Vaccination to prevent COVID-19

International Parkinson and Movement Disorder Society

Scientific Issues Committee

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Emergency use authorization of COVID-19 vaccines

- The U.S. Food & Drug Administration (FDA), the European Medicines Agency (EMA), and Health Canada among other agencies have recently approved BNT162b2 (Pfizer/BioNTech) and mRNA-1273 (Moderna) vaccines for emergency use authorization or regular authorization for one year in the case of EMA.

- The approval process by these regulatory entities includes thorough analyses of completed Phase III data provided by vaccine developers in a transparent process that includes peer-reviewed publication of full data sets.

- The approval of both vaccines met the high standards required for use authorization after complete data scrutiny and validation, as required in the normal process of a vaccine approval.

- Additional COVID-19 vaccines that are still in experimental phases II and III will eventually undergo the same scrutiny before emergency use authorization.

Questions and Concerns

The development and approval of COVID-19 vaccines reached record times compared with the typical timeframes of previous vaccines.

The regulatory agencies have also expedited the vaccines approval for emergency use authorization or limited authorization for one year.

As a result of this accelerated pace, there are doubts and concerns about the benefits and risks of these new vaccines that need to be addressed.

In this presentation we will discuss critical points about:

- Properties of the novel mRNA-based vaccines,

- Efficacy data,

- Safety data,

- Clinical significance particularly for patients with Parkinson's disease (PD).

Antigen in COVID-19 Vaccines

SARS-CoV 2 Glycoprotein S

- The envelope "spike protein" of SARS-CoV 2 (SARS-CoV 2 glycoprotein S) is a trimeric glycoprotein, which is one of the structural proteins that stud the surface of the virus.

- Early preclinical work found that SARS-CoV 2 glycoprotein S was highly immunogenic and protective against SARS-CoV challenge, in contrast to other SARS-CoV 2 surface proteins that did not induce a substantial immune response or provide protection.

- SARS-CoV 2 glycoprotein S contains a receptor-binding domain that interacts strongly with angiotensin-converting enzyme 2 (ACE2) receptors on host cells, and this interaction mediates entry of the virus into host cells.

- Additional preclinical studies demonstrated that SARS-CoV 2 glycoprotein S elicited polyclonal antibody responses and vigorously neutralized SARS-CoV 2 S-mediated entry into cells.

- Based on the above, SARS-CoV 2 glycoprotein S has been the primary focus as the antigen in COVID-19 vaccine development to date.

Vaccine Platforms

- WHO estimates that there are 233 COVID-19 vaccines currently in development: 61 in clinical development and 172 in preclinical development.

- Classic vaccine platforms and next-generation vaccine platforms are being used to develop COVID-19 vaccines.

- Nucleic acid-based (DNA or mRNA) vaccines are next-generation vaccine platforms that can be adapted quickly when new viruses emerge, which is why mRNA vaccines were among the very first COVID-19 vaccines to enter clinical trials.

- mRNA vaccines consist of a synthetic mRNA encoding the vaccine antigen (and bypass nuclear translocation and transcription required for DNA vaccines).

- Since mRNA is not very stable, the mRNA constructs may include modified nucleosides to prevent degradation. In addition, carrier molecules (e.g., lipid nanoparticles) are required to enable entry of the mRNA into cells.

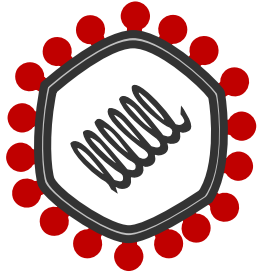- mRNA vaccines induce humoral and cellular immune responses, but multiple doses are required.

