Key messages:

- *Pre-clinical results*
  - Sinovac (inactivated), *in vivo*: vaccine induces neutralizing antibodies.
  - Inovio (DNA vaccine):
    - *In vitro:* induced expression of the spike protein,
    - *In vivo:* antibody and I cell responses generated.
  - Collaboration of various institutes (DNA vaccines), *in vivo*:
    - "Humoral and cellular responses, including neutralizing antibody titres".
    - After challenge there was a significant viral load reduction.
- *Clinical trial results*
  - CanSinoBio (Adenovirus vectored, S protein based):
    - Vaccine elicited both antibody and T cell responses.
    - Blood from participants fought off SARS-CoV-2.
    - Diminished vaccine efficacy in patients with adenovirus immunity.
    - Side effects: occurred in most patients, mild to moderate, max 48h.
- ***Repurposing existing vaccines:*** proposed are the flu-, hepatitis A-, MMR-, and BCG vaccines. No causal relationships have been found.

Summary:

Research questions & methods

The aim is to provide updates on various aspects SARS-CoV-2 vaccine development specifically in published literature. Methods comprised of an Embase search. Additional information and a full picture of COVID-19 vaccine development can be found at KNVM (only in Dutch) (1), WHO (2), CEPI (3), Milken Institute (4), and LSHTM (5).

An overview table that presents non-peer-reviewed information on the candidate vaccines, as well as information on similar vaccines by the same developer, can be requested from the authors.

Results

Pre-clinical

Sinovac published *in vivo* data on their inactivated vaccine (6), which induced SARS-CoV-2-specific neutralizing antibodies in mice, guinea pigs, and non-human primates, against ten different SARS-CoV-2 strains. Upon challenge, macaques that received three immunisations of either 3 or 6 ug were partially or completely protected, without disease enhancement.

Inovio showed that their S-protein targeting DNA-vaccine (INO-4800) caused:

- *In vitro* expression of the spike protein.
- *In vivo (*mice & guinea pigs) antibody and T cell responses after one immunisation (7).

A **collaboration** mainly within Harvard Medical School tested an S-protein based, DNA vaccine candidates in rhesus macaques (8).

- They elicited "humoral and cellular immune responses, including neutralizing antibody titres comparable to convalescent humans and macaques".
- Challenge of macaques that received the full-length S-protein vaccine resulted in significant reductions of median viral loads.

Clinical trials

CanSinoBio created an adenovirus vector vaccine expressing the SARS-CoV-2 S-protein that they administered to 108 participants in their phase 1 clinical trial (9). The participants received one of three doses (5×10^{10}, 1×10^{11}, and $1{\cdot}5 \times 10^{11}$ viral particles, all groups n=36), which elicited both antibody and T cell responses, respectively peaking at 28 days and 14 days after vaccination. After 28 days, blood drawn from participants showed *in vitro* capability to fight off SARS-CoV-2.
Considering CanSino's use of an adenovirus vector, vaccine effectivity suffered under adenovirus immunity, reflected in decreases in both SARS-CoV-2 antibody production and T cell activity. However, while 20, 19, and 16 participants of the respectively low, mid, and high dose groups produced Ad5 neutralising antibodies before the vaccine was administered,

most of them still showed positive responses at both the 14-day mark (75%, 95%, and 94% respectively) and 28-day mark (60%, 84%, and 100% respectively).
Side effects were mostly short lived and mild to moderate, but did occur in 75% to 83% of participants, depending on the dose. While the high dose caused more adverse reactions, some of which severe (grade 3), it also proved to be the most immunogenic.

Repurposing existing vaccines

N.B.: no causal relationships currently support repurposing of vaccines as SARS-CoV-2 immunisation strategies.

- **Flu vaccine:** proposed because children are mostly unaffected by SARS-CoV-2 and are also the group that suffers most from the flu (10).
- **Hepatitis A (HAV) vaccine:** based on analysis of dialysis patients (11). Claims are supported as follows:
  - In countries with mandatory HAV vaccination, children <1yr (unvaccinated) are more susceptible to SARS-CoV-2 than older children (vaccinated; vaccination occurs between 12-18 months) (11).
  - 50.5% of tested infected patients on the Princess Diamond cruise ship, a trip for which HAV vaccination was recommended, were asymptomatic (11,12).
- **MMR vaccine:**
  - Increased infection and fatality in patients who have not received the MMR vaccine.
  - The MMR vaccine protects against respiratory illnesses (13).

