

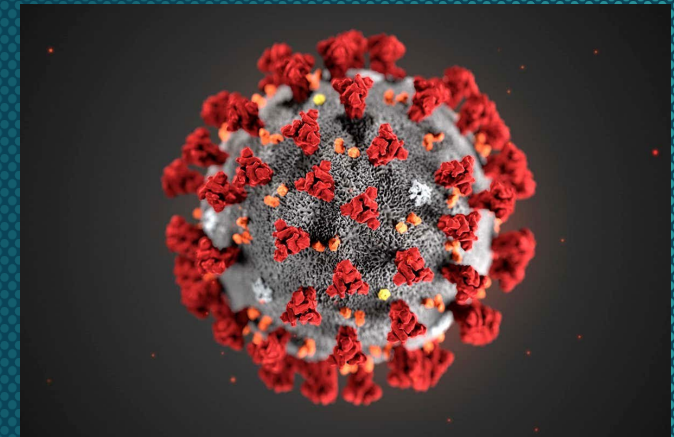


*University of Washington
Public Health Capacity Building Center*

COVID-19 Clinical Update

I-TECH Videoconference April 12, 2021

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Last Updated: April 12, 2021



I-TECH

International Training and Education Center for Health

Overview

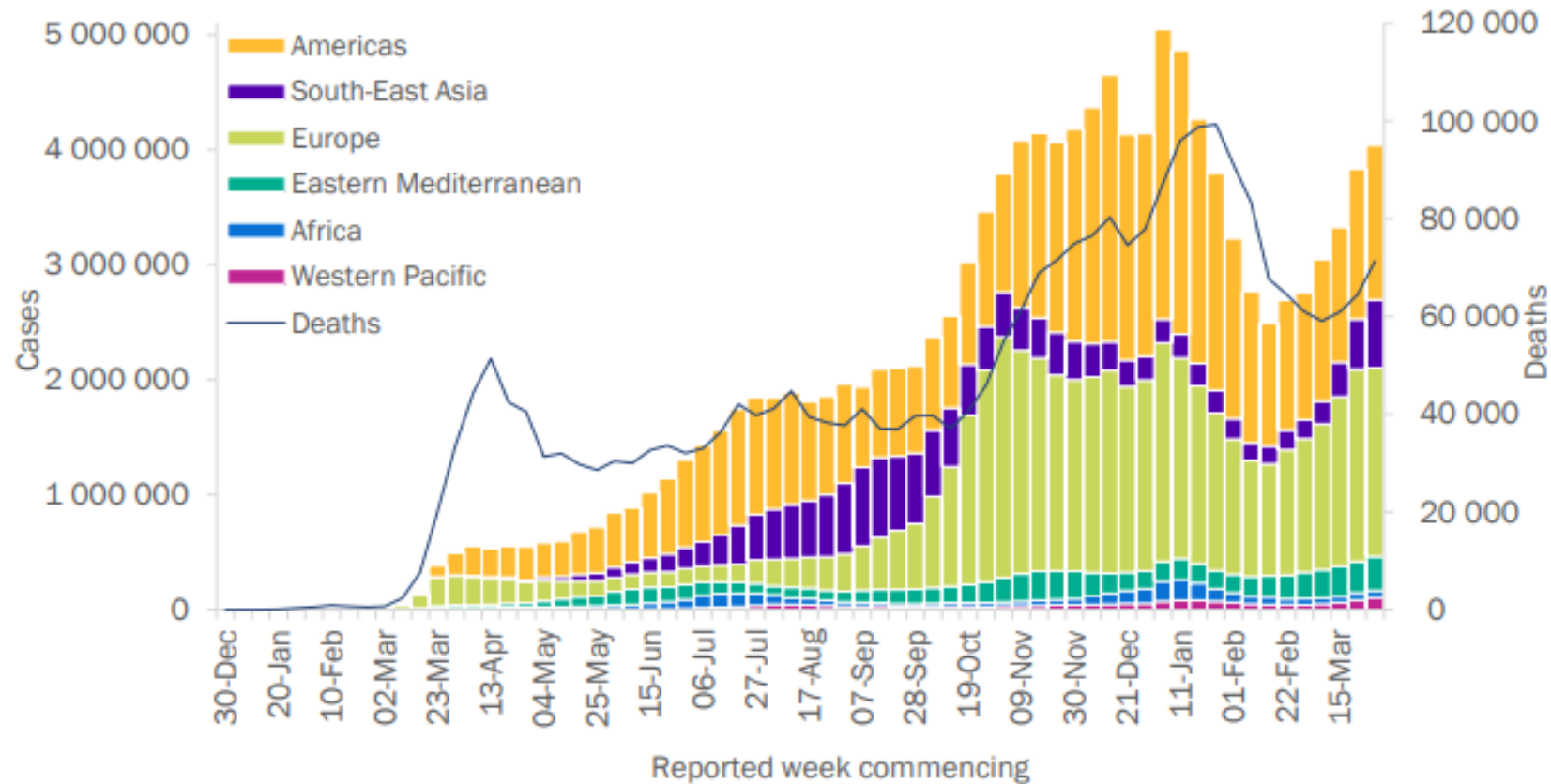
- Epidemiology
- SARS-CoV-2 Variants
- Vaccines
 - Vaccine induced thrombotic thrombocytopenia
 - Potential impact on transmission

