SARS-CoV-2 and COVID-19 Clinical Trials and Vaccine Safety

Dr. Stephen D. Prior

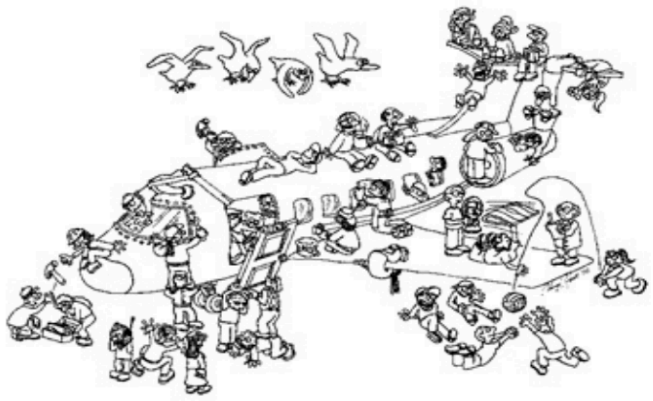
21st May 2021

Disclaimer: The views expressed herein are those of the author. Any mistakes or omissions in any of the information or the commentary provided herein are those of the author. The information, views and opinions are personal: They are based on information in the public domain and personal experience. Any decision regarding health or medical practice must be discussed with a professional healthcare provider.

Topics:

- Vaccination, vaccine safety and efficacy
- Comparison of Vaccine Development Processes
- COVID-19 Vaccine Clinical Trials

SARS CoV-2/ COVID-19 - “Building the Plane as We Fly”



Good news:

- Not our first vaccine (or our last)
- Vaccine technologies/ platforms are adaptable
- Prior CoV disease and vaccines provided information
- Pandemic concerns facilitated unprecedented:
  - Cooperation
  - Collaboration
  - Adoption of cost risk

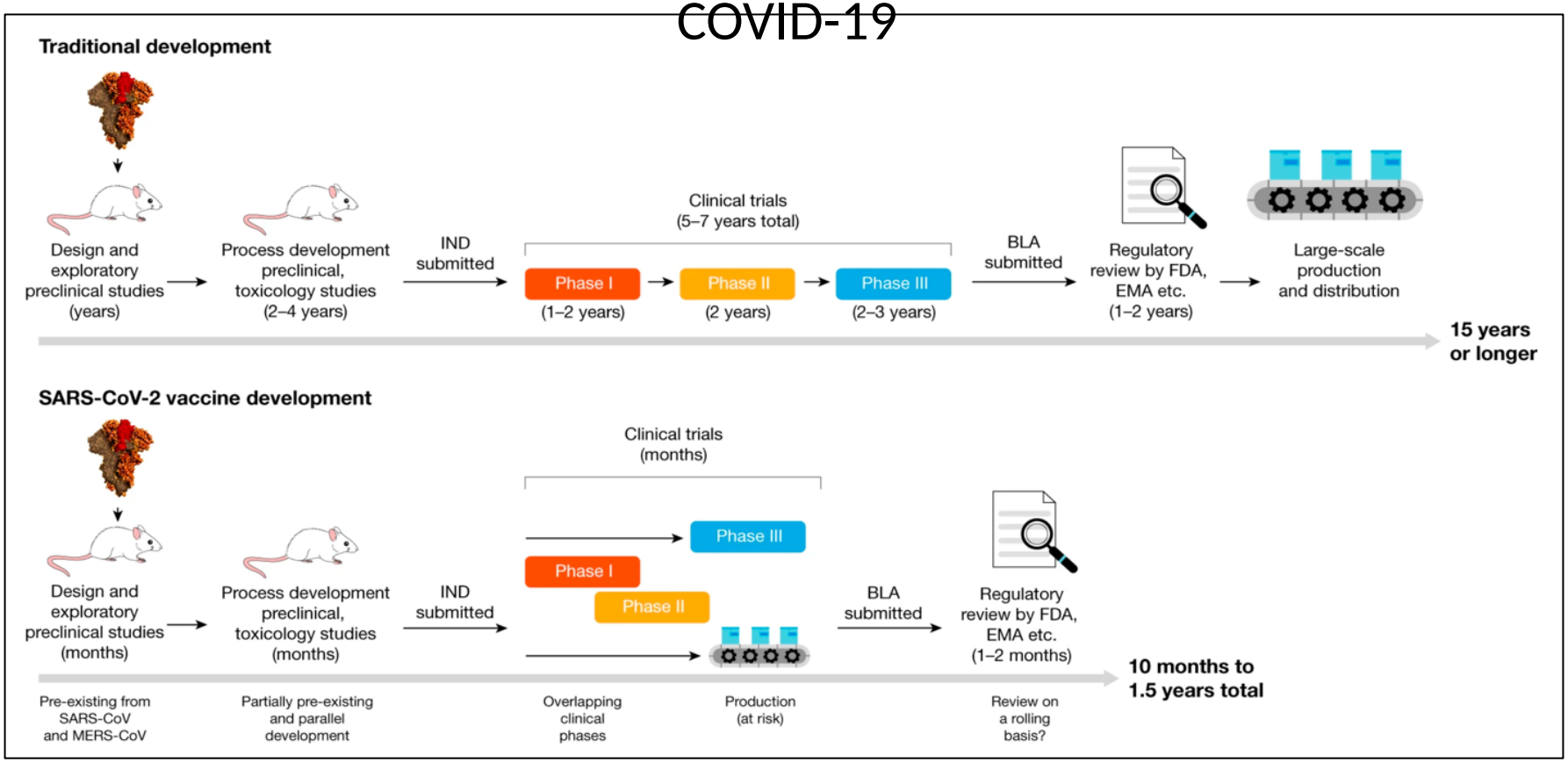
Vaccination: Stimulation of one or more components of the adaptive immune system and development of a memory response that targets a pathogen.

