Overview

• Epidemiology
• SARS-CoV-2 Variants
• Vaccines
  – Vaccine induced thrombotic thrombocytopenia
  – Potential impact on transmission
Global Trends in COVID-19 Diagnoses & Deaths

>134 Million Confirmed Cases
>4 million cases/week - ↑ 11%

>2.9 Million Confirmed Deaths
71,000 deaths/week - ↑ 11%

Figure 1. COVID-19 cases reported weekly by WHO Region, and global deaths, as of 4 April 2021**
Global Trends in COVID-19 Diagnoses & Deaths

Africa

- ↑ Ethiopia ↓ South Africa & Kenya

Americas

- ↑ US & Argentina ↓ Brazil (still high)

Europe

- ↑ Turkey – Very high Poland
- ↑ Iran – High deaths in Jordan

Western Pacific

- ↑ Philippines & Japan

South-East Asia

- ↑ India & Bangladesh

Eastern Mediterranean

- ↑ Poland
### Country Rates – Hard to Compare

#### Incidence of Cases last 7 days

<table>
<thead>
<tr>
<th>Country</th>
<th>Rate per 100,000</th>
</tr>
</thead>
<tbody>
<tr>
<td>Turkey</td>
<td>419</td>
</tr>
<tr>
<td>France</td>
<td>408</td>
</tr>
<tr>
<td>Poland</td>
<td>358</td>
</tr>
<tr>
<td>Hungry</td>
<td>349</td>
</tr>
<tr>
<td>Jordan</td>
<td>349</td>
</tr>
<tr>
<td>Argentina</td>
<td>276</td>
</tr>
<tr>
<td>Chile</td>
<td>256</td>
</tr>
<tr>
<td>Ukraine</td>
<td>246</td>
</tr>
<tr>
<td>Brazil</td>
<td>218</td>
</tr>
<tr>
<td>USA</td>
<td>117</td>
</tr>
<tr>
<td>India</td>
<td>63</td>
</tr>
<tr>
<td>Namibia</td>
<td>29</td>
</tr>
<tr>
<td>South Africa</td>
<td>10.2</td>
</tr>
</tbody>
</table>

#### Mortality Rate last 7 days

<table>
<thead>
<tr>
<th>Country</th>
<th>Rate per 100,000</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hungry</td>
<td>17.4</td>
</tr>
<tr>
<td>Brazil</td>
<td>9.6</td>
</tr>
<tr>
<td>Poland</td>
<td>9.2</td>
</tr>
<tr>
<td>Ukraine</td>
<td>6.1</td>
</tr>
<tr>
<td>Jordan</td>
<td>5.7</td>
</tr>
<tr>
<td>Italy</td>
<td>5.4</td>
</tr>
<tr>
<td>Chile</td>
<td>4.1</td>
</tr>
<tr>
<td>France</td>
<td>3.2</td>
</tr>
<tr>
<td>Argentina</td>
<td>2.9</td>
</tr>
<tr>
<td>Turkey</td>
<td>1.9</td>
</tr>
<tr>
<td>Jamaica</td>
<td>1.9</td>
</tr>
<tr>
<td>Namibia</td>
<td>1.3</td>
</tr>
<tr>
<td>USA</td>
<td>1.3</td>
</tr>
<tr>
<td>India</td>
<td>0.34</td>
</tr>
</tbody>
</table>

[https://covid19.who.int/table](https://covid19.who.int/table)
## Variant of Concerns – 501Y

<table>
<thead>
<tr>
<th>Mutations</th>
<th>Epidemiology</th>
<th>Impacts</th>
</tr>
</thead>
</table>
| UK – B.1.1.7 N501Y (increases viral binding affinity for ACE), 69/70 deletion (viral escape), D614G | Described UK – 111 countries in all regions                                | ~56% More transmissible  
- More severe  
- ? Decreased Novavax & J&J efficacy |
- More transmissible  
- Possible immune escape  
- Decreased neutralization by sera from convalescent sera and sera from Moderna vaccine recipients (not seen with B.1.1.7)  
- ? Decreased Novavax, J&J and AZ efficacy |
| Brazil – P1 N501Y, D614G, E484K, K417T,                                  | Brazil – 32 countries (Americas, Europe, India)                            | - Reinfections  
- Resurgent epidemic |
### Variant of Concerns – 501Y Lineages