Global Trends in COVID-19 Diagnoses & Deaths

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

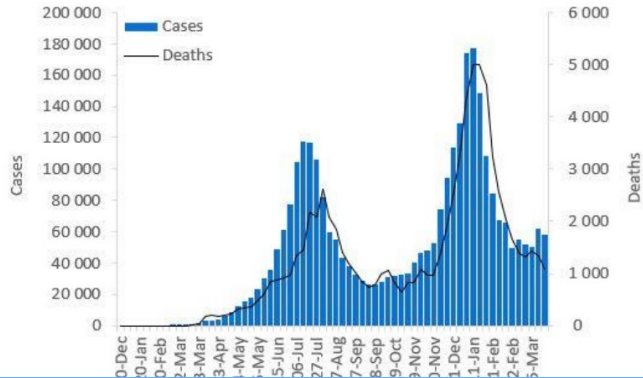
>2.9 Million Confirmed Deaths
71,000 deaths/week - ↑ 11%

Figure 1. COVID-19 cases reported weekly by WHO Region, and global deaths, as of 4 April 2021**



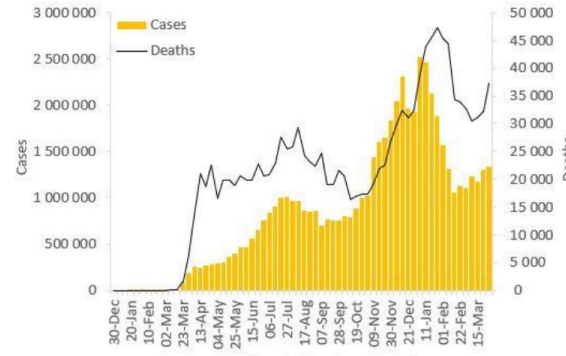
Global Trends in COVID-19 Diagnoses & Deaths

Africa



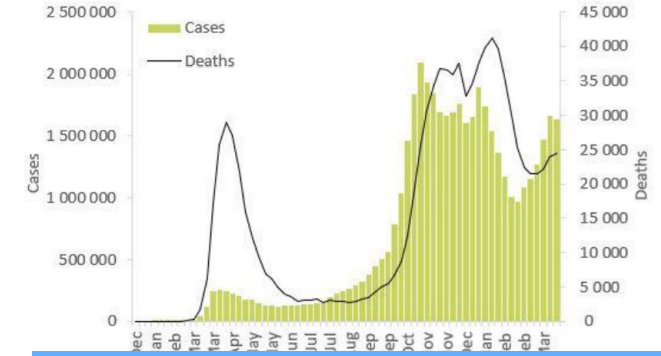
↑ Ethiopia ↓ South Africa & Kenya

Americas



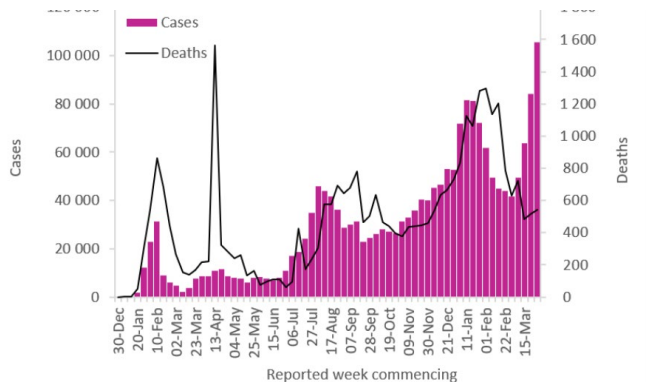
↑ US & Argentina ↓ Brazil (still high)

