PANDEMIC RNA VIRUSES AND VACCINES

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Virus: "A piece of bad news wrapped up in a protein"

Sir Peter Medawar

Introduction

That viruses are different from bacteria has been known for about one hundred years. That some viruses contain DNA and some RNA as their genetic material has become clear only in the second half of the 20th century. With this biological knowledge, we became aware that some of the worst infectious diseases in humans are caused by viruses. Smallpox, caused by a DNA virus, is high on the list of harmful diseases to humans; it was responsible for untold numbers of deaths for centuries. But also among RNA viruses there are major disease-causing pathogens, especially those associated with pandemic, global epidemics.

Fortunately, vaccines against viruses have been successfully developed. In fact, several RNA viruses have been eliminated by vaccination – or close to. New platforms for the development of vaccines have dramatically improved the health in many countries globally. But much remains to be done to provide vaccines and vaccinations to those who need it.

Pandemic influenza and pandemic corona viruses

In the last 100 years members of the influenza virus family have caused four pandemics. The 1918/1919 pandemic influenza virus is estimated to have been responsible for the deaths of up to 100 million people (Fig. 1). While the more recent influenza viruses (pandemic and epidemic) have been less virulent than the one of 100 years ago, we are concerned about the emergence of new pandemic influenza virus strains, which arise from "genetic mixing" of human and animal influenza strains [1]. My laboratory was involved in the reconstruction of the pandemic 1918 influenza virus using a technology, reverse genetics, developed at Mount Sinai [2, 3, 4]. We were able to identify what made the 1918 virus so virulent and we showed that presently available antivirals and influenza vaccines are highly effective against that early pandemic strain.

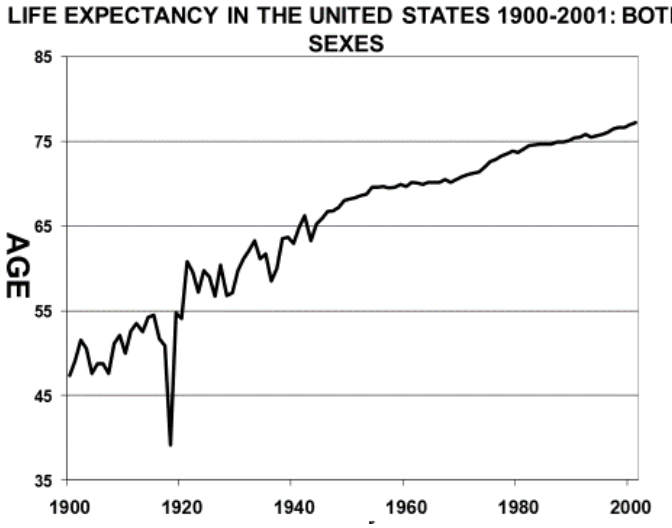

Fig. 1. The 1918 influenza pandemic caused a reduction in average life expectancy of 11 years.

Vaccines against influenza were developed as far back as the 1940's, barely ten years after the discovery of the virus. The early vaccines consisted of whole virus treated with chemicals to make them non-infectious. This inactivated material was then injected to induce a protective immune response in the patient. Though not perfect, these vaccines have lowered the number of deaths and hospitalizations, and they have shown to reduce the severity of disease in patients who were immunized, but became ill. More recently, live attenuated influenza virus vaccines and synthetic protein vaccines have been introduced to better protect children and the elderly, respectively.

