Covid-19 vaccines

Classical Vaccines

- Vaccines for human use can roughly be divided into:
  - **virus-based vaccines** can consist of *inactivated virus* that is no longer infectious, or *live-attenuated virus*. Since whole-inactivated viruses do not replicate, adjuvants are required to stimulate the immune system. Live-attenuated virus vaccines are classically generated by passaging in cell culture until it loses its pathogenic properties and causes only a mild infection upon injection.
  - **protein-based vaccines** can consist of a protein purified from the virus or virus-infected cells, recombinant protein or virus-like particles. Virus-like particles consist of the structural viral proteins necessary to form a virus particle, but lack the viral genome and non-structural proteins. Protein-based vaccines require the addition of an adjuvant to induce a strong immune response.
- In the case of SARS-CoV-2, large quantities of virus would need to be grown under biosafety level 3 (BSL3) conditions for a whole-inactivated vaccine; extensive safety testing is required to ensure live-attenuated viruses are safe and do not easily revert to wild type, and several recombinant proteins need to be produced simultaneously for virus-like particle vaccines.

Classical vs. Next-generation vaccine

- Viral vector vaccines consist of a recombinant virus (that is, the viral vector), often attenuated to reduce its pathogenicity, in which genes encoding viral antigen(s) have been cloned using recombinant DNA techniques and can be:
  - **Replicating** - infect cells in which the vaccine antigen is produced as well as more infectious viral vectors able to infect new cells that will then also produce the vaccine antigen
  - **Non-replicating** - initially enter cells and produce the vaccine antigen, but no new virus particles are formed. Because viral vector vaccines result in endogenous antigen production, both humoral and cellular immune responses are stimulated.
- One advantage of these viral vector-based vaccines is that a single dose can be sufficient for protection, as in the case of the vesicular-stomatitis virus-based Ervebo vaccine against Ebola virus (1)
- The **next-generation vaccines** can be developed based on a protein sequence information.
- Any viral protein able to induce immune response important to neutralize viral infection (that is, the vaccine antigen), when sequence known, can be produced and be tested to start vaccine development.
  - This makes vaccine production highly adaptable and speeds up its development, as is in the case of COVID-19 vaccine
- For COVID-19, several viral vector, nucleic acid-based vaccines and antigen-presenting cells are in (pre) clinical development.

1. *Henao-Restrepo, A. M. et al. Lancet 389, 505–518 (2017).*

Next-generation vaccine

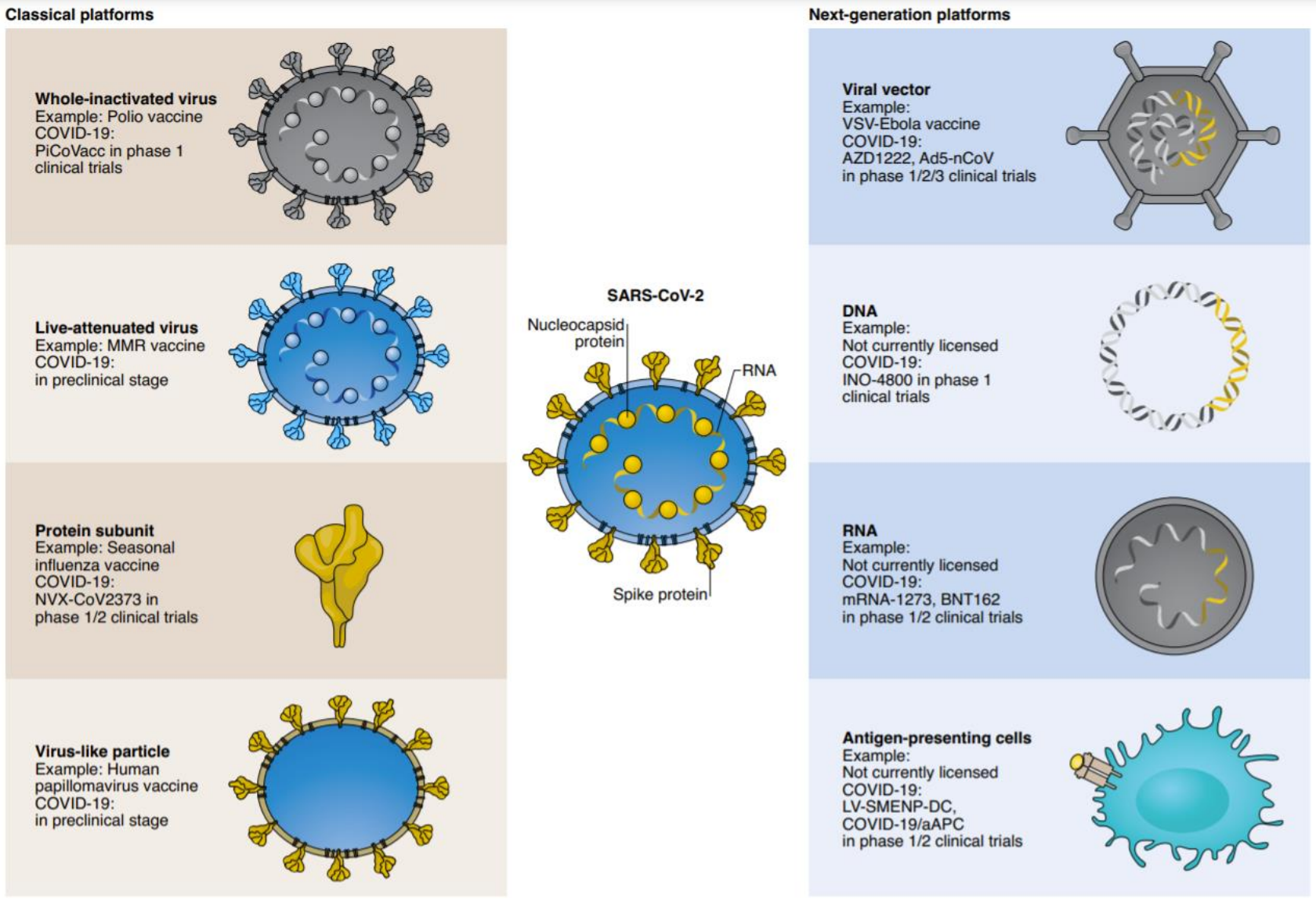
- **Nucleic acid-based vaccines** consist of DNA or mRNA and can be adapted quickly when new viruses emerge
  - **DNA vaccines** consist of a synthetic DNA construct encoding the vaccine antigen. For efficient uptake of the construct into cells, injection needs to be followed by electroporation or virus protein packed into other virus. After uptake into cells, the vaccine antigen is expressed from the DNA construct.
  - **mRNA-based vaccines** work on the same principle as DNA vaccines, except that the first steps (nuclear translocation of the DNA construct and transcription into mRNA) are bypassed. Self-replicating RNA vaccines are likely to induce protective immunity using a lower dose, because more vaccine antigen is expressed per cell (3). Since mRNA is not very stable, these constructs include modified nucleosides to prevent degradation. A carrier molecule is necessary to enable entry of the mRNA into cells; lipid nanoparticles are most commonly used.
- Nucleic acid-based vaccines induce a humoral and cellular immune response, but multiple doses are required

