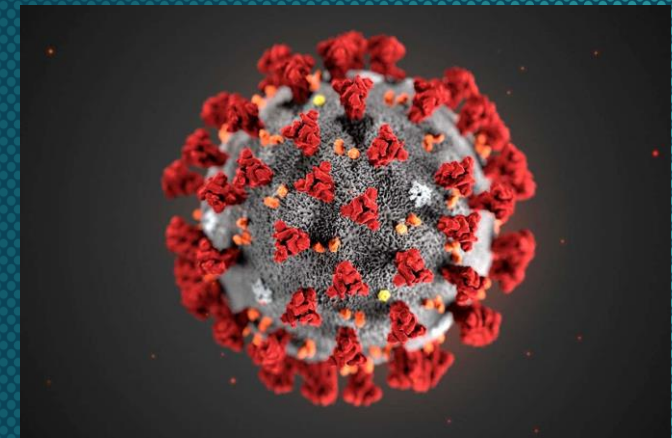


COVID-19 Clinical Update

I-TECH Videoconference December 14, 2020

Matthew Golden, MD, MPH
Professor of Medicine, University of Washington
Director, PHSKC HIV/STD Program
Director, UW Center for AIDS and STD



Last Updated: December 14, 2020

Overview

- Epidemiology
- Vaccines & herd immunity
- Isolation and quarantine
- Treatment

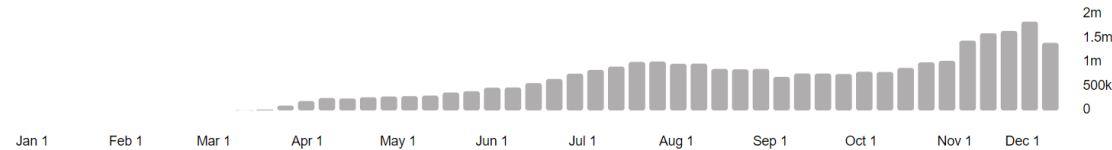
Global Trends in COVID-19 Diagnoses

>70 Million Confirmed Cases

>1.6 Million Confirmed Deaths

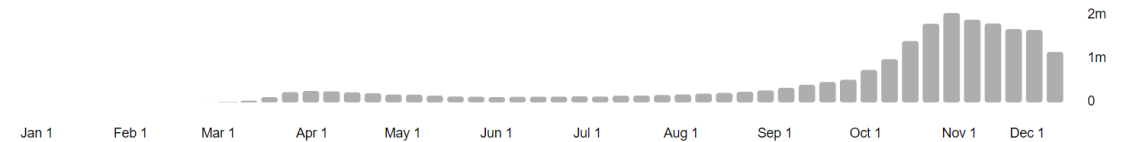
Americas

29,467,378
confirmed cases



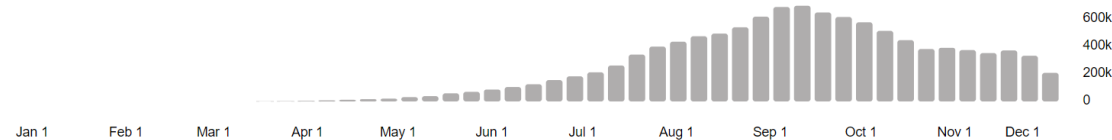
Europe

21,413,786
confirmed cases



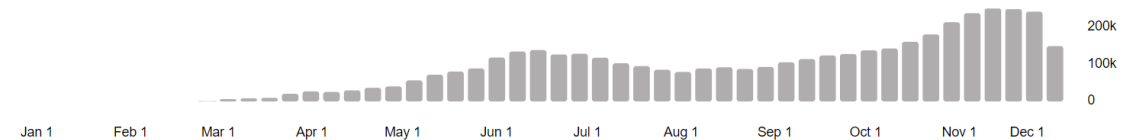
South-East Asia

11,279,038
confirmed cases



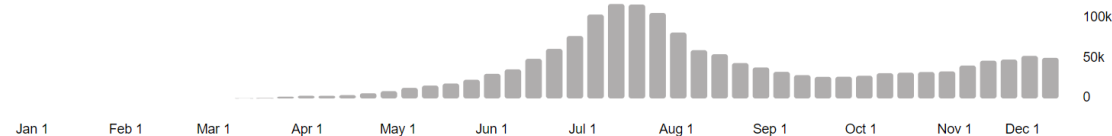
Eastern Mediterranean

4,438,471
confirmed cases



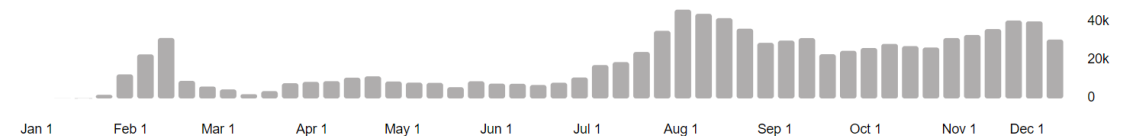
Africa

1,598,266
confirmed cases



Western Pacific

945,334
confirmed cases

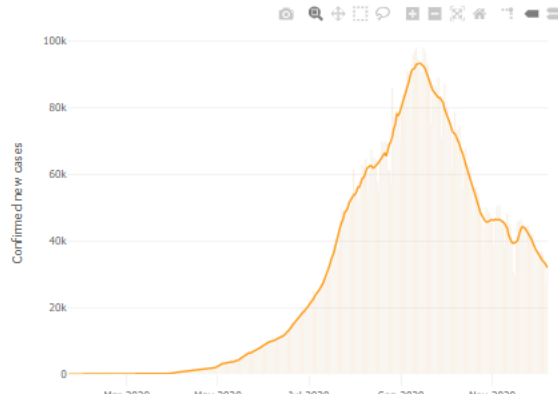


Cumulative Global COVID-19 Diagnoses

INDIA

New cases confirmed each day (7-day-average) ▼ DOWN

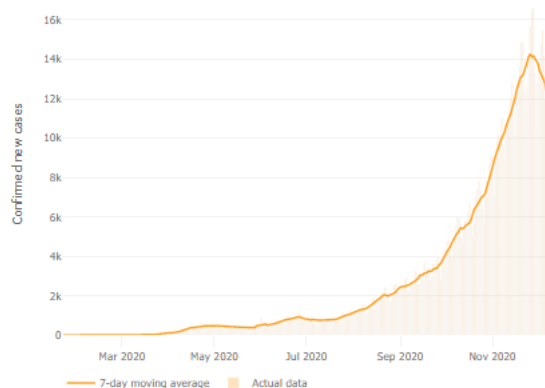
The first case of COVID-19 in India was reported 313 days ago on 1/29/2020. Since then, the country has reported 9,735,850 cases, and 141,360 deaths.



UKRAINE

New cases confirmed each day (7-day-average) ▼ DOWN

