COVID-19 Vaccines
The way out of the pandemic…?

11 March 2021, Virtual Event Series - Session 1
“Are COVID-19 Vaccines a Way Out of the Pandemic?”

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Virtual Event Series - Session 1

COVID Pandemic Update
  • Numbers, trends
  • Variants: General information, UK South Africa, Brazil

Immunology and vaccines
  • Ab, nAb, cellular immunity
  • Vaccine development - principles
  • Currently important approaches
  • Vaccine protection – efficacy

Some common questions
Poll question #1

Would you want to be vaccinated with a COVID-19 vaccine today?

1. Yes
2. No
3. Still thinking about it
Coronavirus – SARS-CoV-2
SARS-CoV-2 Lifecycle in Host Cells

Endosome

Endoplasmatic Reticulum (ER)

Golgi bodies
COVID Pandemic Update

First wave ... Second wave ... and now a third wave ... ?!

Measures (lockdown, shutdown, etc.) - effect, meaning and connection with progress:
“Virus characterisation, health care system, containing the spread, masks, diagnostics, vaccinations, etc.”

Are vaccines the way out of this pandemic?
COVID Variants Update

New variants
- South Africa
- UK/Ireland
- Brazil

Spike mutations (501)

Nextstrain.org
End Jan 2021
COVID Variants Update

October 2020

January 2021

Nextstrain.org
Accessed 2 Feb 2021
COVID Variants Update

New variants
- South Africa
- UK / Ireland
- Brazil

Spike mutations (501)

Data reflecting entire pandemic
(visualisation based on approx 3’000 genomes from all regions)

31st January 2021

Today - March 2021

Accessed 11 Mar 2021
CoV-2 Variants – *Evading the immune and vaccine response?*

**Variants**
- Spontaneous mutations
- Immune selection process
- Implications - diagnosis and vaccines
- Herd immunity
- First step to “vaccine escape”
- Cyclically seasonal patterns - adjustments to a vaccine (similar to influenza)

**501 mutations**
- Mutations in the virus receptor (RBD)
- “Better binding to the ACE2 receptor”
- Additional deletions in S1 provide an evasion of the immune response
- **Furin**: S1 cleavage simplifies virus entry

**N501Y**
- **S1** = attachment RBD / **S2** = fusion
- **N** = Asp / **Y** = Tyr
“Neutralising” versus “Binding” Antibodies (nAb vs. bAb)

Particle or virus when “neutralised” is no longer infectious or hazardous...
501Y.V1 = B.1.1.7 = ‘Kent (UK)’ Variant

<table>
<thead>
<tr>
<th>Country first detected</th>
<th>Date first Detected</th>
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<th>AKA</th>
<th>Notable mutations</th>
<th>Transmissibility</th>
<th>Virulence</th>
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<td>UK</td>
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<td>501Y.V1</td>
<td>N501Y; 69–70del; P681H</td>
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N501Y  
P681H  
H69-V70del
501Y.V2 = B.1.351 = ‘South African’ Variant

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<tr>
<td>South Africa</td>
<td>Dec.20</td>
<td>B.1.351</td>
<td>501.V2</td>
<td>N501Y; K417N; E484K</td>
<td></td>
<td>=</td>
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Partial Immune Escape to “South African” Variant

Convalescent Plasma

Post-vaccination sera

Plaque reduction neutralization test
“higher amount of nAbs needed”
mRNA-BNT162b2 sera (n=20)

Does this mean that vaccines will be 1-3x less effective…?! 

89-96% (WT & UK variant)  \textit{versus}  50-60% efficacy in S-Africa

72% (USA)  \textit{versus}  57% efficacy in S-Africa (95% had B.1.351)

2-fold reduced neutralization  
(\textit{Brasil} variant)
Vaccine Development - Immune Response

Immune responses

Cellular
Humoral
The COVID-19 vaccines were developed very rapidly within one year (instead of >10 years). How would you state your trust in them?