- 3 primary variants – B.1.1.7 (UK - V1), B.1.351 (South Africa, V2), P1 (Brazil, V3)
- Changes mostly affect spike protein – binds ACE
- Phenotypic effects
  - Increased binding affinity for ACE2 receptor (V1, V2, V3)
  - Increased transmissibility (V1 and V2)
  - Increased capacity to overcome prior infection and/or vaccine induced immunity (V2, V3)
  - Increased virulence (V1)

<table>
<thead>
<tr>
<th>Mutation</th>
<th>Variants</th>
<th>Impact</th>
</tr>
</thead>
<tbody>
<tr>
<td>Deletion 11288 &amp; 11296</td>
<td>V1, V2, V3</td>
<td>• Affects nonstructural protein&lt;br&gt;• Decreases cellular response to type 1 interferon – autophagosome</td>
</tr>
<tr>
<td>501Y</td>
<td>V1, V2, V3</td>
<td>• Increase affinity spike protein for ACE2 receptor 3.5-fold</td>
</tr>
<tr>
<td>E484K</td>
<td>V2, V3, some V1</td>
<td>• In presence of 501Y increases affinity for ACE2 receptor 12.7-fold (epistasis)&lt;br&gt;• Decreased neutralization by convalescent sera, vaccine elicited antibody, monoclonal antibody</td>
</tr>
<tr>
<td>S/417</td>
<td>V2 (K417N), V3 (K417T)</td>
<td>• Reduce affinity for ACE2&lt;br&gt;• Increase spike expression – decreased antibody neutralization</td>
</tr>
<tr>
<td>L18F</td>
<td>Some V2, V3</td>
<td>• Some decreased antibody neutralization</td>
</tr>
</tbody>
</table>
New CDC Variant Classification System

- **Variant of interest** – Has **specific genetic markers** associated with changes to receptor binding, reduced neutralization by antibodies generated against previous infection or vaccination, reduced efficacy of treatments, potential diagnostic impact, or predicted increase in transmissibility or disease severity.
  - Examples per CDC – P2 (Brazil), B.1.526 and B.1.525 (New York)
- **Variant of concern** - A variant for which there is evidence of an increase in transmissibility, more severe disease (increased hospitalizations or deaths), significant reduction in neutralization by antibodies generated during previous infection or vaccination, reduced effectiveness of treatments or vaccines, or diagnostic detection failures.
  - Examples – B.1.1.1.7 (UK), P1 (Brazil), B.1.351 (South Africa), B.1.427 and B1.429 (California)
- **Variant of high consequence** - A variant of high consequence has clear evidence that prevention measures or medical countermeasures (MCMs) have significantly reduced effectiveness relative to previously circulating variants.
  - No examples per CDC

**Background:** ChAdOx1 nCoV-19 vaccine previously found to be 66.7% effective, with 75% efficacy against B.1.1.7. Efficacy against B.1.351 variant is uncertain. 

**Design:** Double-blind RCT 

**Population:** 2026 HIV-adults aged 18-65 in South Africa 

**Outcome:** PCR+ symptomatic COVID-19 >14 days post 2nd dose – 95% cases were B.1.351 – no severe cases 

Overall efficacy=21.9% 
B.1.351 efficacy =10.4% 

Source: Madhi SA NEJM 2021
Blood Clots & AstraZeneca Vaccine

- 37 cases of blood clots reported in vaccine recipients in Europe
- 16 EU countries halted use of the vaccine
- Prior to halt, 7 million people in EU and 11 million in UK had received the vaccine
- European Medicine Agency review

Analysis 3/18/21

- The benefits of the vaccine in combating the still widespread threat of COVID-19 (which itself results in clotting problems and may be fatal) continue to outweigh the risk of side effects;
- The vaccine is not associated with an increase in the overall risk of blood clots (thromboembolic events) in those who receive it;
- There is no evidence of a problem related to specific batches of the vaccine or to particular manufacturing sites;
- The vaccine may be associated with very rare cases of blood clots associated with thrombocytopenia
  - Disseminated intravascular coagulation (DIC)
  - 5 cases in vaccine recipients
  - Expected 1 case
  - Mostly younger women

Blood Clots & AstraZeneca Vaccine

- 62 cases cerebral venous sinus thrombosis and 24 splanchnic vein thrombosis as of 3/22/21 – 18 fatalities
- 25 million people vaccinated in EU and UK