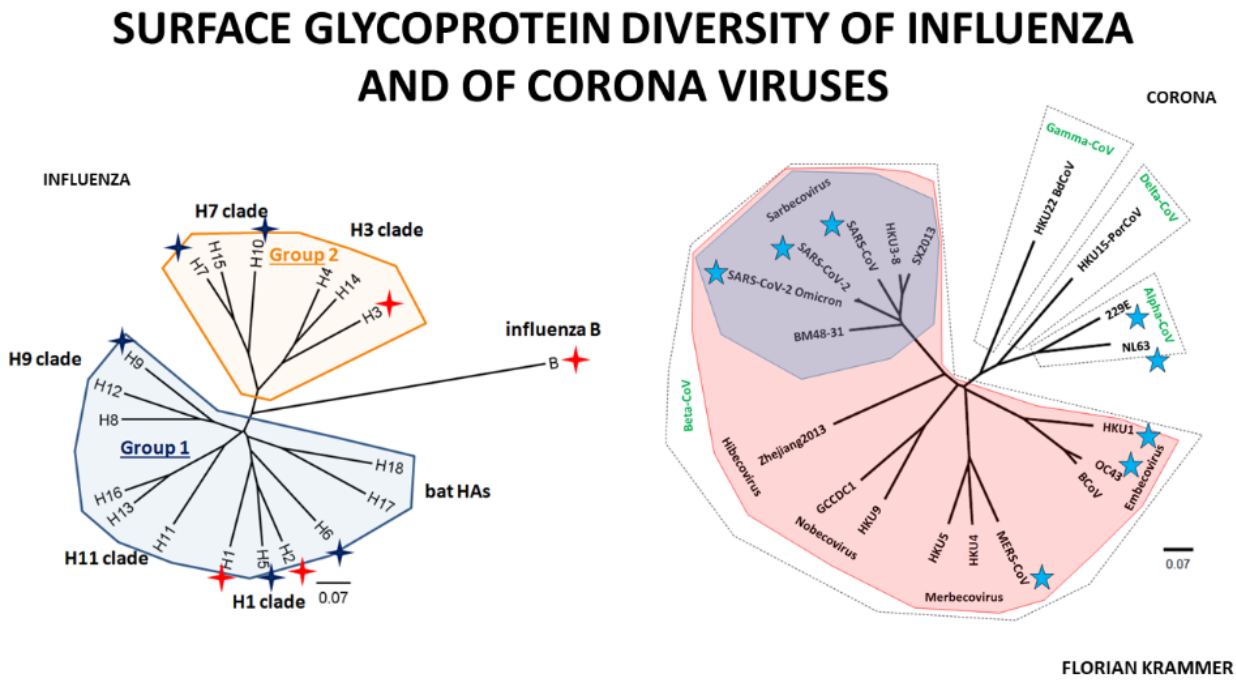

Fig. 2. Left. Dendrogram of the 18 hemagglutinin subtypes of influenza viruses. Red asterisks identify the human H1, H2 H3, and B hemagglutinins. Blue asterisks highlight avian hemagglutinins of viruses having been observed to infect humans. Bar (0.07) identifies 7% amino acid differences. Right. Dendrogram of the S spike proteins of the alpha, beta, gamma and delta corona viruses. Blue asterisks identify S spike proteins of coronaviruses isolated from humans. Bar (0.07) identifies 7% amino acid differences.

Unfortunately, influenza viruses come in different flavors defined by the major surface glycoproteins of the virus, the hemagglutinins. We now know of 18 such subtypes of viruses infecting different species, but we have only seen three of these flavors in humans: H1, H2, and H3 (Fig. 2). Each time a virus with a new subtype emerges in humans we experience a pandemic. In addition to pandemic changes the virus also undergoes annual variations which forces the annual reformulation of the vaccines and annual influenza virus (re)-vaccinations. Many efforts are underway to develop a universal influenza virus vaccine which does not have to be administered annually and would last for 1-20 years or even longer. The same technology, reverse genetics, which allowed us to resurrect the 1918 virus is now used to develop better influenza virus vaccines for humans as well as for animals. We take advantage of having identified a conserved region in the stalk of the viral hemagglutinin. A vaccine that directs the human immune response towards this conserved domain in the hemagglutinin is presently in phase 1/2 trials (Fig. 3). In terms of improving veterinary vaccines against avian respiratory pathogens we again use reverse genetics [5]. Several of these veterinary vaccines have been commercialized.

