chikungunya, Lyme disease, Meningococcus, Pneumococcus, Malaria, Tuberculosis, Chlamydia, Gonorrhea, Zika, Rotavirus, Chagas, H. Pylori, C. Difficile, Dengue, EBV, HSV, RSV/common cold, and Hepatitis C. Several of these diseases lack effective treatment and the bulwark of medical efforts will be in disease prevention. Vaccine technology is advancing rapidly with a diverse approach to identifying vaccine targets and developing immunogenic materials to induce a protective host response.

We evaluated a total of 23 diseases in our review, with a sample of 6 presented on this poster. Of the 23 evaluated, 10 have currently available vaccines, 11 have vaccines in clinical trials, and 2 (Chagas and Hep C) have no viable vaccine candidates at this time. As such, alongside startling successes, many diseases still present serious challenges to vaccine development.

Future Directions

The fragility of the public health system in the United States was painfully exposed during the recent COVID-19 pandemic. Improved response to infectious threats will require investment in vaccine and antimicrobial technology, as well as commitment to developing a more robust and prepared public health system. Considerable work is needed to better assess disease immunity and duration of that immunity. Vaccine immunity surveillance requires sustained vigilance to assess adverse effects and waning immunity for decades after deployment of new vaccination programs.

Manuscript and References

For the complete manuscript & references, contact Dr. Kravitz:
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Relevance to Family Practice

Family physicians are at the front line for disease prevention and are critical players in educating the public on new illness prevention measures and technology. They are a vital link between basic science and dissemination knowledge that advances medical care. This is particularly important in infectious disease where the disease landscape is evolving at an accelerating rate.

Acknowledgements & Conflict of Interest

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