Europe



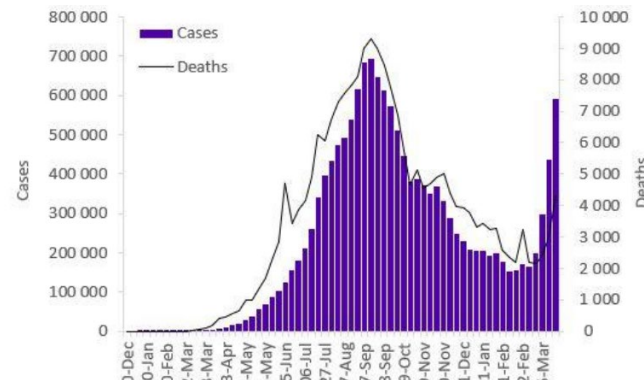
↑ Turkey – Very high Poland

Western Pacific



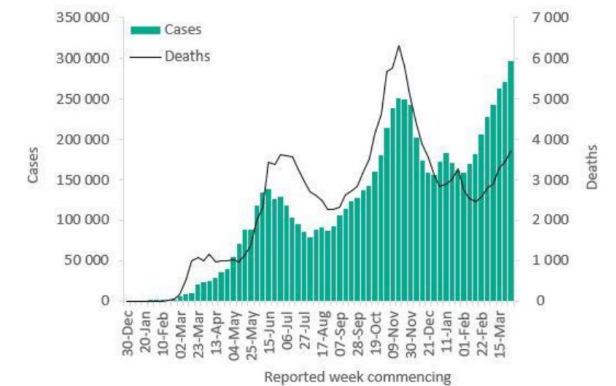
↑ Philippines & Japan

South-East Asia



↑ India & Bangladesh

Eastern Mediterranean



↑ Iran – High deaths in Jordan

Country Rates – Hard to Compare

Incidence of Cases last 7 days

	Rate per 100,000
Turkey	419
France	408
Poland	358
Hungry	349
Jordan	349
Argentina	276
Chile	256
Ukraine	246
Brazil	218
USA	117
India	63
Namibia	29
South Africa	10.2

Mortality Rate last 7 days

	Rate per 100,000
Hungry	17.4
Brazil	9.6
Poland	9.2
Ukraine	6.1
Jordan	5.7
Italy	5.4
Chile	4.1
France	3.2
Argentina	2.9
Turkey	1.9
Jamaica	1.9
Namibia	1.3
USA	1.3
India	0.34

Variant of Concerns – 501Y

	Mutations	Epidemiology	Impacts
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
South Africa - B.1.351	N501Y, D614G, E484K, K417N/T,	Described South Africa – 52 countries in 4 WHO regions (none in South America)	- Higher viral load - 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)

Mutation	Variants	Impact
Deletion 11288 & 11296	V1, V2, V3	<ul style="list-style-type: none">• Affects nonstructural protein• Decreases cellular response to type 1 interferon – autophagosome
501Y	V1, V2, V3	<ul style="list-style-type: none">• Increase affinity spike protein for ACE2 receptor 3.5-fold
E484K	V2, V3, some V1	<ul style="list-style-type: none">• In presence of 501Y increases affinity for ACE2 receptor 12.7-fold (epistasis)• Decreased neutralization by convalescent sera, vaccine elicited antibody, monoclonal antibody
S/417	V2 (K417N), V3 (K417T)	<ul style="list-style-type: none">• <u>Reduce</u> affinity for ACE2• Increase spike expression – decreased antibody neutralization
L18F	Some V2, V3	<ul style="list-style-type: none">• Some decreased antibody neutralization