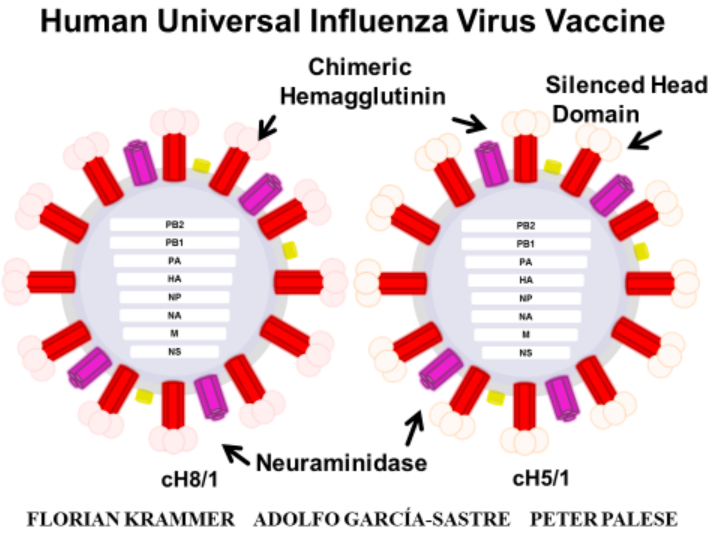

Fig. 3. Vaccination with influenza viruses expressing chimeric hemagglutinins to boost preexisting antibody responses against the conserved hemagglutinin stalk (red) domain. The head domains (light orange) of the chimeric hemagglutinins (cH8/1) and (cH5/1) are silenced. By sequential vaccination with vaccine strains expressing different heads, but the same hemagglutinin stalk domain (red), the immune system preferentially targets the epitopes that remain constant (red).The neuraminidase is also conserved (purple) and induces protective immune responses [6,7].

Fig. 4. Each dot represents one death in the US caused by SARS-CoV-2 (January 2020 – May 13, 2022).

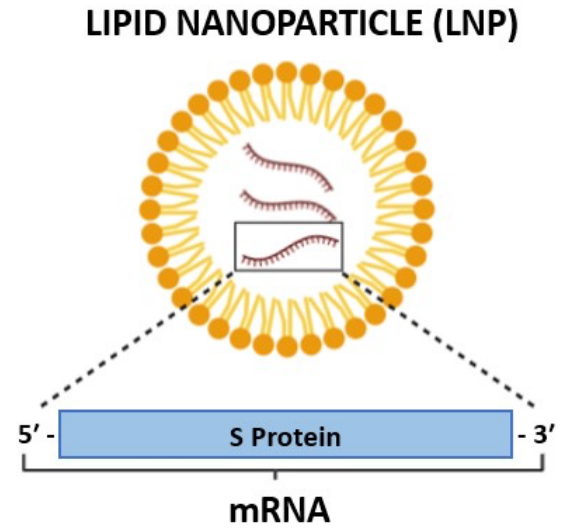

Fig. 5. LNP encapsulated mRNA expressing the S Protein of SARS-CoV-2.

Highly surprising was the emergence of SARS-CoV-2 at the end of 2019. This RNA-containing virus is also a respiratory pathogen and it has been declared by the WHO a pandemic virus on March 11, 2020. Like the influenza virus in 1918/1919, SARS-CoV-2 has also contributed to a loss of average life expectancy. In the last two years, 2020 and 2021, the average life expectancy in the US dropped by 1.9 and 0.9 years, respectively. The impact on lives and economies has seriously affected people in the US (Fig. 5) and around the world. Like influenza virus, SARS-CoV-2 comes in different flavors with respect to its spike surface proteins. The genetic (antigenic) diversity of SARS-CoV-2 is even broader than that of influenza viruses (Fig. 2). Major efforts have been directed towards the development of protective vaccines and they were effective beyond all expectations. Foremost are the mRNA platforms which use lipid naoparticles (LNP) to engulf mRNA molecules (Fig. 4) [8].

Extraordinary development work was done with "warp" speed and the resulting vaccines have saved millions of lives. The LNP platform is a real game changer which cannot be under-appreciated. The mRNA vaccines are wonderfully effective and are extraordinarily safe. In addition to the LNP-mRNA platform COVID-19 vaccines have been produced based on viral vectors or by employing conventional methodologies such as inactivated whole virus preparations. Extensive trials have shown that many of these vaccines are effective and protective against SARS-CoV-2.