Classic vaccine platforms

Virus-based vaccines:
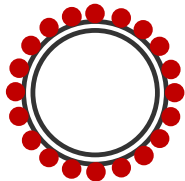
Inactivated virus
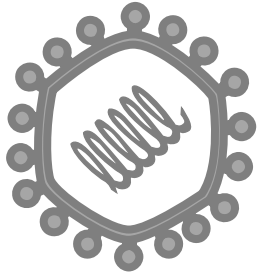
Live-attenuated virus

Protein-based vaccines:

Protein purified from the virus
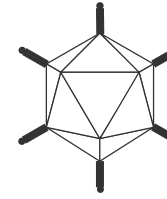or virus-infected cells,
recombinant protein

Virus-like particles

Limitations: extensive safety testing is required for live-attenuated viruses, less amenable to fast vaccine production
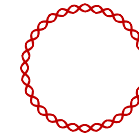
Next-generation vaccine platforms

Viral vectors

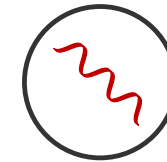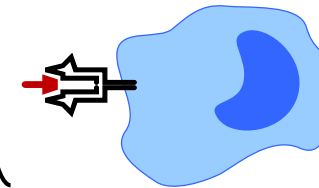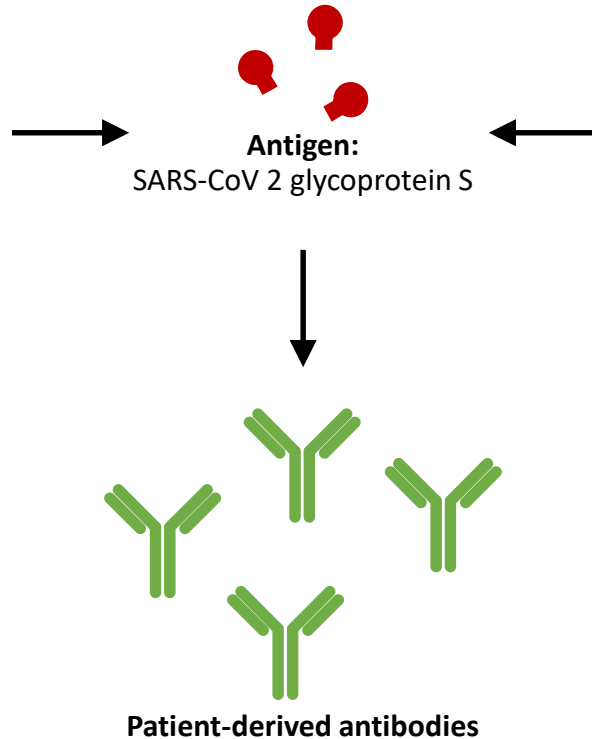**Nucleic acid-based vaccines:**

DNA vaccines

mRNA vaccines

Antigen-presenting cells

Advantages: vaccines can be developed based on sequence information alone (e.g., sequence of SARS-CoV 2 glycoprotein S), more amenable to fast vaccine production

Antigen:
SARS-CoV 2 glycoprotein S

Patient-derived antibodies

Modified from van Riel & de Wit *Nat Mater* 2020 doi: 10.1038/s41563-020-0746-0

Efficacy of Vaccines with Published Phase III Trial Data

Name	Sponsor	Type	Efficacy (%)	Reference
BNT162	Pfizer & BioNTech	mRNA encoding SARS-CoV 2 glycoprotein S	**95.0** IC95%[1] 90.3 - 97.6	Polack, F. et al. (2020)
mRNA-1273	Moderna	mRNA encoding SARS-CoV 2 glycoprotein S	**94.5** IC95%[1] 86.5 - 97.8	Baden, L. et al. (2020)
AZD1222	Oxford University, AstraZeneca, IQVIA, Serum Institute of India	Adenoviral vector containing the SARS-CoV-2 glycoprotein S	**70.4** IC95%[1] 54.8 - 80.6	Voysey, M. et al. (2020)

*Source: IDSA and listed references. [1] IC95%: 95% Confidence Interval of the estimation

Pfizer/BioNTech – BNT162b2 Study

- 30 µg of mRNA encoding SARS-CoV 2 glycoprotein S vaccine vs placebo.

- Enrolled 44,820 participants.

- Efficacy data on 36,523 participants that had negative COVID status and received 2 doses of the vaccine (N=18198) or placebo (N=18325).

