**Progress report on the mode of actions (vaccine) and vaccine efficacy**

5.1.2e 5.1.2e

6 October 2020

**Aim and Research questions**

- **Aim:** to calculate the impact per dose of vaccine, by age, by region, and by profession. The calculation follows those of Wallinga 2010 PNAS
- **Assigned questions:**

  (1) how large is the expected vaccine efficacy? ($q$ in Eq-1, Wallinga 2010 PNAS)

  (2) what is the plausible mode of action of vaccines?

  (3) age-, sex-, region-, or profession- dependent effect?

  (4) how large is the variation in susceptibility?

- **Tentative answers on 6 Oct:**

  (1) how large is the expected vaccine efficacy? -> as a baseline 60% and as a lower bound 30% (This value is based on the target efficacies that pharmaceutical companies set for Phase III. If VE in the trial is less than 30%, the vaccine will not be approved by FDA [ref] .)

  (2) what is the plausible mode of action of vaccines? -> Leaky (based on the observation in some trials that the lung was protected but the upper respiratory tract was not perfectly )

  (3) age-, sex-, region-, or profession- dependent effect? -> The elderly did not induce enough antibody responses, and the elderly need higher-boosted titer compared to activate the protective function in theory (based on Sinovac (Zhang et al. 2020) and Pfizer trials (Mulligan et al. 2020)). For sex-, region-, and profession-dependency, there is no clue how to stratify (Krammer 2020).

  (4) how large is the variation in susceptibility? -> CV =< 1.7, smaller than Gomes' group's estimates [ref]

- **Other possible extrapolations?**

  (1) To wait for Phase III results that will appear (around end of October)?

  (2) Modelling the correlation between surrogates of immune responses vs protections? -> (World Health Organization 2013)

  (3) Primate models? -> This might not be a good idea[ref]

**Pharmaceutical companies that open their protocol about Phase III trial**

| | Pfizer | Moderna | Astra-Zeneca | JNJ |
|---|---|---|---|---|
| Sample size | | 5.1.1c | | |
| Participants getting vaccine | 22000 | 15000 | 20000 | 30000 |
| Type of vaccine | mRNA | mRNA | Adeno vector | Adeno vector |
| Efficacy target | 60% | 60% | 60% | 60% |
| Lower 95% CI efficacy | 30% | 30% | 30% | 30% |
| No of events at completion | 164 | 151 | 150 | 154 |
| Primary endpoint severity* | + | ++ | ++ | ++1/2 |
| No of Interim Analyses | 4 | 2 | 1 | NA |
| No of events 1st look | 32 | 53 | 75 | 20 |
| Alpha-spending function at interim analysis for stopping rule | Procock-type | O'Brien-Fleming type | Lan-DeMets | NA |
| No of shots | 2 | 2 | 2 | 1 |
| Deep freezing required | yes | yes | yes | no |
| References for taget VE | https://pfe-pfizercom-d8-prod.s3.amazonaws.com/2020-09/C4591001_Clinical_Protocol_0.pdf | https://www.modernatx.com/sites/default/files/mRNA-1273-P301-Protocol.pdf | https://s3.amazonaws.com/ctr-med-7111/D8110C00001/52bec400-80f6-4c1b-8791-0483923d0867/c8070a4e-6a9d-46f9-8c32-cece903592b9/D8110C00001_CSP-v2.pdf | https://www.jnj.com/coronavirus/covid-19-phase-3-study-clinical-protocol |

Note: I did not include candidates that do not open their detailed protocol. For living view, LSHTM's COVID-19 vaccine tracker is highly recommended [ref].

**Current related evidence**

- (5.1.2e): A review on vaccine development status, as of 23 Sep (publish date)
  - Only partial protection might occur in upper resipiratory and lung, based on the experimental results with non-human primates and vaccine trials.
  - Eldery needs high increase in antibody titer to induce the immune protection, and even the titer itself sometimes does not increase sufficiently (Pfizer, Sinovac)
  - (In terms of actual vaccine allocation, some vaccines such as mRNA vaccines require deep-freezing, and it is difficult to distribute vaccines keeping such conditions)
- (5.1.2e): A review on antibody responses, including old coronaviruses

- Using coronaviruses (SARS-CoV-2, SARS-CoV, MERS-CoV, and endemic HCoVs) antibody kinetics, 2) correlates of protection, 3) immunopathogenesis, 4) antigenic diversity and cross-reactivity, and 5) population seroprevalence were reviewed.
- There might be limited cross-reactivity between endemic HCoV and emerging CoVs.
- The systematic review includes articles before 22 March 2020 only. For SARS-CoV-2 this is a bit outdated, so other new review papers should be referred.

- 5.1.2e : human challenge study with HCoV-229E and HCoV-OC43
  - Re-challenged (n = 6) volunteers who had been experimentally infected 8-12 months previously. On the first challenge, all 6 developed symptoms and detectable viruses and 5 of 6 experienced significant rise in titer. In the second season, 0/6 experienced illness, detectable virus or significant rise in titer. (Inoculated viral dose is unknown)
  - Re-challenged (n=12) volunteers with heterologous viruses (not identical to first experimental infection) 8-14 months after first infections. 7/12 developed cold symptoms (Inoculated viral dose is unknown)

**References**

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*Krammer, Florian. 2020. "SARS-CoV-2 Vaccines in Development." Nature, September. https://doi.org/10.1038/s41586-020-2798-3.*

*Mulligan, Mark J., Kirsten E. Lyke, Nicholas Kitchin, Judith Absalon, Alejandra Gurtman,* 5.1.2e 5.1.2e *, Kathleen Neuzil, et al. 2020. "Phase 1/2 Study of COVID-19 RNA Vaccine BNT162b1 in Adults." Nature, August. https://doi.org/10.1038/s41586-020-2639-4.*

*Reed, S. E. 1984. "The Behaviour of Recent Isolates of Human Respiratory Coronavirus in Vitro and in Volunteers: Evidence of Heterogeneity among 229E-Related Strains." Journal of Medical Virology 13 (2): 179–92.*

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(Webpages are referred as [ref] with attached comments. )