  The proposed effect is attributed to (limited) sequence and amino acid homology between the MMR viruses and SARS-CoV-2 (14).
- **BCG vaccine:** ecological studies found lower COVID-19 fatality rates in countries that routinely administer BCG to new-borns (a.o. 14,15). Other studies disconfirm this finding (17,18).

Conclusions

More research is necessary. Because no human challenge studies have been planned, it is impossible to judge the efficacy of the vaccines.

5.1.2e (5.1.2e @rivm.nl), 5.1.2e (5.1.2e @rivm.nl), 5.1.2e
5.1.2e (5.1.2e @rivm.nl)

References

1. COVID-19 [Internet]. Available from: https://www.knvm.org/vaccinologie/covid-19
2. DRAFT landscape of COVID-19 candidate vaccines – 18 June 2020.
3. CEPI publishes analysis of COVID-19 vaccine development landscape [Internet]. Available from: https://cepi.net/news_cepi/cepi-publishes-analysis-of-covid-19-vaccine-development-landscape/
4. COVID-19 treatment and vaccine tracker [Internet]. Available from: https://milkeninstitute.org/covid-19-tracker

5. COVID-19 vaccine development pipeline [Internet]. Available from: https://vac-lshtm.shinyapps.io/ncov_vaccine_landscape/
6. 5.1.2e et al. Development of an inactivated vaccine candidate for SARS-CoV-2. Science (80-) [Internet]. 2020 May 6;eabc1932. Available from: https://www.sciencemag.org/lookup/doi/10.1126/science.abc1932
7. 5.1.2e et al. Rapid development of a synthetic DNA vaccine for COVID-19 CURRENT STATUS: UNDER REVIEW. 2020.
8. 5.1.2e et al. DNA vaccine protection against SARS-CoV-2 in rhesus macaques. Science [Internet]. 2020; Available from: https://www.embase.com/search/results?subaction=viewrecord&from=export&id=L631836389
9. 5.1.2e 5.1.2e, et al. Safety, tolerability, and immunogenicity of a recombinant adenovirus type-5 vectored COVID-19 vaccine: a dose-escalation, open-label, non-randomised, first-in-human trial. Lancet [Internet]. 2020;6736(20):1–10. Available from: https://linkinghub.elsevier.com/retrieve/pii/S0140673620312083
10. 5.1.2e The possible beneficial adjuvant effect of influenza vaccine to minimize the severity of COVID-19. Med Hypotheses [Internet]. 2020;140. Available from: https://www.embase.com/search/results?subaction=viewrecord&from=export&id=L2005692985
11. 5.1.2e. Can hepatitis a vaccine provide protection against COVID-19? Exp Clin Transplant [Internet]. 2020;18(2):141–3. Available from: https://www.embase.com/search/results?subaction=viewrecord&from=export&id=L2004158140
12. 5.1.2e Estimating the asymptomatic proportion of coronavirus disease 2019 (COVID-19) cases on board the Diamond Princess cruise ship, Yokohama, Japan, 2020. Eurosurveillance. 2020;25(10):1–5.
13. Hanker VS. Measles Immunization: Worth Considering Containment Strategy for SARS-CoV-2 Global Outbreak. Indian Pediatr [Internet]. 2020; Available from: https://www.embase.com/search/results?subaction=viewrecord&from=export&id=L631419557
14. 5.1.2e et al. Homologous protein domains in SARS-CoV-2 and measles, mumps and rubella viruses: preliminary evidence that MMR vaccine might provide protection against COVID-19. medRxiv [Internet]. 2020;2020.04.10.20053207. Available from: https://www.medrxiv.org/content/10.1101/2020.04.10.20053207v1.full.pdf+html
15. 5.1.2e Is BCG vaccination causally related to reduced COVID-19 mortality? EMBO 5.1.2e Med [Internet]. 2020; Available from: https://www.embase.com/search/results?subaction=viewrecord&from=export&id=L631705633
16. 5.1.2e Could BCG Vaccination Induce Protective Trained Immunity for SARS-CoV-2? Front Immunol [Internet]. 2020;11. Available from: https://www.embase.com/search/results?subaction=viewrecord&from=export&id=L631822067

17. [redacted] SARS-CoV-2 Rates in BCG-Vaccinated and Unvaccinated Young Adults. JAMA [Internet]. 2020; Available from: https://www.embase.com/search/results?subaction=viewrecord&from=export&id=L631751610

18. [redacted] Stop playing with data: There is no sound evidence that bacille calmette-guérin may avoid SARS-CoV-2 infection for now. Acta Biomed [Internet]. 2020;91(2):207–13. Available from: https://www.embase.com/search/results?subaction=viewrecord&from=export&id=L2004403340