Primary Function: Protect the individual who is vaccinated

Secondary Benefit: Protect the population by limiting disease spread (transmission)

Safety: Vaccine safety systems ensure that vaccines are as safe as possible. This includes manufacture, clinical trials and post-authorization/ licensure safety studies.

Comparing Traditional Vaccine Development with SARS-CoV-2/ COVID-19



Critical features:

- Parallel versus batch processes
- Assume cost risks of product failure
- Collaborative, rolling wave for regulatory reviews
- Emergency Use Authorization (versus Product Licensure)

https://www.nature.com/articles/s41586-020-2798-3

COVID-19 Vaccine – Clinical Trials (1)

All vaccines for use in humans are subject to review by regulatory authorities.

Safety reviews include vaccine manufacturing standards (purity, potency, stability)

Clinical studies with thousands of volunteer participants are conducted to assess vaccine:

- Safety
- Efficacy

Safety involves monitoring and follow-up of all volunteers for vaccine-related issues. These can be as simple as soreness at the injection site, through mild, moderate to severe side effects.

Efficacy is assessed in trials involving volunteers receiving the vaccine (~50%) or a placebo. In the case of COVID-19, both volunteer groups are monitored for infection with the SARS CoV-2 virus and development of COVID-19 disease (mild, moderate and severe cases).

Immediate approvals by many regulatory authorities were limited to '(Emergency) Use Authorizations' that permitted widespread use while additional data was collected. The first vaccine application for full licensure by the US FDA was announced by Pfizer on May 7th.

Authorization for use in the context of vaccine safety may address issues of liability.