1. **Very high** – no problem at all
2. **High** – I trust them, but remain a little skeptical
3. **Medium** – They are OK, but there are some issues that concern me
4. **Low** – I am worried that they are incompletely evaluated
Principle of a Vaccine

Induce immune response against antigens

Antigen = antibody generators

A molecule which triggers an immune response

Such as viral surface protein; polysaccharide (pneumococci capsule), attenuated infectious agent, etc.
Vaccine Development – “the clinical trial phases”

**Laboratory development**
Investigations in animals
1-2 years

**Clinical trials in phases**
- **Phase I**: Safety and efficacy, dosage
- **Phase II**: Safety, immune response, dosage - placebo
- **Phase III**: Safety (rare AEs), randomised, double-blind, efficacy

**FDA Review**
To confirm safety and effectiveness

**Approval**

**Duration of development**: 5 to 15 years!

**Further investigations**
Safety, including logistics, use, storage, other effects, etc.

**Preclinical**
- 20-80 Participants

**Phase 1**
- 100-300 Participants

**Phase 2**
- 1,000-3,000 Participants

**Phase 3**
- FDA Review

**Phase 4**
- 1,000+ Participants

**FDA, EMA, SwissMedic**
COVID-19 Vaccine Development “the vaccine race” …from new CoV-2 to vaccine in less than one year!

COVID-19 VACCINES IN DEVELOPMENT

181 vaccines are being explored in lab experiments and animals
28 vaccines are undergoing safety tests in healthy young individuals
28 vaccines are being tested in broader groups of people
21 vaccines are in large international trials to test their impact on COVID-19
12 vaccines are approved and licensed for general use
4 vaccines are being monitored in the wider population after being approved

N=77 in clinical development (as of March 10, 2021)

https://www.gavi.org/vaccineswork/covid-19-vaccine-race
Characteristics of an *ideal* COVID vaccine

- Low-cost (estimated vaccine dose < $40)
- Good antibody production (neutralising Ab) and cellular immunity
- **FDA/EMA**: min. 50% protection (or 50% protection against severe course)
- Safety demonstrated in at least 2 studies with >10,000 subjects
- Sterilising immunity (no viruses in blood, saliva or stool)
- Protects all age groups (risk: older and immune-suppressed people)
- Single dose preferred - *if needed*, booster after 4-8 weeks
- Heat stable and not light-sensitive (store at 2-8 deg. C)
Coronavirus Vaccine Candidates

GENETIC SUBSTANCE

VIRAL VECTORS

VIRUS-BASED

PROTEIN-BASED

Vaccine

Body

Cell

Antigen-presenting cell

Coronavirus peptide

Immune response

AstraZeneca

janssen

Pfizer

moderna

NOVAVAX

Sputnik V
# COVID-19 Vaccination Strategies

## Nucleic acids
- mRNA or virus vector

## Protein
- Particle

## Virus
- inactivated or attenuated

### Major contenders

<table>
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<tr>
<th>Type of vaccine</th>
<th>Licensed vaccines using this technology</th>
<th>First introduced</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Viral vectored</strong></td>
<td>Ebola</td>
<td>2019 (Ebola)</td>
</tr>
<tr>
<td><strong>Nucleic acid vaccine</strong></td>
<td>SARS-CoV-2</td>
<td>2020 (SARS-CoV-2)</td>
</tr>
<tr>
<td><strong>Subunit (purified protein, recombinant protein, polysaccharide, peptide)</strong></td>
<td>Pertussis, influenza, hepatitis B, meningococcal, pneumococcal, typhoid, hepatitis A</td>
<td>1970 (anthrax)</td>
</tr>
<tr>
<td><strong>Live attenuated (weakened or inactivated)</strong></td>
<td>Measles, mumps, rubella, yellow fever, influenza, oral polio, typhoid, Japanese encephalitis, rotavirus, BCG, varicella zoster</td>
<td>1798 (smallpox)</td>
</tr>
<tr>
<td><strong>Killed whole organism</strong></td>
<td>Whole-cell pertussis, polio, influenza, Japanese encephalitis, hepatitis A, rabies</td>
<td>1896 (typhoid)</td>
</tr>
</tbody>
</table>
Virus Vector Vaccine