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

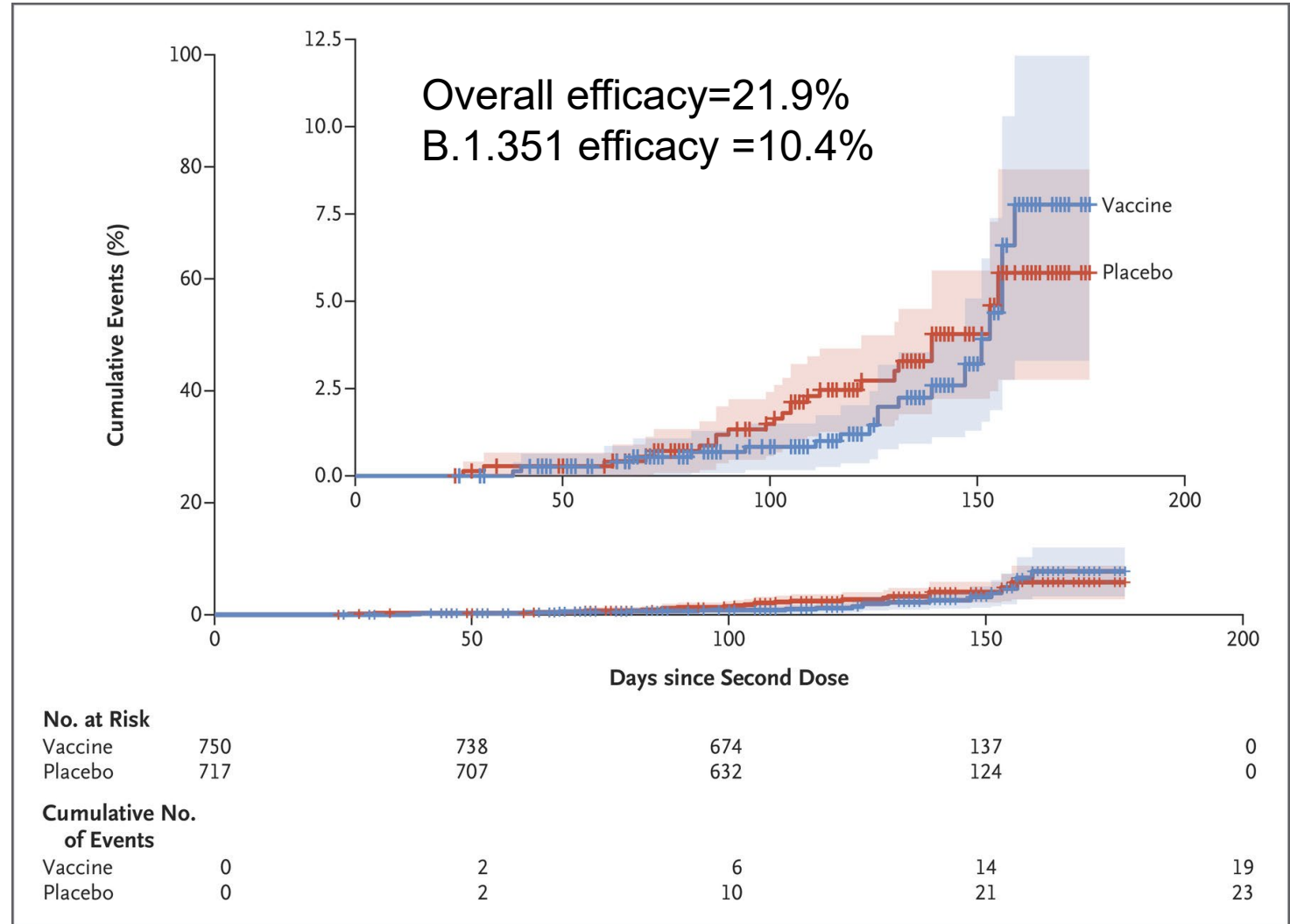
AstraZeneca Vaccine Against B.1.351

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**



Source: Madhi SA NEJM 2021

Blood Clots & AstraZeneca Vaccine

Analysis 3/18/21

- 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

- 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.
- Mechanism - ? immune response -> atypical heparin-induced-thrombocytopenia like disorder.
- 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)

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

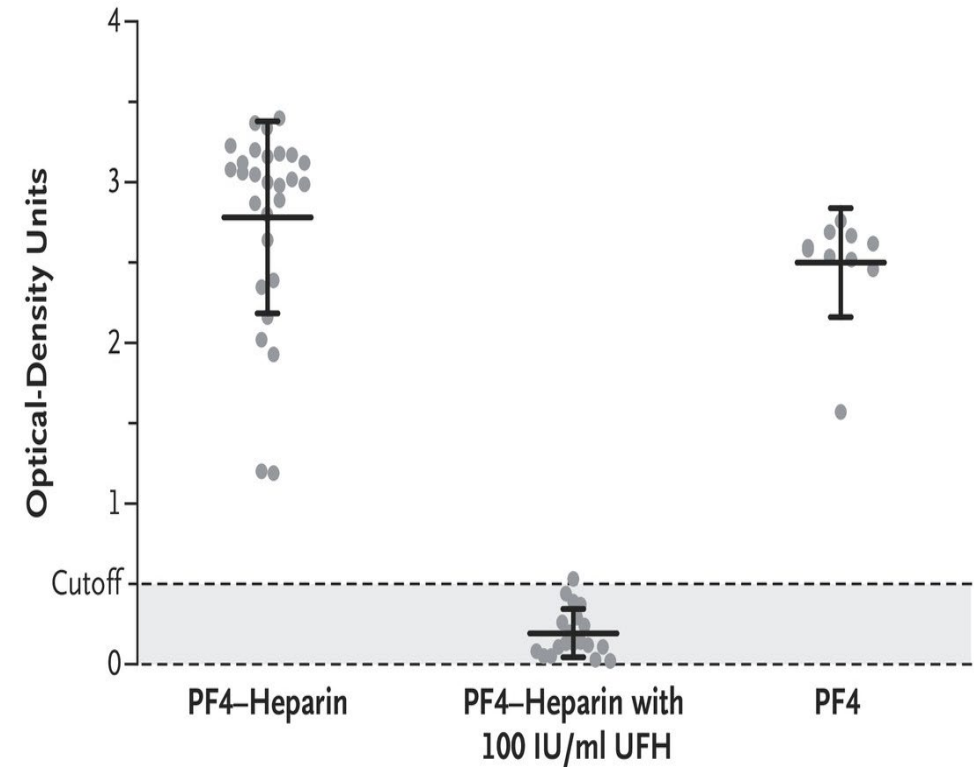
Second report in NEJM from Norway presents similar findings in 5 patients