Pros	Cons
Easily adaptable	Not as stable as classical vaccines
Cheaper to produce	Low temperature needed for storage and transport
Production without egg usage	Multiple doses required
Vaccination can not induce infection	Possible incorporation into genome (DNA vaccines)
Rapidly produce large quantities of vaccine doses against a new pathogen	Lower efficiency

3. Vogel, A. B. et al. *Mol. Ther.* **26**, 446–455 (2018).

Next-generation vaccine

- Antigen-presenting cells are an essential component in the immune system's response to a vaccine.
- Loading antigen-presenting cells with peptides that would otherwise be produced by vaccination bypasses the first steps after vaccination.
- Dendritic cells are harvested from the individual, expanded and manipulated to present the desired antigen, and transplanted back into the same individual.
  - Costly and
  - Time-consuming
- However, artificial antigen-presenting cells are developed, where immortalized cells are transduced with lentiviruses to effectively mimic antigen-presenting cells, as is the case for COVID-19/aAPC.
- There is active clinical trial developing universal vaccine
- Innovative Covid-19 minigenes engineered based on multiple viral genes, using an efficient lentiviral vector system (NHP/TYF) to express viral proteins and immunomodulatory genes to modify artificial antigen presenting cells (aAPC) and to activate T cells. In this clinical study, the safety and immune reactivity of this aAPC vaccine will be investigated. ClinicalTrials.gov Identifier: NCT04299724 by Shenzhen Geno-Immune Medical Institute



van Riel, Debby ; de Wit, Emmie. Nature materials, 2020-08, Vol.19 (8), p.810-812

There is a worldwide effort to develop an effective vaccine against SARS-CoV-2 and, as of late August 2020, there are 30 vaccines in clinical trials with over 200 in various stages of development

Most advanced vaccine options for Covid-19 for now are developing:

- RNA vaccines:
  - Pfizer/BioNTech
  - Moderna vaccine
- Viral vector vaccine:
  - Oxford/AstraZeneca vaccine