- Evaluated Vaccine Efficacy (VE) in preventing COVID-19 occurring at least 7 days after dose 2.

- There were 9 COVID-19 cases in the vaccine group and 169 in the placebo group.

- The estimated Vaccine Efficacy was 95.0% (95% confidence Interval 90.3% - 97.6%) meeting the primary goal.

- Results were similar across different age groups and ethnicities.

Moderna – mRNA-1273 Study 301

- 100 µg of mRNA encoding SARS-CoV 2 glycoprotein S vaccine vs placebo.

- Enrolled 30,420 participants.

- Presented interim efficacy data on 28,817 participants that had negative COVID status and received 2 doses of the vaccine (N=13934) or placebo (N=13883).

- Evaluated Vaccine Efficacy (VE) in preventing COVID-19 occurring at least 14 days after dose 2.

- There were 5 COVID-19 cases in the vaccine group and 90 in the placebo group.

- The estimated Vaccine Efficacy was 94.5% (95% confidence Interval 86.5% - 97.8%) meeting the primary goal of a VE > 30%.

- Results were similar across different age groups and ethnicities.

Oxford/AstraZeneca – AZD1222

- COV001, COV002, COV003 and COV005
- Different ranges (2.2 x10^{10} – 6.5 x10^{10}) of adenoviral vector ChAdOx1, containing the SARS-CoV-2 structural surface glycoprotein antigen vs meningococcal vaccine.
- Enrolled 23,848 participants across all four studies.
- Efficacy data on 11,636 participants that had negative COVID-19 status and received 2 doses of the vaccine (N=5807) vs meningococcal vaccine (N=5829).
- Evaluated Vaccine Efficacy (VE) in preventing COVID-19 occurring at least 14 days after dose 2.
- There were 30 COVID-19 cases in the vaccine group and 101 in the control group.
- The estimated Vaccine Efficacy was 70.4% (95% confidence Interval 54.8% - 80.6%) meeting the primary goal.
- Results were similar across different age groups and ethnicities.

Ramasamy et al. Lancet. 2021 Dec 19;396(10267):1979-1993.

Safety of Pfizer/BioNTech – BNT162b2 (30µg)

- Local Reactions
  - Pain at injection site, mostly mild, was common (83% (18-55y); 67%(65-85y)).
  - Redness and swelling were rare.

- Systemic Events*
  - These include **fever** (16.7%(18-55y;); 8.3%(65-85y)), **fatigue** (most common; 75%(18-55y); 41.7%(65-85y)), **headache** (66.7%(18-55y); 25.0 %(65-85y)), **chills** (58.3%(18-55y); 16.7 %(65-85y)), **diarrhea** (0%(18-55y); 0%(65-85y))**, **muscle pain** (58.3%(18-55y); 25.0 %(65-85y)), **joint pain** (16.7%(18-55y); 8.3 %(65-85y)).
  - Younger adults (18-55y) tend to have more severe reactions than older adults (65-85y).
  - Systemic side effects were more common after second immunization.
  - No grade 4 reactions.
  - Allergic reaction has been reported rarely. This rare reactogenicity is similar with other vaccines.

*The data displayed in this slide are the events following second dose of injection.
**Diarrhea was only reported after first dose of injection.

Walsh et al. N Engl J Med. 2020 Dec 17;383(25):2439-2450.

Safety of Moderna – mRNA-1273 (100µg)

- Common local and systemic adverse events were: headache, fatigue, myalgia, chills, injection site pain.

- Adverse events were more common and severe after second immunization.

- These events were dose-dependent.

- These events were mostly mild to moderate in severity:
  - Any systemic symptom (after 2nd dose): none (11.1%(56-70y); 30.0%(≥70y)); mild (33.3%(56-70y); 30.0%(≥70y)); moderate (55.6%(56-70y); 30.0%(≥70y)); severe (10.0%(≥70y));
  - Any local symptom (after 2nd dose):none (11.1%(56-70y); mild (66.7%(56-70y); 60.0%(≥70y)); moderate (22.2%(56-70y); 40.0%(≥70y));

- No serious adverse event was reported.