- High levels antibody to PF4-polyanion complex
- Inhibited by heparin

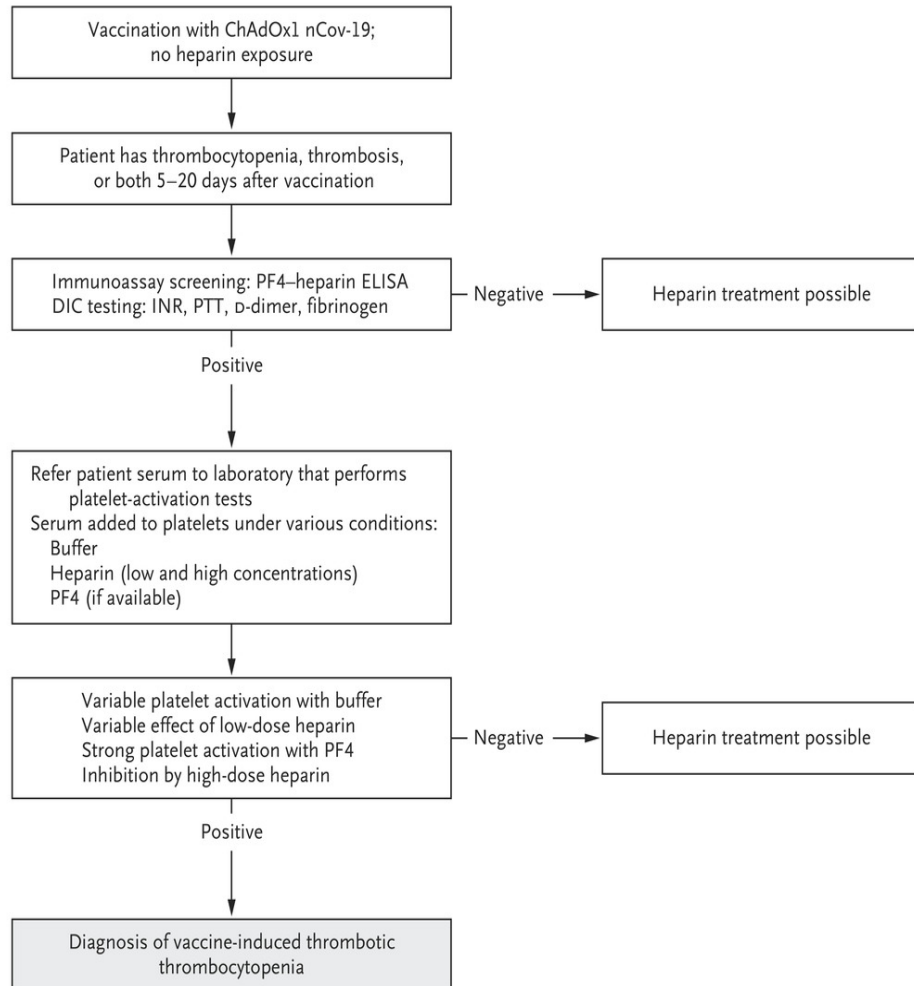
Does this happen with J&J or Sputnik vaccines?

- All use adenovirus vectors

C ELISA Results for Combined Serum Samples from 28 Patients with VITT



Vaccine Induced Immune Thrombotic Thrombocytopenia



Treatment Options

High-dose intravenous immune globulin
(1 g per kg for 2 days)

Comment

Raises platelet count and decreases hypercoagulability (by analogy with autoimmune HIT); inhibits platelet activation by platelet-activating anti-PF4 antibodies (platelet Fcγ receptors)

Anticoagulants often used to treat heparin-induced thrombocytopenia

Direct oral Xa inhibitors (apixaban, rivaroxaban)
Direct thrombin inhibitors (argatroban, bivalirudin)
Indirect (antithrombin-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)

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

International Response

Countries Halting Use of AstraZeneca Vaccine

Cameroon
Congo
Denmark
Norway
Philippines

Countries Limiting Use of AstraZeneca Vaccine Persons <50-60

Australia
Belgium
Netherlands
Portugal
South Korea
Spain

List likely incomplete

Chinese Vaccines

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

Sinopharm (2 vaccines)	
Interim analysis press release	79%
UAE report	86%
Wuhan vaccine	72.5%
Sinovac (Coronavac)	
Turkish study – subgroup report	91%
Brazil (two reports)	78%→50%*
Indonesia	65%
Report from Chile	3% After first dose 56.5% 20 days after second dose
CanSinBio	
Pakistan	75%

Vaccines in Media

The New York Times

[The Coronavirus Outbreak](#) > | [LIVE](#) Latest Updates | [Maps and Cases](#) | [Risk Near You](#) | [Who Can Get Vaccinated?](#) | [Vaccine Q](#)

Slovakia Claims a Bait-and-Switch With the Russian Vaccines it Ordered

Slovakia says that Sputnik V doses it received did “not have the same characteristics and properties” as a version endorsed by a respected British medical journal.

The Washington Post

Democracy Dies in Darkness

Asia & Pacific

Effectiveness of Chinese vaccines ‘not high’ and needs improvement, top health official says



The New York Times

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Johnson & Johnson Coronavirus Vaccine Deliveries Are About to Take Big Dip in the U.S.