Phase 3 trial results - vaccine efficacy:

**Efficacy** = Preventing symptomatic disease, COVID-19 (np PCR pos.)

- **AstraZeneca**: 70% efficacy (ChAd, poor results in S-Africa)
- **Janssen J&J**: 85% efficacy (Ad26, 72% USA, 64% SA, 61% Brasil)
- **Sputnik V**: 91% efficacy (Ad26 – Ad5)

Subjects:
- 24,000 (AZ Ox)
- 44,000 (Janssen)
- 22'000 (Sputnik V)

Storage in refrigerator at 2-8 deg C

Immune response to the virus vector (!)

Ab and cellular responses

Data for people >70 years

Sputnik to be produced in Italy (Swiss ADIENNE)

**Janssen J&J**: single-shot scheme

**Vectors**
- non-replicating viruses
  - ChAd, Ad26 or Ad5
  - such as Ebola vaccine

**Vectors**
- "replicating" virus vector
- "non-replicating" virus vector

mRNA Vaccines

Phase 3 trial results - vaccine efficacy:

Efficacy = Preventing symptomatic disease, COVID-19 (np PCR pos.)

- Moderna 94% efficacy
- BNT-Pfizer 95% efficacy

Subjects
- >30,000 (Moderna)
- >37,000 (BNT-Pfizer)

Storage -20 to -70 deg C

Minimal side effects

nAb - cellular immunity (BNT good, Moderna pending)

Fast to adapt (variants, seasonal cycles, etc.)

Sanofi supports production of the BNT-Pfizer vaccine

Kaplan Meier Graphs

- **Moderna mRNA1273**: Efficacy 80% after the first dose after 14 days

- **AstraZeneca-Oxford ChAdOx1**: Efficacy 76% after the first dose after 28 days

- **BioNTech-Pfizer BNT162b2**: Efficacy
Protein-Based Vaccines

Phase 3 trial results - vaccine efficacy:

**Efficacy** = Preventing symptomatic disease, COVID-19 (np PCR pos.)

**Novavax** 95% efficacy (original CoV-2 strain)
Subjects: >15,000 - a further 30,000 planned

**Variants:**
- UK 86%
- S-Africa 60% (HIV-neg. pop) / 49% (mixed pop.)
  *comparison to influenza approx. 50-60%*

Vaccination = S1 protein and adjuvants
Proven methods: Influenza, Hep B, HPV
Possible to store at 2-8 deg C
Approval imminent
**Attenuated and Inactivated Viruses**

**Phase 3 trial results - vaccine efficacy:**
Robust immune response and long-lasting cellular immunity (immune memory) against SARS-CoV-2

**SINOVAC and SINOPHARM**
Traditional vaccines - storage at 2-8 deg C
Dead viruses = all proteins presented to the immune system

**Efficacy:**
SINOVAC - interim 65% (Indonesia), 78% (Brazil), 91% (Turkey)
SINOPHARM - interim data 79% to 86%

**New: COVI-VAC**
Intra-nasal spray - no needle - single-dose
Living, attenuated virus (phase 1 studies)
Poll question #4

If you could choose one vaccine from the following – which one would you prefer?

1. An attenuated virus vaccine (p.ex. SINOVAC)
2. An mRNA-based vaccine (p.ex. MODERNA)
3. A protein-based vaccine (p.ex. NOVAVAX)
4. A viral-vectored vaccine (p.ex. JANSSEN)
Approx. 10-30% of people have pre-existing T cell responses to SARS-CoV2

Common cold strains (endemic CoV): OC43, HKU1, NL63 and 229E

Possibly more rapidly induced antibody responses? Better neutralising antibodies?
T-cell epitopes in the SARS-CoV-2 genome (CD8) (colour MHC restriction)

Four endemic human coronaviruses: OC43, HKU1, NL63 and 229E
- Almost no reactivity to OC43 and HKU1 (2 of 29 epitopes)
- No reactivity to NL63 and 229E
- No reproducible cross-reactivity to the four endemic corona-viruses

Prior exposure to these viruses is unlikely to provide CD8 T-cell-mediated immune protection from SARS-CoV-2
Herd Immunity - Vaccines and Natural Infection

Not vaccinated

Vaccination protection **under** the threshold of herd immunity

Vaccination protection **over** the threshold of herd immunity

Infection passes from individuals with disease to susceptible individuals and spreads throughout the population.