COVID-19 Vaccine – Clinical Trials (2)

The types of vaccine currently in use for COVID-19 are well-established technologies and proven vaccine platforms

Vaccine Type	First Use (Decade)	Virus Vaccines	COVID-19 Manufacturer
mRNA	2010	Influenza/Zika/Rabies	Pfizer-BioNTech/ Moderna
Adenovirus	1980	HIV/EBOV/SARS/MERS	AstraZeneca/ Gamaleya/ Janssen J&J
Sub-Unit	1970	Influenza/Hepatitis/HPV	Novavax
Inactivated	1890	Rabies/Polio/Influenza	Sinopharm/ Sinovac

Focus Areas for Clinical Trials
Phase 1: Immunogenicity, dose, batch consistency, tolerance, SAFETY
Phase 2: Efficacy, SAFETY

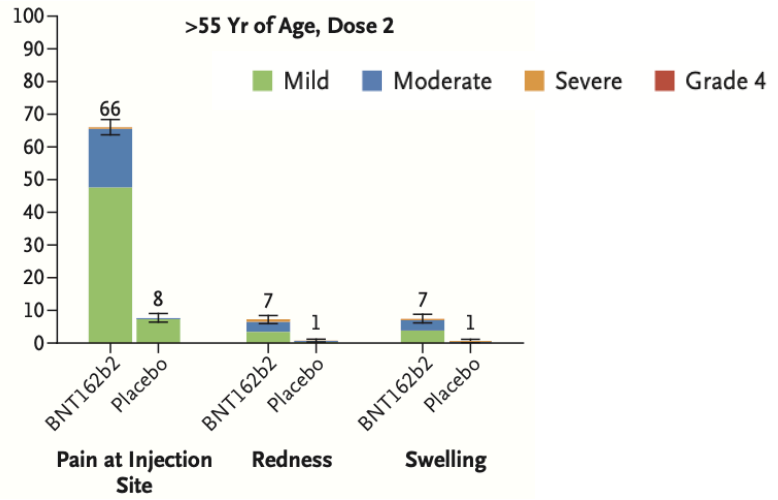
Phases 1 & 2 recruit volunteers and use inclusion criteria for enrollment. Initial studies focus on dose escalation/ response, tolerance and vaccine-related safety. Initial results report:

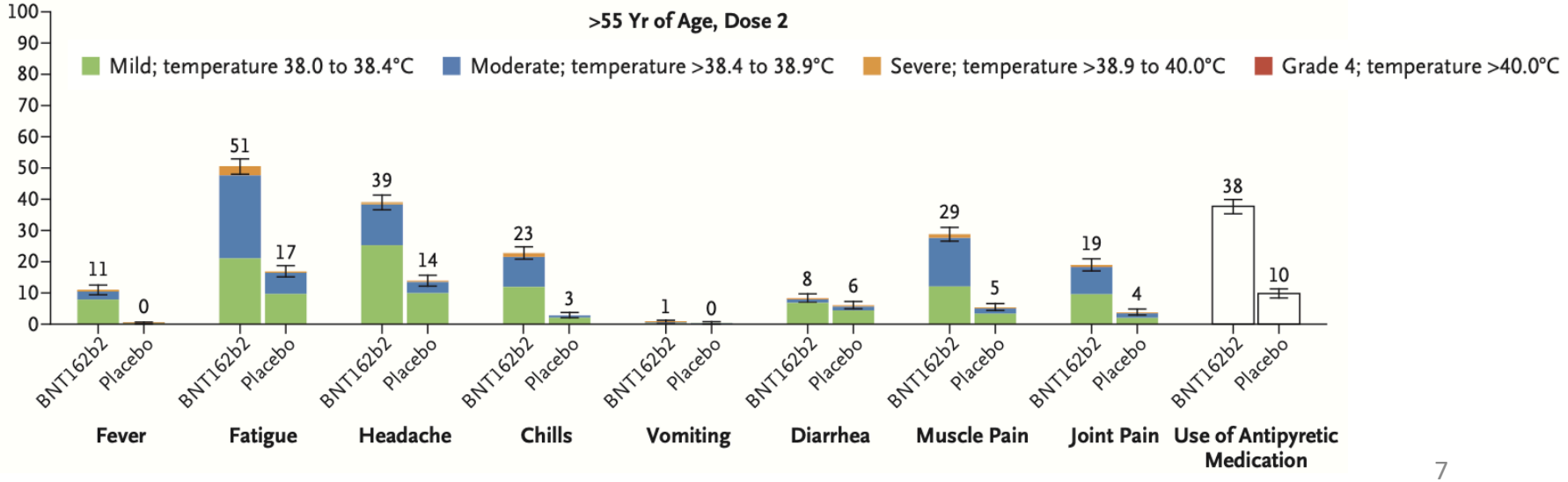
- Adverse event
- Life-threatening adverse event or life-threatening suspected adverse reaction
- Serious adverse event or serious suspected adverse reaction
- Suspected adverse reaction
- Unexpected adverse event or unexpected suspected adverse reaction

