Subject: Scientific Considerations and Recommendations on mRNA-based COVID-19 vaccine candidates

From: Dutch Science Board COVID-19 vaccines (29-07-2020)

This Note was provided to the Ministry of Public Health, Welfare and Sport and the Task Force of the Dutch Government on Covid-19 vaccine initiatives, 29 July 2020

Considering that:

- Three teams are currently most advanced in the development of COVID-19 vaccines based on mRNA encoding Sars-CoV-2 Spike protein or domains thereof,
- These teams being:
  i. The Moderna team (Moderna) developing an mRNA vaccine candidate, mRNA-1273, encoding the SARS-CoV-2 Spike protein (full length) stabilized by substitution of a few amino acids, containing modified uridines, transported into cells by lipid nanoparticles, which is (soon) in phase 3
  ii. The BioNTech/Pfizer (BioNTech) team developing an series of mRNA vaccine candidates (BNT162 a1/b1/b2/c2), the BNT162b1 product containing modified uridine and encoding trimerized SARS-CoV-2 spike glycoprotein receptor binding domain (RBD), which is in phase 1 /2
  iii. The Curevac team (Curevac) developing an unmodified mRNA vaccine candidate encoding the full length SARS-CoV-2 Spike protein, transported into cells by lipid nanoparticle, being in Phase 1
- The Dutch Science Board has seen data for the Moderna product (preclinical mouse data https://www.biorxiv.org/content/10.1101/2020.06.11.145920v1, very recent preclinical non-human primate data https://www.nejm.org/doi/pdf/10.1056/NEJMoa2024671?listPDF=true and clinical Phase 1/2 data https://pubmed.ncbi.nlm.nih.gov/32702298/)
- The committee has seen data for the BioNTech product (clinical Phase 1, 2 data https://doi.org/10.1101/2020.06.30.20142570 ; no preclinical data);
- The committee has seen data for the Curevac product (preclinical https://www.pei.de/SharedDocs/Downloads/EN/newsroom-en/dossiers/presentation-curevac-another-clinical-trial-sars-cov-2-vaccine.pdf?__blob=publicationFile&v=7 ; no Phase 1, 2 data);
- The vice-chair of the Board has attended a webinar and Q&A from the Moderna team presenting published and unpublished (pre)clinical data on July 15th 2020 under confidentiality;
- The Board has seen recommendations from the French scientific committee COVID-19 vaccines on these products;
- The vice-chair of the Board participated in the science discussion during the July 27th 2020 meeting of the science boards of France, Spain and NL with their JNT-members;
- Moderna is leading in clinical development, with Phase 1 and 2 trials completed and Phase 3 started on July 27th, while BioNTech has already Phase 1-2 results but has yet to decide which candidate vaccine will be used for Phase 3, and CureVac is behind its competitors, with no Phase 1 immunogenicity and safety data available yet

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- Agrees with the French experts that being an unmodified mRNA product, the Curevac vaccine may have an advantage over the modified mRNA products from Moderna and BioNTech in terms of be being sensed by the immune system, driving the expression of interferon and thus potentially inducing a better **immune response**. The limited preclinical data seen for the Curevac product in mice indeed indicate strong induction neutralizing antibodies and both Th1 type CD4+ T-cell responses and IFNg+TNFa+ CD8+ T cell responses. No NHP data were reviewed. **However**, the Dutch Board notices good neutralizing antibody profiles for the Moderna and BioNTech products in their Phase 1 /2 reports (on day 21 after a single dose for the BioNTech product). Also, human Th1 type CD4 T cell immunogenicity and protective capacity in upper and lower respiratory tract in the NHP model were reported for the Moderna product after two doses. For the BioNTech

product no information on CD8+ T-cell immunogenicity has been reported. Notably, the Moderna product did not evoke detectable CD8+ T-cells in the phase 1 /2 study nor in the NHP model. Since the Curevac product is in a less advanced clinical stage no human immunogenicity data have been disclosed;

- Agrees with the French experts that the CureVac product, being administered at a lower dose (2, 4, 8 µg) than the Moderna (100µg) and BioNTech (30µg) products, may potentially induce lower **reactogenicity** and thus be better tolerated. However the Dutch Board emphasizes that the published (interim) reports of the phase 1/ 2 safety data for the BioNTech BNT162b1 vaccine and the Moderna product seem to indicate that both these products, especially in the lower doses, exhibit a tolerability and safety profile, consistent with those previously observed for mRNA-based vaccines. The pseudo-uridine modification of the BioNTech BNT162b1 vaccine is claimed to dampen innate immune sensing, and hence reactogenicity, and increase mRNA translation in vivo;
- Agrees with the French experts that an advantage of the Moderna and CureVac vaccines is the use of full-length SARS-CoV-2 Spike protein as antigen, as opposed to the BioNTech BNT162b1 candidate encoding the RBD only. Use of a reduced Spike protein domain may have a negative impact on the breadth of the cellular immune response (reduction of the number of T epitopes) and could facilitate the emergence of SARS-CoV-2 mutant viruses that could escape neutralization by antibodies directed exclusively against the RBD. The RBD has not yet been found to mutate strongly (although evidence for mutations escaping certain neutralizing specificities is emerging). The data so far indicate that one dose of the BioNTech BNT162b1 product already within 21 days induces strong neutralizing antibodies, indirectly indicating that CD4+ helper T cell responses were induced as well;
- Acknowledges that a 1:1 comparison of the (pre)clinical for the Moderna, BioNTech and Curevac products is not fully possible due to the incompleteness of preclinical and clinical data, differences in the design of the preclinical models used, and the absence of standardized covid-19 antibody and T-cell test platforms;
- Agrees with the French experts that the CureVac product is potentially an excellent vaccine in terms of anticipated (low) adverse effects and protection, but development lags behind compared to other mRNA vaccines and there are no verifiable data on antibody and T cell responses. It is advisable to stay in contact with CureVac;
- Considers the BioNTech BNT162b1 product a candidate of interest, eliciting virus neutralizing antibodies in a one dose schedule within 21 days and having received Fast Track Status from US-FDA;
- In view of the above, unlike the French experts, prioritizes the frontrunner mRNA vaccine candidates of Moderna and BioNTech over the CureVac product

Furthermore the Dutch Science Board-COVID-19 RECOMMENDS :

- To consider Moderna and BioNtech as front running safe and immunogenic vaccine candidates, but to stay in contact with CureVac;
- That apart from mRNA-based COVID-19 vaccine candidates it is important to include candidates based on other technologies, especially the innovative viral vectored vaccines, DNA-based vaccines and the more traditional subunit/protein based technologies, in the COVID-19 vaccine candidate portfolio;
- Recommends to include the time of delivery of sufficient doses of vaccines as a selection criterion;
- Recommends to intensify efforts to establish a pharmacovigilance program for COVID-19 vaccines;
- Recommends standardization of test platforms independent of companies;
- Recommends collaboration between all stakeholders by requesting and making available clinical samples from different trials and products for centralized testing in a qualified laboratory, enabling science-based comparison of vaccine products, schedules and platforms