RNA vaccines Pfizer/BioNTech and Moderna vaccine

- RNA vaccines provide flexibility in the design and expression of vaccine antigens that can mimic the structure and expression of the antigen during natural infection.
- For this vaccine RNA
  - is required for protein synthesis, and does not integrate into the genome,
  - RNA is transiently expressed,
  - RNA is metabolized and eliminated by the natural mechanisms of the body
  - is considered safe (4–7).
- RNA-based prophylactic infectious-disease vaccines and RNA therapeutic agents have been shown to be safe and well-tolerated in clinical trials.
- Vaccination with RNA elicits a robust innate immune response
- Vaccine RNA can be modified by incorporating 1-methylpseudouridine, which dampens innate immune sensing and increases mRNA translation in vivo.
- The BNT162b1 vaccine (Pfizer/BioNTech) candidate that is currently investigated clinically incorporates such nucleoside-modified mRNA and encodes the SARS-CoV-2 receptor–binding domain, a key target of virus-neutralizing antibodies or BNT162b2, which encodes a membrane-anchored SARS-CoV-2 full-length spike.
  - Pain at the injection site was a common side effect and after second dose commonly occurring systemic events included fatigue, headache, chills, muscle and joint aches. Mulligan MJ et al. medRxiv. (2020)
- Phase 3, dose-escalation, open-label trial of a messenger RNA vaccine, mRNA-1273, which encodes the stabilized prefusion SARS-CoV-2 spike protein (S-2P) of Modena vaccine
  - Side effects were predominantly mild or moderate in severity and most frequently included fatigue, chills, headache, myalgia, and pain at the injection site. Jackson LA et al. N Engl J Med. (2020)

4. Alberer, M. et al. Lancet 390, 1511–1520 (2017).
5. Feldman, R. A. et al. Vaccine 37, 3326–3334 (2019).
6. Kranz, L. M. et al. Nature 534, 396–401 (2016).
7. Şahin, U. et al. Nature 547, 222–226 (2017).

DNA vaccine – Oxford vaccine

- Oxford vaccine is made from a cold-causing adenovirus that was isolated from the stool of chimpanzees and modified so that it no longer replicates in cells.
- When injected, the vaccine instructs human cells to produce the SARS-CoV-2 spike protein — the immune system's main target in coronaviruses.
- The vaccine developed by the University of Oxford, UK, and pharmaceutical company AstraZeneca was found to be, on average, 70% effective in a preliminary analysis of phase III trial data
- The vaccine is stable at refrigerator temperatures, in contrast to the Pfizer and BioNTech vaccine, which must be stored at −70°C until hours before vaccination.
- A high neutralizing antibody (NAb) response was seen in 91% of participants across different assays after the first dose. All participants of the booster dose group had a high NAb response thus supporting the need for a two-dose regimen to increase the NAb response. Folegatti PM, et al. Lancet. (2020) 396:467–78
- T cell response, observed in all participants, peaked at day 14 and remained elevated through day 56. However, participants in the booster group did not observe an increase in T cell response following the second dose.

Conclusions

- The vaccine should be **safe** and **effective**, and should not induce enhanced disease upon subsequent infection, whether through vaccine-associated enhanced respiratory disease or antibody-dependent enhancement, as has been observed with certain SARS-CoV vaccines in animal models in the past (4)
- In order to prevent severe disease after infection, vaccination should result in either (a) complete abrogation or significant reduction of transmission within the population by the induction of herd immunity or (b) prevention of severe disease in all vaccinated individuals.
- A single dose vaccine that would not require a cold chain would contribute to the timeframe in which large-scale, global vaccination can be achieved.
- Vaccination that would induce long-lived immunity is preferable, but annual vaccination as like flue would be feasible
- Herd immunity for SARS-CoV-2 would require vaccination of ~67% of the population (5), which is an average and would not prevent clusters of susceptible individuals.
- In recent years vaccine hesitance, increased in many countries, and a recent study showed that 26% of the French population would not take a SARS-CoV-2 vaccine (6).

4. *Graham, B. S. Science 368, 945–946 (2020).*
5. *Randolph, H. E. & Barreiro, L. B. Immunity 52, 737–741 (2020)*
6. *Coconel Group Lancet Infect. Dis. 20, 769–770 (2020)*

Risk groups

- Two important risk groups for developing severe COVID19, elderly (>65 years old) and obesity (body mass index > 40) have previously been linked to reduced vaccine efficacy using classical vaccination approaches
- Other risk groups are patients on chemotherapy, immunocompromised patients, patients undergoing irradiation due to immunosuppression of immune system where they might not be able to fight unwelcome viruses
  - many patients with cancer carry an excess risk of infection from both underlying malignancy and cancer-directed therapy.
- Given advanced age, comorbidities, and immune dysfunction, chronic lymphocytic leukemia (CLL) patients may be at particularly high risk of infection and poor outcomes related to coronavirus disease 2019 (COVID-19), and CLL patients have high mortality rates when admitted for COVID-19. Mato AR. et al. *Blood* (2020) 136 (10): 1134–1143
- Whether new vaccine platforms have an increased immunogenicity in these risk groups compared to classical vaccination approaches remains to be determined

Open questions

- There is the chance that those who are vaccinated could remain susceptible to asymptomatic infection — and could transmit that infection to others who remain vulnerable.

- “In the worst case scenario, you have people walking around feeling fine, but shedding virus everywhere,”

says virologist Stephen Griffin of the University of Leeds, UK.