COVID-19 Vaccine – Clinical Trials (3)

The first published results leading to EUA – Pfizer mRNA

43,548 participants
July 27 – November 20, 2020
6 countries
152 sites
Minimum 2 months follow-up after dose #2
42% over 55 years
35% obese (BMI>30)
21% one coexisting condition





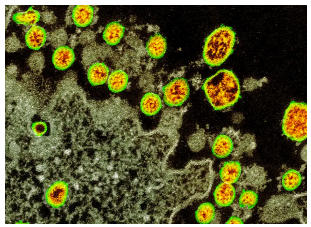
COVID-19 Vaccine – Clinical Trials (4)

Clinical Trial Safety Considerations

- Trial protocol – ensure safety and meet stated objectives
- Is the dose escalation scheme appropriate? Numbers of subjects appropriate?
- Appropriate monitoring scheme – Direct clinical and prolonged observation
- Frequency of monitoring for observation
- Follow-up laboratory test data
- Safety stopping rules – pause and halt

Manufacturer	Date Paused	Information
Astra Zeneca	September 2020	Adverse reaction (n=1)
J&J	October 2020	Unexplained illness (n=1)
J&J	April 2021	Cerebral Venous Thrombosis

Maarten Postma (UK JCVI): Regarding the recent issues with the Janssen/ J&J COVID-19 vaccine: Statistically 1,000 Covid-19 deaths would be prevented for every 1m people inoculated, while scientists would expect one fatal case of vaccine-linked blood clotting. "But people do not think in terms of risk-benefit," he said. "We give these vaccines to healthy people so there's zero tolerance when it comes to severe side effects."



It Is Hard To Make Predictions – Especially About the Future *(Yogi Berra, NY Yankees)*

- Regulatory authority monitoring will review patient data for safety and efficacy
- Vaccines will help prevent severe/moderate COVID-19 and reduce hospitalizations
- Some vaccines may reduce virus spread (transmission); herd immunity will help
- New vaccines will become available with new properties (cold-chain, number of doses, etc.)
- The virus will continue to mutate, resulting in new ‘variants’ and ‘strains’
- The current vaccines may be less effective against some of the variants and strains
- Vaccines will need to be modified to account for the ‘resistant’ variants/ strains
- For the immediate future we may need to receive additional booster vaccines; it is possible that like influenza COVID-19 will require annual vaccination.


рахмат
danke
謝謝
ngiyabonga
spas
teşekkür ederim
Баярлалаа
mersi
kia ora
barka
welalin
tack
mahalo
tapadh leat
спасибо
faafetai lava
vinaka
blagodaram
dank je
misaotra
paldies
grazzi
matondo
спасибі
kiitos
dankie
thank you
gracias
хвала
nanni
nandri
dhanyavad
maururu
köszönöm
ačiū
asante
manana
bedankt
hvala
bayarlalaa
gràçie
dankon
akun
obrigada
tenki
murakoze
enkosi
djiere dieuf
tau
mochchakkeram
dziękuję
дякую
mamnun
chnorakaloutioun
gratias ago
gràcies
sulpáy
chokrane
go raibh maith agat
sobodi
děkuji
sukriya
kop khun krap
taiku
obrigado
sagolun
arigatô
takk
dakujem
trugarez
mèsi
ありがとう
tanemirt
grazie
didi madloba
najis tuke
terima kasih
rahmet
мерси
kam sah hamnida
rahmat
diolch
dhanyavadagalu
shukriya
mercé
তোমাকে ধন্যবাদ
감사합니다
xièxie
ευχαριστώ
merci