Last Updated April 11, 2021

- 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)

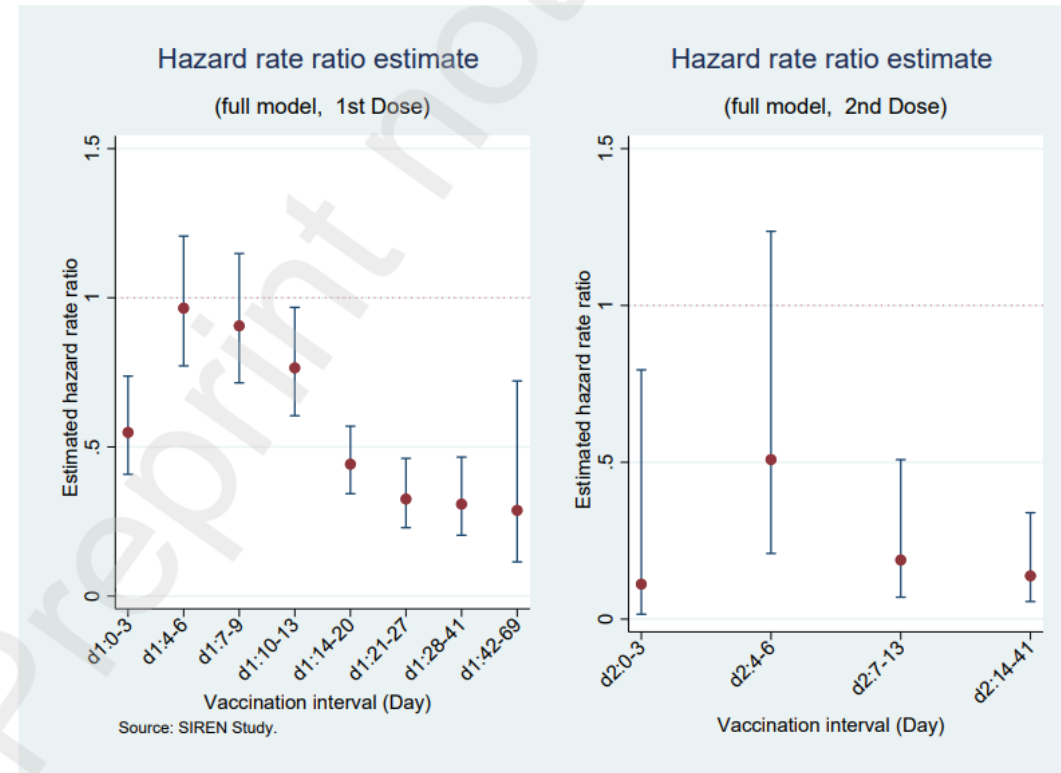
Exposure: ≥ 1 dose mRNA vaccine (94% Pfizer)

Outcome: Relative risk PCR+ asymptomatic infection

- Adjusted – age, race, place residence, local vs. referred

Hall HV. Lancet (in press)

Figure 2a: Graph of adjusted Hazard Ratios at post-vaccination intervals, 7 December 2020 – 5 February 2021, full cohort (n=23,324)