Anderson et al. N Engl J Med. 2020 Dec 17;383(25):2427-2438.

Safety of Oxford/AstraZeneca – AZD1222 (standard dose: $3{\cdot}5$–$6{\cdot}5 \times 10^{10}$ virus particles)

- Local reactions:
  - Pain, tenderness, warmth (at least one local symptom after first dose in 88%(18-55y); 73%(56-69y); 61%(≥70y) and a similar proportion in boost dose).

- Systemic reactions:
  - Fatigue, feverish, headache, and muscle ache were more frequent. Chills, fever, joint pain, malaise, and nausea were also observed.
  - At least one systemic symptom after first dose in 86%(18-55y); 77%(56-69y); and 65%(≥70y), and after boost dose in 65%(18-55y); 72%(56-69y); 43%(≥70y).

- Adverse effects were less common in older adults.

- No serious adverse event was related to vaccine.

Ramasamy et al. Lancet. 2021 Dec 19;396(10267):1979-1993.

Summary of Safety Data

- Similar side effects among vaccines BNT162, mRNA-1273, AZD1222:
  - Local reactions (pain).
  - Systemic reactions (fatigue, myalgia, headache).

- No reported serious vaccine-related side effects.

- The vaccine is safe for older adults with less side effects than in younger adults.

Clinical Considerations: COVID-19 Vaccine versus Infection

COVID-19 Outcomes among People with PD

1. The first included clinical information of 117 community-dwelling patients with COVID-19 followed in 21 tertiary centers in Italy, Iran, Spain, and the UK, reported a mortality rate of 19.7% (Fasano, Elia et al. 2020).

2. The second reported mortality rate of 40% was in a case series of 10 PD patients with COVID-19 from hospital units in Italy and the UK (Antonini, Leta et al. 2020).

3. A case-control survey from a single tertiary center in Lombardy, Italy, reported that of the 1,486 surveyed PD participants, 105 (7.1%) developed COVID-19 and 6 of the 105 (5.7%) died (Fasano, Cereda et al. 2020).

IN SUMMARY, THE LOWEST MORTALITY RATE FROM COVID-19 AMONG PEOPLE WITH PD REPORTED TO DATE WAS 5.7%.

PD Symptoms May Worsen after COVID-19 Infection

Cilia and colleagues reported that among 12 residents in Lombardy, Italy, with concomitant PD and COVID-19, motor and non-motor symptoms significantly worsened in the COVID-19 group, requiring therapy adjustment in a third of the cases (Cilia, Bonvegna et al. 2020).

An additional case report suggested that worsening PD symptoms can be the presenting expression of COVID-19 (Hainque and Grabli 2020).

COVID-19 Vaccines – Benefits outweigh risks

-Based on efficacy and safety from Phase III data, the benefits of the approved vaccines outweigh their risks for the general population.

-The same reported efficacy is expected to apply to patients with PD because there is no data to support a different vaccine performance in PD.

-Similarly, the same reported data about the types or incidence of side effects of the approved vaccines are expected to apply to patients with PD.

-No changes in PD symptoms or responses to PD treatments are known from the reported data in Phase III trials of the approved vaccines.

Conclusions for Vaccination to Prevent COVID-19

-The COVID-19 vaccine development and approval has been achieved at record time with concerted efforts of involved parties and utilizing new technologies of mRNA delivery. These efforts also ensured rigorous compliance with the necessary data analyses for a vaccine approval.

-The efficacy of approved vaccines is remarkably high (>90%). The safety data so far has been reassuring. Moreover, no changes in PD symptoms or responses to PD treatments following vaccination are known thus far, whereas PD symptoms may worsen after COVID-19 in PD.

- Based on efficacy and safety from Phase III data and considering the risks of COVID-19 in PD population, the approved vaccines are strongly recommended for patients with Parkinson's Disease.