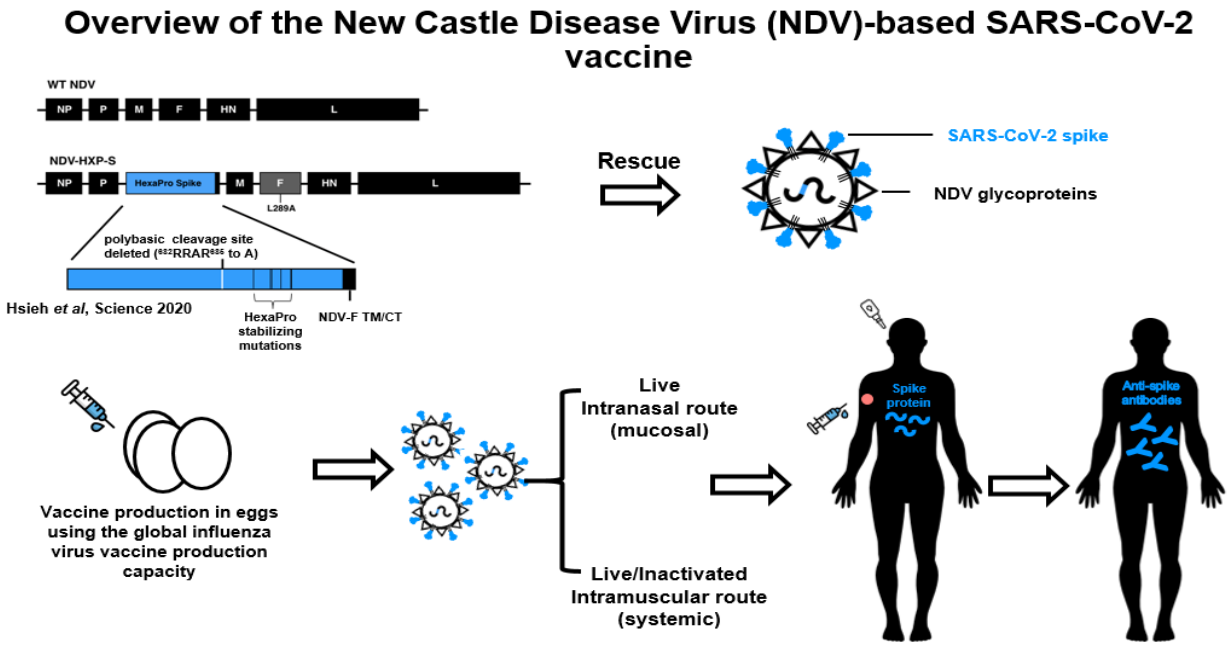

Fig. 6. NDV-based SARS-CoV-2 vaccine which is cheaply produced in embryonated eggs (like the influenza virus vaccine). Also, when given intranasally it induces mucosal immunity preventing reinfection with the virus and reduces transmission from person to person [9-11].

While the success of COVID-19 vaccines has been exceptional, breakthrough infections after (multiple) vaccinations continue to be a problem; also present vaccines do not efficiently prevent transmission from one patient to the other. Our efforts at Mount Sinai are directed to develop a viral vector-based vaccine, which can induce mucosal immune responses in the respiratory tract (Fig. 6). Such a vaccine should further reduce infections in vaccinated patients and it should minimize transmission of the virus [9-11]. As the S spike protein of a corona viruses defines its antigenicity, it is the extraordinary variation of the viral surface protein, which makes it likely that novel pandemic SARS-CoV will emerge in the future. Since corona viruses are also zoonotic (can jump from animals to humans) like influenza viruses, the emergence of four influenza pandemics over the last 100 years may foretell additional catastrophes caused by corona viruses.