Infection can still pass to susceptible individuals and spread throughout the population except to those who are vaccinated.

Infection cannot spread in the population and susceptible individuals are indirectly protected by vaccinated individuals.

sick  susceptible  protected
Herd Immunity - Vaccines and Natural Infection

\[ R_0 = \beta \tau \]

- \( R_0 \): Basic reproduction number
- \( \beta \): Infection producing contacts per unit time
- \( \tau \): Mean infectious period

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### Values of \( R_0 \) of well-known infectious diseases

<table>
<thead>
<tr>
<th>Disease</th>
<th>Transmission</th>
<th>( R_0 )</th>
</tr>
</thead>
<tbody>
<tr>
<td>Measles</td>
<td>Airborne</td>
<td>12–18</td>
</tr>
<tr>
<td>Diphtheria</td>
<td>Saliva</td>
<td>6–7</td>
</tr>
<tr>
<td>Smallpox</td>
<td>Airborne droplet</td>
<td>3–7</td>
</tr>
<tr>
<td>Polio</td>
<td>Airborne droplet</td>
<td>5–7</td>
</tr>
<tr>
<td>Rubella</td>
<td>Fecal-oral route</td>
<td>3–7</td>
</tr>
<tr>
<td>Airborne droplet</td>
<td></td>
<td>5–7</td>
</tr>
<tr>
<td>Smallpox</td>
<td>Airborne droplet</td>
<td>4–7</td>
</tr>
<tr>
<td>Measles</td>
<td>Airborne droplet</td>
<td>2–5</td>
</tr>
<tr>
<td>Pertussis</td>
<td>Airborne droplet</td>
<td>2–3</td>
</tr>
<tr>
<td>Mumps</td>
<td>Bodily fluids</td>
<td>1.5–2.5</td>
</tr>
</tbody>
</table>

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### Table: Infectious duration, \( D \)

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<th>Disease</th>
<th>( R_0 )</th>
<th>Infectious duration, ( D )</th>
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<tbody>
<tr>
<td>Swine flu 2009</td>
<td>1.2 to 1.6</td>
<td>3 days</td>
</tr>
<tr>
<td>Seasonal flu</td>
<td>1.2</td>
<td>3–6 days</td>
</tr>
<tr>
<td>1918 flu</td>
<td>~2 (up to 20)</td>
<td>4 days</td>
</tr>
<tr>
<td>SARS</td>
<td>~3</td>
<td></td>
</tr>
<tr>
<td>Measles</td>
<td>&gt;10</td>
<td></td>
</tr>
<tr>
<td>Chickenpox</td>
<td>&gt;7</td>
<td></td>
</tr>
<tr>
<td>Mumps</td>
<td>&gt;10</td>
<td></td>
</tr>
</tbody>
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Swine 'flu from Fraser et al. [13], seasonal influenza from Mills et al. [38], SARS from Lipsitch et al. [39], from Anderson and May [10]. doi:10.1371/journal.pone.0012951.t001
Transmission-blocking effect of vaccines...?

Difficult trials!

Confounders: Lockdown effects, behaviour changes, asymptomatic carriers...

Approach: Following close contacts of vaccinated individuals, households etc.

- Moderna: During trial 2/3 drop in asymptomatic carriers in vaccinees (only 2 sampling timepoints 1 month apart)
- AstraZeneca: 49% drop of asymptomatic carriers (vaccinated vs. placebo)
- Pfizer: Ongoing study – swabbing performed every 2 weeks

Evidence supporting sterile immunity regarding post-vaccination status is incomplete!

So... we need to wear a mask even if vaccinated!!
Poll question #3

What safety measures would you consider applying even after the pandemic is over?