Analysis 4/7/21

- Very rare types of thrombosis (with thrombocytopenia) included venous thrombosis in unusual sites and arterial thrombosis.
  - Most of the cases in women < 60 years.
  - Most cases within 2 weeks of 1st dose. Limited experience 2nd dose.
- Healthcare professionals - be alert to the signs and symptoms of thromboembolism and thrombocytopenia
- Tell people receiving the vaccine to seek medical attention if they develop:
  Shortness of breath, chest pain, leg swelling, persistent abdominal pain, neurological symptoms (e.g., headaches and blurred vision) petechiae beyond the site of vaccination after a few days.
- The benefits of the vaccine continue to outweigh the risks for people who receive it.
Vaccine Induced Immune Thrombotic Thrombocytopenia

**Background:** Cause of thromboses following SARS-CoV-2 uncertain. Syndrome resembles heparin-induced thrombocytopenia (HIT)
- Plt activating antibodies against a complex PFR and heparin

**Design:** Case series (11 pts) & testing of 28 suspected cases

**Population:**
- Cases - 11 patients in Germany & Austria
- Blood – 28 people

**Clinical Characteristics**
- 9 women
- Median age 36
- 5-16 days post vaccination
- No one had received heparin prior to onset
- 10 patients had >1 thrombosis - 9 cerebral, 3 splanchnic vein, 3 PE (1 presented with cerebral hemorrhage)
- 6 died

**Laboratory findings**
- Thrombocytopenia – all 11 patients (nadir 20K [range 9-107K])
- 5 patients had lab evidence DIC (elevated d-dimers + abnormal INR, PTT or fibrinogen)

Source: Greinacher A. NEJM 2021
Vaccine Induced Immune Thrombotic Thrombocytopenia

- High levels of platelet activation against PF4-heparin (assay widely available)
  - Platelet factor 4 – cytokine released by platelets and promotes coagulation
- Activation inhibited by heparin
- Activation induced by PF4

Suggests possible mechanism - vaccine either
- Induces a strong immunologic response and autoantibodies that cross react with PF4 OR
- Vaccine induces antibodies against PF4

Second report in NEJM from Norway presents similar findings in 5 patients
- High levels antibody to PF4-polyanion complex
- Inhibited by heparin

Does this happen with J&J or Sputnik vaccines?
- All use adenovirus vectors

Source: Greinacher A. NEJM 2021
Vaccine Induced Immune Thrombotic Thrombocytopenia

**Clinical implication**
- Be alert that vaccine can induce thrombosis with thrombocytopenia
- Test using HIT ELISA – positive test in symptomatic patient in the absence of heparin exposure highly suggestive
- Treat with IVIG +/- non-heparin anticoagulation (DOAC) and steroids

**Table:**

<table>
<thead>
<tr>
<th>Treatment Options</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>High-dose intravenous immune globulin (1 g per kg for 2 days)</td>
<td>Raises platelet count and decreases hypercoagulability (by analogy with autoimmune HIT); inhibits platelet activation by platelet-activating anti-PF4 antibodies (platelet Fcγ receptors)</td>
</tr>
</tbody>
</table>
| Anticoagulants often used to treat heparin-induced thrombocytopenia | Direct oral Xa inhibitors (apixaban, rivaroxaban)  
Direct thrombin inhibitors (argatroban, bivalirudin)  
Indirect (anti-thrombin-dependent) Xa inhibitors: danaparoid (not available in U.S.), fondaparinux |
| Platelet transfusions | Avoid unless presence of bleeding (theoretical prothrombotic risk) |
| Vitamin K antagonist | Contraindicated during acute thrombocytopenia and disseminated intravascular coagulation (microthrombosis associated with protein C depletion) |

**Flowchart:**
- Vaccination with ChAdOx1 nCoV-19; no heparin exposure
- Patient has thrombocytopenia, thrombosis, or both 3–20 days after vaccination
- Immunoassay screening: PF4–heparin ELISA  
  DIC testing: INR, PTT, d-dimer, fibrinogen
- Refer patient serum to laboratory that performs platelet activation tests  
  Serum added to platelets under various conditions: Buffer  
  Heparin (low and high concentrations)  
  PF4 (if available)
- Variable platelet activation with buffer  
  Variable effect of low-dose heparin  
  Strong platelet activation with PF4  
  Inhibition by high-dose heparin
- Diagnosis of vaccine-induced thrombotic thrombocytopenia
- Heparin treatment possible
  Positive
- Heparin treatment possible
  Negative