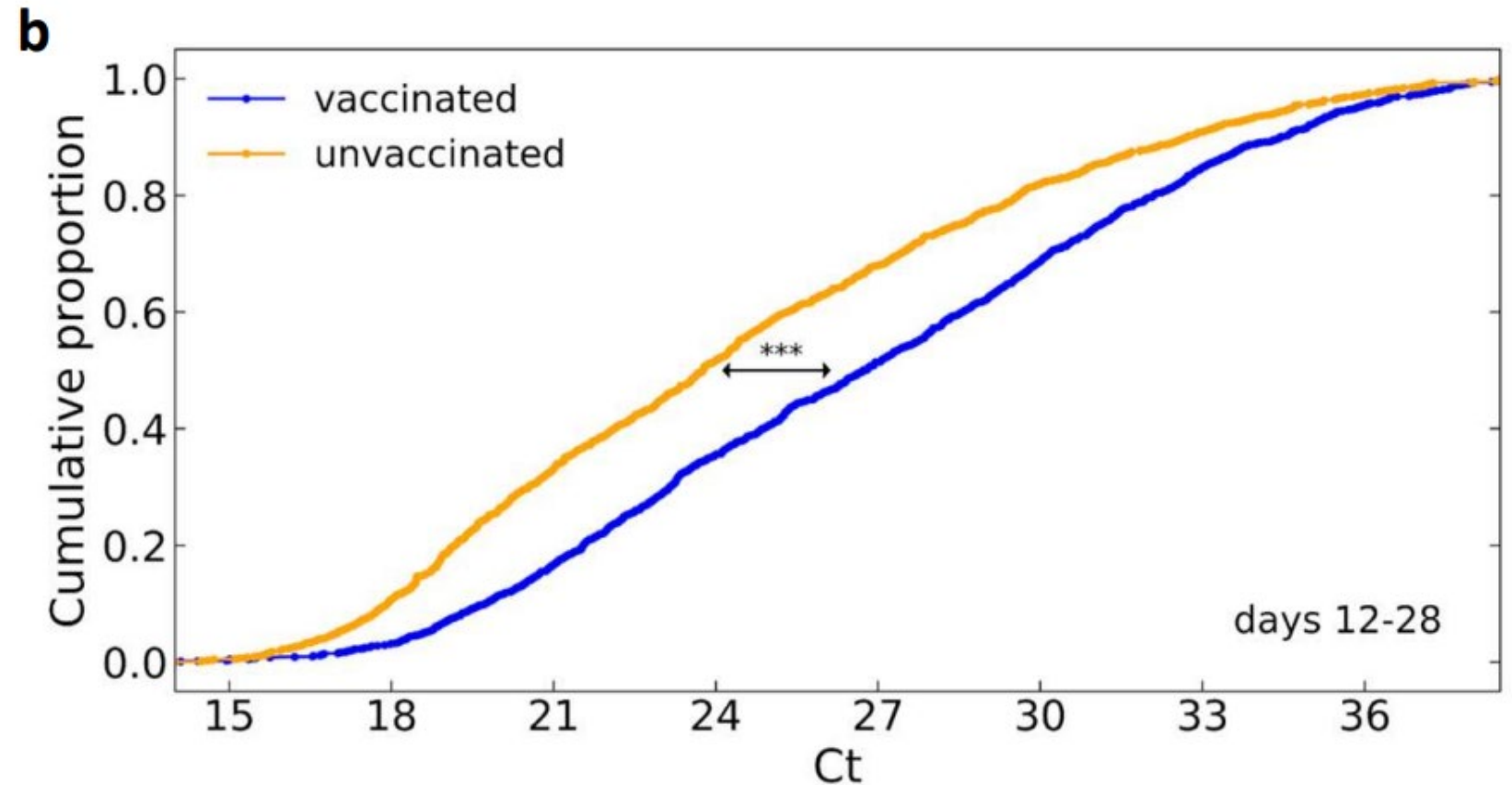
Vaccine at least 70% effective against both asymptomatic and symptomatic infection 21 days after first dose

Impact mRNA Vaccine on Quantity of Virus

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

Single Dose Vaccine Efficacy in Elderly

Background: Effectiveness of COVID-19 vaccines in elderly uncertain. Trials includes relatively small numbers of persons aged >70. UK delaying second dose

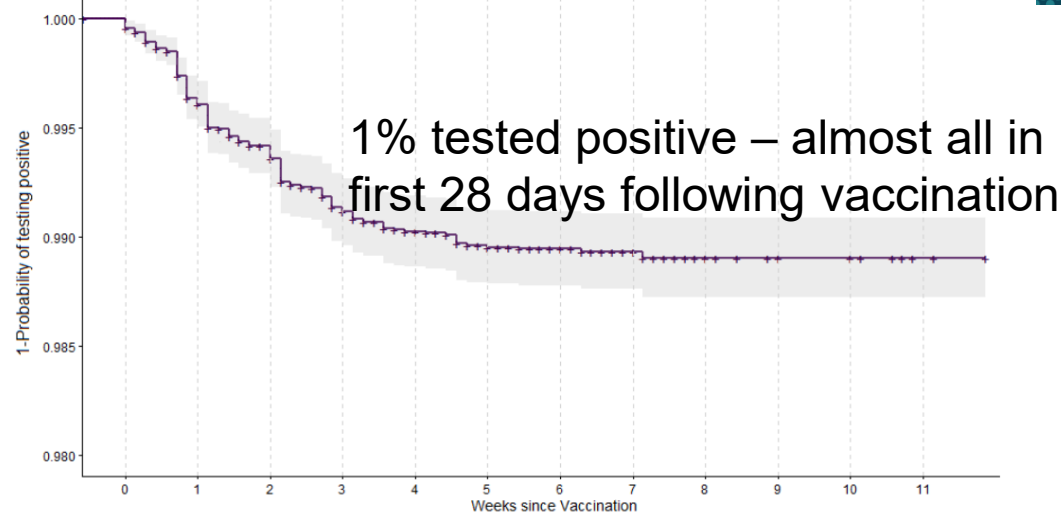
Design: Observational data linkage study using electronic health records

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 2011

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



Factors Associated with Testing SARS-CoV-2+

	>7 days after immunization	21 days after immunization
Prior COVID-19	0.54 (0.30-0.95)	0.69 (0.23-2.0)
Frailty risk score		
Low	1.60 (0.79-3.24)	4.58 (1.23-17.12)
Intermediate	1.77 (1.01-2.93)	4.85 (1.68-14.04)
High	1.37 (0.82-2.3)	2.57 (0.81-8.15)
Vaccine		
Astrazeneca	Ref	Ref
Pfizer	3.83 (2.45-6.0)	2.20 (0.82-5.87)

mRNA Vaccine Antibody Response in Solid Organ Transplant Recipients

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

How Protective is Natural Infection?