1. Wearing a mask in public transport
2. Wearing a mask in the office
3. No more hand-shaking in future!
4. Avoiding large event gatherings (p.ex. cultural, music or sports)
5. All of the above!
What exactly is “long COVID”...?!

Persisting symptoms / sequelae after the normal convalescence

- Fatigue, headaches, shortness of breath, anosmia (loss of smell), muscle weakness, low fever and cognitive dysfunction (brain fog)
- Lingering symptoms 13% (>1 month) – 5% (>2 months) – 2.3% (>3 months)
- Occurs in any age group
- Never observed after vaccination

- Risk Factors: age>50y, obesity (BMI), asthma, >5 symptoms in acute phase
- Chronic fatigue syndrome / myalgic encephalitis (ME) – EBV, Parvovirus

- Role of mitochondria, oxidative stress and the response to antioxidants
  - Mitochondria energy metabolism dysfunctional
  - Impaired recycling of ADP to ATP
  - Impaired correction of reactive oxygen species (ROS)
Delivery Problems: *The Delayed Second Dose...?!*

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<tr>
<th>Company</th>
<th>Schedule</th>
<th>Efficacy</th>
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<td><strong>BNT-Pfizer:</strong></td>
<td>Second dose after three weeks</td>
<td>95% efficacy</td>
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<td>12-14 days after the first dose</td>
<td>about 85-90% efficacy</td>
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<tr>
<td><strong>Moderna:</strong></td>
<td>Second dose after four weeks</td>
<td>94% efficacy</td>
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<td></td>
<td><em>No data for single doses</em></td>
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<tr>
<td><strong>Astra-Zeneca:</strong></td>
<td>Two doses four weeks</td>
<td>70% efficacy</td>
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<td><em>No data for single doses</em></td>
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**Comparisons:** Placebo groups / natural infection / data about BNT-Pfizer (single shot)

- suggest positive vaccination effect after about 12-14 days after first vaccination
- suggest that latency is possible up to 12 weeks for the second dose (now 6 weeks)
- All COVID-19 patients have antibodies - IgA (after 12 days) and IgG (after 21 days)

!!! *Current data does not provide conclusive assessment...*
Benefits of a Vaccine-Induced Immune Response...?

Natural immune response against CoV seems to be short-lived... max. three years (SARS, MERS)
Currently limited available data about the role of immune memory
So far, few cases of re-infections with SARS-CoV-2 have been described

Problems:
- Asymptomatic carrier of the virus in the event of re-exposure (throat)
- SARS-CoV-2 seems to modulate our immune response, to “dampen”
- i.e. Ab production is lower, as is immune memory...

This does not happen, however, with vaccine-induced immune responses
Thus, longer-lasting immune responses against virus proteins and particles are possible

!!! Virus variants and mutations - suboptimal Ab protection from previous infection / vaccination
Vaccine immunity “selection pressure” and “immunity evasive mutations”
LMICs – Impact in Africa…

**Issues:**
- Refusal / avoidance of COVID-19
- Way too few tests
- No prospective vaccination strategy
- Massively underestimated numbers (testing!)

Figures from morgues (Zambia): approx. 19% COVID-19 victims
- RF: Tuberculosis, high blood pressure, HIV/AIDS, alcohol consumption and diabetes
- Massive misjudgement possible...

**COVAX Global Initiative**  
[https://www.gavi.org/covax-facility](https://www.gavi.org/covax-facility)

- Access to vaccinations: 190 participating economies
- Donor-financed doses: 1.3 billion vaccinations for 92 economies
- Goal: Population coverage of 20% by the end of 2021
Outlook – Next Generation Vaccines…

Nasal spray or inhalation vaccines

Synthetically attenuated living virus development (SAVE), synthetic biology to recode genes

-> potentially safe and stable vaccines

Attenuated live vaccines = very effective

• offer long-lasting and broad immunity
• only one dose needed in general

Measles (live) $T_{1/2} 3014\text{ years}$

Tetanus (Protein) $T_{1/2} 11\text{ years}$
Thank you for your attention!

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