Source: Greinacher A. NEJM 2021
## International Response

<table>
<thead>
<tr>
<th>Countries Halting Use of AstraZeneca Vaccine</th>
<th>Countries Limiting Use of AstraZeneca Vaccine Persons &lt;50-60</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cameroon</td>
<td>Australia</td>
</tr>
<tr>
<td>Congo</td>
<td>Belgium</td>
</tr>
<tr>
<td>Denmark</td>
<td>Netherlands</td>
</tr>
<tr>
<td>Norway</td>
<td>Portugal</td>
</tr>
<tr>
<td>Philippines</td>
<td>South Korea</td>
</tr>
<tr>
<td></td>
<td>Spain</td>
</tr>
</tbody>
</table>

List likely incomplete.
Chinese Vaccines

- No published phase III RCT data – Makes it hard to interpret data

<table>
<thead>
<tr>
<th>Vaccine</th>
<th>Location/Study</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sinopharm (2 vaccines)</td>
<td>Interim analysis press release: 79%</td>
</tr>
<tr>
<td></td>
<td>UAE report: 86%</td>
</tr>
<tr>
<td></td>
<td>Wuhan vaccine: 72.5%</td>
</tr>
<tr>
<td>Sinvovac (Coronavac)</td>
<td>Turkish study – subgroup report: 91%</td>
</tr>
<tr>
<td></td>
<td>Brazil (two reports): 78%–&gt;50%*</td>
</tr>
<tr>
<td></td>
<td>Indonesia: 65%</td>
</tr>
<tr>
<td></td>
<td>Report from Chile: 3% After first dose</td>
</tr>
<tr>
<td></td>
<td>56.5% 20 days after second dose</td>
</tr>
<tr>
<td>CanSinBio</td>
<td>Pakistan: 75%</td>
</tr>
</tbody>
</table>

BMJ 2021 *50% effective against P1
Vaccines in Media

- Some problems in bringing vaccines to scale
- Need for greater transparency in presenting data on all vaccines
Pfizer Vaccine Efficacy in Adolescents

Background: Effectiveness of COVID-19 vaccines adolescents is unknown

Vaccine: Pfizer mRNA vaccine

Population: 2,260 adolescents aged 12-15 in the U.S.

Outcome: PCR+ SARS-CoV-2 test

Results

- 18 cases in placebo group vs. 0 in vaccinated group
- One month following 2nd dose, neutralizing antibody titers higher than observed in vaccinated persons aged 18-25 in a prior study

Trial in children 6 months to 11 years ongoing

Efficacy mRNA Vaccines Against Asymptomatic Infections: SIREN Study

**Background:** Prevention impact of mRNA vaccines on asymptomatic infection – not just disease – uncertain.
- Mayo Clinic data – decreased asymptomatic infection in HCWs

**Design:** Prospective cohort study healthcare workers in UK – screened 2x weekly for SARS-CoV-2 8/12/20-5/2/21 (B.1.1.7 prevalent)

**Exposure:** $\geq 1$ dose mRNA vaccine (94% Pfizer)

**Outcome:** Relative risk PCR+ asymptomatic infection
- Adjusted – age, race, place residence, local vs. referred

Vaccine at least 70% effective against both asymptomatic and symptomatic infection 21 days after first dose
**Background:** Prevention impact of mRNA vaccines on asymptomatic infection – not just disease – uncertain.

**Design:** RT-PCR used to estimate the quantity of SARS-CoV-2 in specimens taken from people post vaccine and matched unvaccinated persons in Israel

**Outcome:** RT-PCR cycle threshold - higher means less virus

~4 fold reduction in SARS-CoV-2 viral load 12-28 days post vaccination
**Background**: Effectiveness of COVID-19 vaccines in elderly uncertain. Trials include relatively small numbers of persons aged >70. UK delaying second dose