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

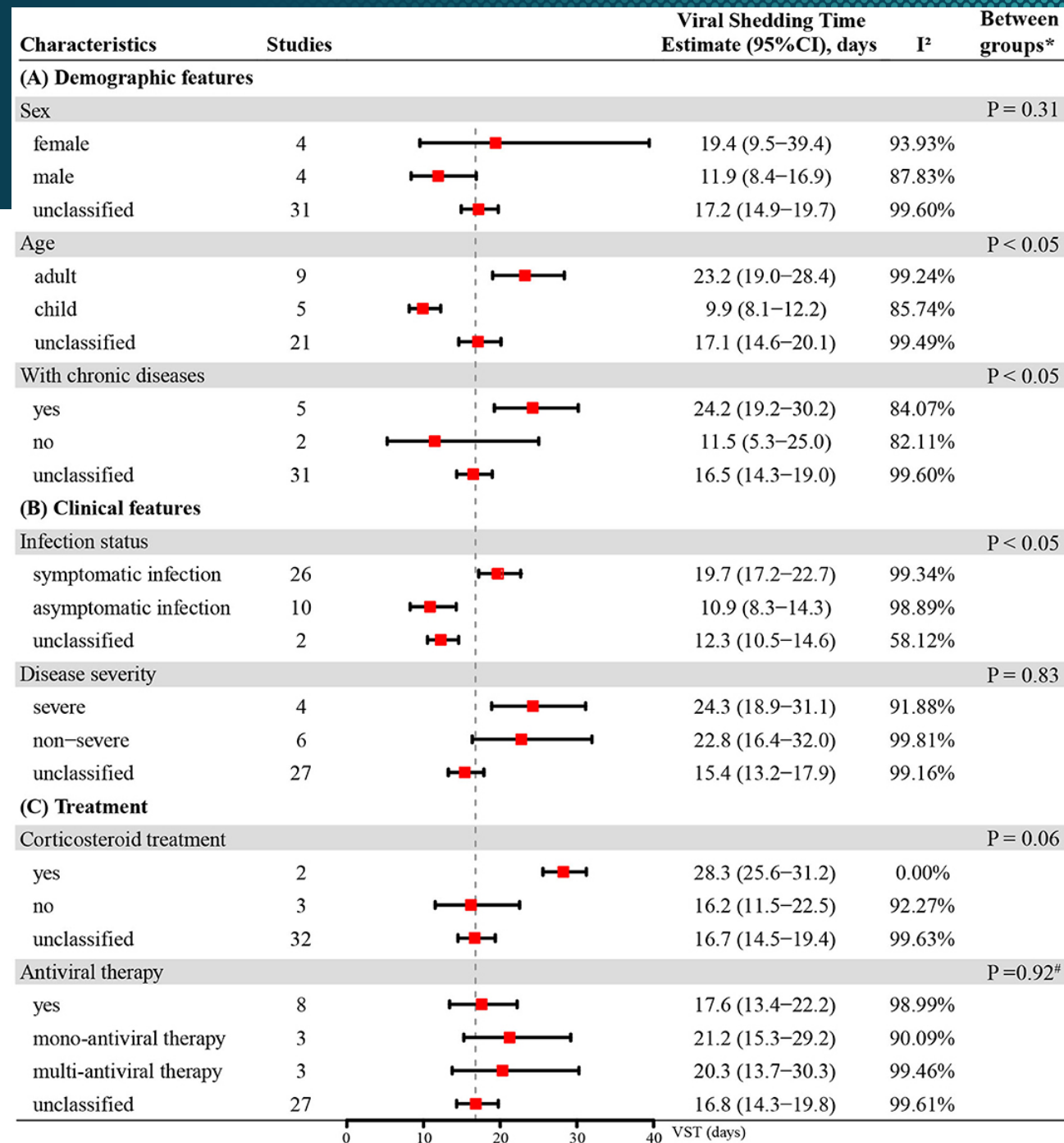
	Population	Infection Rate		Adj Rate Ratio	Estimated Protection
Positive 1 st surge	11,068	5.35		0.195	80.%%
Negative 1 st surge	514,271	27.06		1 (ref)	
		Exposed	Unexposed		
Age					
0-34	26,829	5.92	38.13	0.173	82.7%
35-49	12,071	5.16	31.92	0.199	80.1%
50-64	10,111	4.25	27.42	0.187	81.3%
>=65	4980	8.01	16.92	0.529	47.1%

Protection through natural infection is not complete, particularly in the elderly.
Highlights need to vaccinate people with prior infection

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