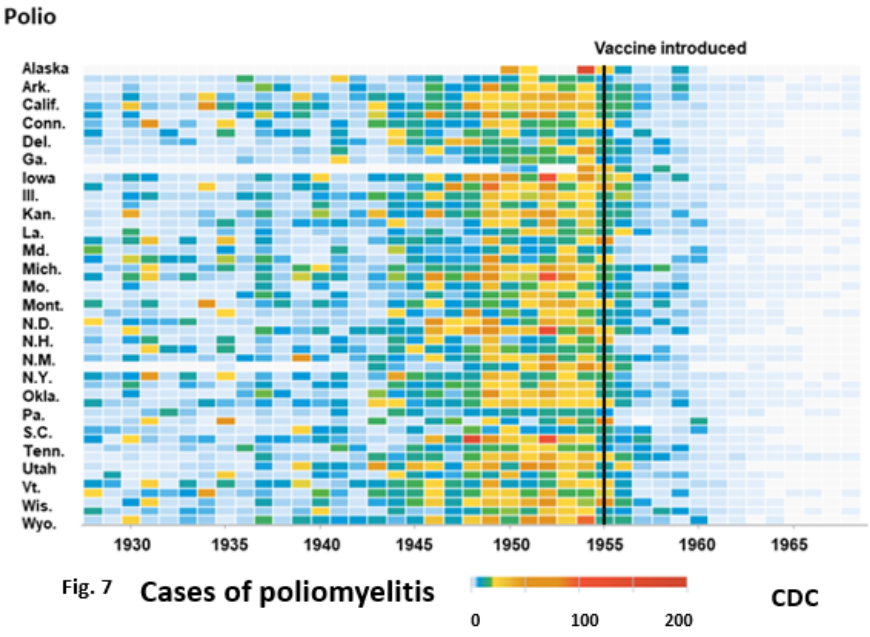

Fig. 7

Poliomyelitis, measles, mumps, rubella, hepatitis A and rota virus vaccines

Classical vaccine developing and manufacturing have been extremely successful following in the footsteps of the Salk (killed poliomyelitis vaccine) and Sabin (live attenuated poliomyelitis vaccine) platforms. In fact six diseases (poliomyelitis, measles, mumps, rubella, hepatitis A and rota virus gastroenteritis) have seen a dramatic decrease in high income countries, because of the development of these vaccines. In some instances (poliomyelitis, measles, mumps and rubella) the diseases have mostly disappeared in the US. Fig. 7 shows the success of the eradication of poliomyelitis as a result of vaccinations in all the States.

The future: Pandemic RNA viruses and vaccines

Influenza and corona viruses have been the two virus families which have caused pandemics in the last 100 years. Both families are characterized by coding for viruses which have on their surface highly variable glycoproteins. Such variable strains are circulating in many different animal species and occasionally they jump into humans. These events are unpredictable but are likely to occur in the future as more humans on the globe are interacting with more animals. To prepare for such eventualities (or rather certainties) we need increased surveillance in humans as well as in animals for novel pathogens. If history is any guide, RNA viruses which are transmitted via the respiratory tract are high on the list of these threats. In addition we need novel methods of pathogen detection, of diagnostic tests and overall substantial resources to do molecular research on host-pathogen interactions. Only the continued advances in molecular biology, immunology, broadly basic research and big data analysis (including artificial intelligence) will prepare us against future pandemics. The development of LNP-RNA was a major accomplishment and has made all the difference with this most recent pandemic virus, but it is not a panacea. It is unlikely that this platform (with our present knowledge) will help to develop an effective HIV/AIDS or hepatitis C virus vaccine. We need certainly more highly visionary research in order to develop new and improved vaccines against present strains and future outbreaks of pathogens which have acquired resistance to present medical interventions. In order to overcome these new challenges brought about by global warming, increases in the world population, bio-safety risks and disturbances in the natural habitat of many animals. It will also be important to have public health systems which can respond to these special demands.

Acknowledgments

It is thankfully acknowledged that work in the author's laboratory was mostly supported by the National Institutes of Health and institutional funds.

References

1. Fields Virology, P. M. Howley, D. R. Knipe, eds. Vol 1, F. Krammer, P. Palese, Chapter **14**, 596 (2021).
2. T. M. Tumpey, C. F. Basler, P. V. Aguilar, H. Zeng, A. Solorzano *et al*., *Science* **310**, 77 (2005).
3. G. Neumann, *Cold Spring Harb Perspect Med* **11**, 4 (2021).
4. P. Palese, H. Zheng, O. G. Engelhardt, S. Pleschka, A. Garcia-Sastre, *PNAS* **93**, 11354 (1996).
5. M. S. Park, J. Steel, A. Garcia-Sastre, D. Swayne, P. Palese, *PNAS* **103**, 8203 (2006).
6. N. Folschweiller, C. Vanden Abeel, P. Van Damme *et al*., *Lancet Infect*. *Dis*. **22**, 1062 (2020).
7. G. R. Nachbagauer, P. Palese, *Annu*. *Rev*. *Med*. **71**, 315 (2020).
8. N. Chaudhary, D. Weissman, K. A. Whitehead, *Nat*. *Rev*. *Drug Discov*. **20**, 817 (2021).
9. A. Duc Dang, T. Dinh Vu, H. Hai Vu *et al*., *Vaccine* **40**, 3621 (2022).
10. P. Pitisuttithum, V. Luviza, S. Lawpoolsri *et al*., *EClinicalMedicine* **45**, 101323 (2022).
11. S. Ponce-De-Leon, M. Torres, L. E. Soto-Ramirez *et al*., *medRxIv* PMID: 35169806.