**Design**: Observational data linkage study using electronic health records

**Population**: 14,104 elderly in “care homes” in UK vaccinated 12/4/20-2/12/21

- **Outcome**: PCR+ SARS-CoV-2 test

Source: Hollinghurst J. MedRxiv 2021

### Time to First Positive SARS-CoV-2 PCR

1% tested positive – almost all in first 28 days following vaccination

### Factors Associated with Testing SARS-CoV-2+

<table>
<thead>
<tr>
<th>Factor</th>
<th>&gt;7 days after immunization</th>
<th>21 days after immunization</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prior COVID-19</td>
<td>0.54 (0.30-0.95)</td>
<td>0.69 (0.23-2.0)</td>
</tr>
<tr>
<td>Frailty risk score</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Low</td>
<td>1.60 (0.79-3.24)</td>
<td>4.58 (1.23-17.12)</td>
</tr>
<tr>
<td>Intermediate</td>
<td>1.77 (1.01-2.93)</td>
<td>4.85 (1.68-14.04)</td>
</tr>
<tr>
<td>High</td>
<td>1.37 (0.82-2.3)</td>
<td>2.57 (0.81-8.15)</td>
</tr>
<tr>
<td>Vaccine</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Astrazeneca</td>
<td>Ref</td>
<td>Ref</td>
</tr>
<tr>
<td>Pfizer</td>
<td>3.83 (2.45-6.0)</td>
<td>2.20 (0.82-5.87)</td>
</tr>
</tbody>
</table>
**Background:** How well vaccines will work in immunocompromised patients is uncertain. Such persons may play an important role in development of SARS-CoV-2 variants

**Design:** Convenience sample 436 solid organ transplant patients in US – median 6.2 years since transplant

**Outcome:** Presence of antibody following first dose of vaccine

- 17% (95% CI 14-21%) of patients had detectable antibody
- Factors associated with not having antibody
  - Type of immunosuppressive medication (anti-metabolites)
  - Older age
  - Receipt of Pfizer vaccine (vs. Moderna)

**Highlights need to Ensure Older and Immunosuppressed People Receive Two Doses**

Boyarsky BJ. JAMA 2021
Background: How much protection natural infection provides is uncertain

Design: Population-based observational study 533,381 people tested in Denmark during surge (<June 2020) (11,068 positive 2.2%)

Outcome: Infection during second surge 9/1/20-12/31/20

<table>
<thead>
<tr>
<th></th>
<th>Population</th>
<th>Infection Rate</th>
<th>Adj Rate Ratio</th>
<th>Estimated Protection</th>
</tr>
</thead>
<tbody>
<tr>
<td>Positive 1st</td>
<td>11,068</td>
<td>5.35</td>
<td>0.195</td>
<td>80.0%</td>
</tr>
<tr>
<td>surge</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Negative 1st</td>
<td>514,271</td>
<td>27.06</td>
<td>1 (ref)</td>
<td></td>
</tr>
<tr>
<td>surge</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age</td>
<td></td>
<td>Exposed</td>
<td>Unexposed</td>
<td></td>
</tr>
<tr>
<td>0-34</td>
<td>26,829</td>
<td>5.92</td>
<td>38.13</td>
<td>82.7%</td>
</tr>
<tr>
<td>35-49</td>
<td>12,071</td>
<td>5.16</td>
<td>31.92</td>
<td>80.1%</td>
</tr>
<tr>
<td>50-64</td>
<td>10,111</td>
<td>4.25</td>
<td>27.42</td>
<td>81.3%</td>
</tr>
<tr>
<td>&gt;=65</td>
<td>4980</td>
<td>8.01</td>
<td>16.92</td>
<td>47.1%</td>
</tr>
</tbody>
</table>

Protection through natural infection is not complete, particularly in the elderly.

Highlights need to vaccinate people with prior infection

Hansen CH. Lancet 2021
Duration of Viral Shedding: Meta-Analysis

• 35 studies 3,385 people – 2,955 symptomatic & 338 asymptomatic

• Results
  – Mean viral shedding time 16.8 days
  – Longer shedding associated with:
    • Adults (vs. children)
    • Chronic disease
    • Symptomatic infections
    • Receipt of steroids (p=0.06)

Source: Yan D. Front Public Health 2021
Summary

- **Epidemiology** - Cases and deaths increasing internationally
- **Variants** - Continue to be a big concern – Increased focus on specific genes – new system for classifying variants
- **Vaccines**
  - **Bad news** – Vaccine induced thrombotic thrombocytopenia with AstraZeneca vaccine, some problems in manufacturing (J&J in US, ? Sputnik), lack of transparency and maybe efficacy issues with Chinese vaccines, need for faster roll out, vaccine hesitancy
  - **Good news** – We have vaccines with very high efficacy, increasing evidence that vaccines prevent transmission, major side-effects are rare
Questions and Comments