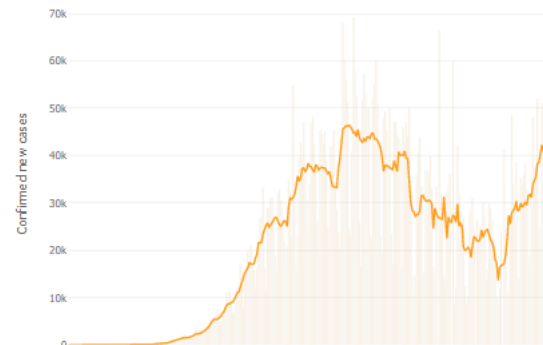
The first case of COVID-19 in Ukraine was reported 280 days ago on 3/2/2020. Since then, the country has reported 855,054 cases, and 14,413 deaths.



BRAZIL

New cases confirmed each day (7-day-average) ▼ DOWN

The first case of COVID-19 in Brazil was reported 286 days ago on 2/25/2020. Since then, the country has reported 6,674,999 cases, and 178,159 deaths.



UNITED STATES

New cases confirmed each day (7-day-average) ▲ UP

The first case of COVID-19 in United States was reported 321 days ago on 1/21/2020. Since then, the country has reported 15,164,885 cases, and 286,237 deaths.



IRAN

New cases confirmed each day (7-day-average) ▼ DOWN

The first case of COVID-19 in Iran was reported 293 days ago on 2/18/2020. Since then, the country has reported 1,062,397 cases, and 50,917 deaths.



GERMANY

New cases confirmed each day (7-day-average) ▼ DOWN

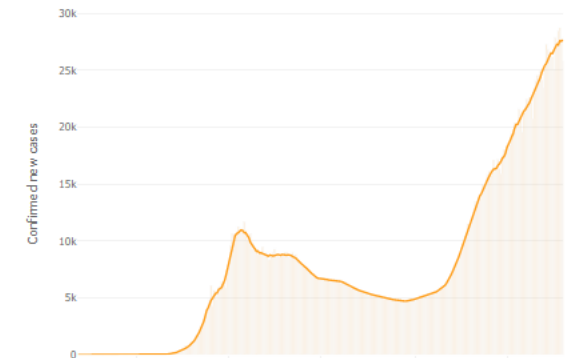
The first case of COVID-19 in Germany was reported 316 days ago on 1/26/2020. Since then, the country has reported 1,229,269 cases, and 20,002 deaths.



RUSSIA

New cases confirmed each day (7-day-average) ▲ UP

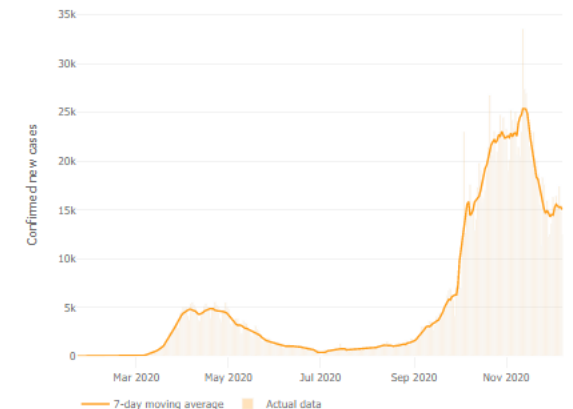
The first case of COVID-19 in Russia was reported 312 days ago on 1/30/2020. Since then, the country has reported 2,492,713 cases, and 43,674 deaths.



UNITED KINGDOM

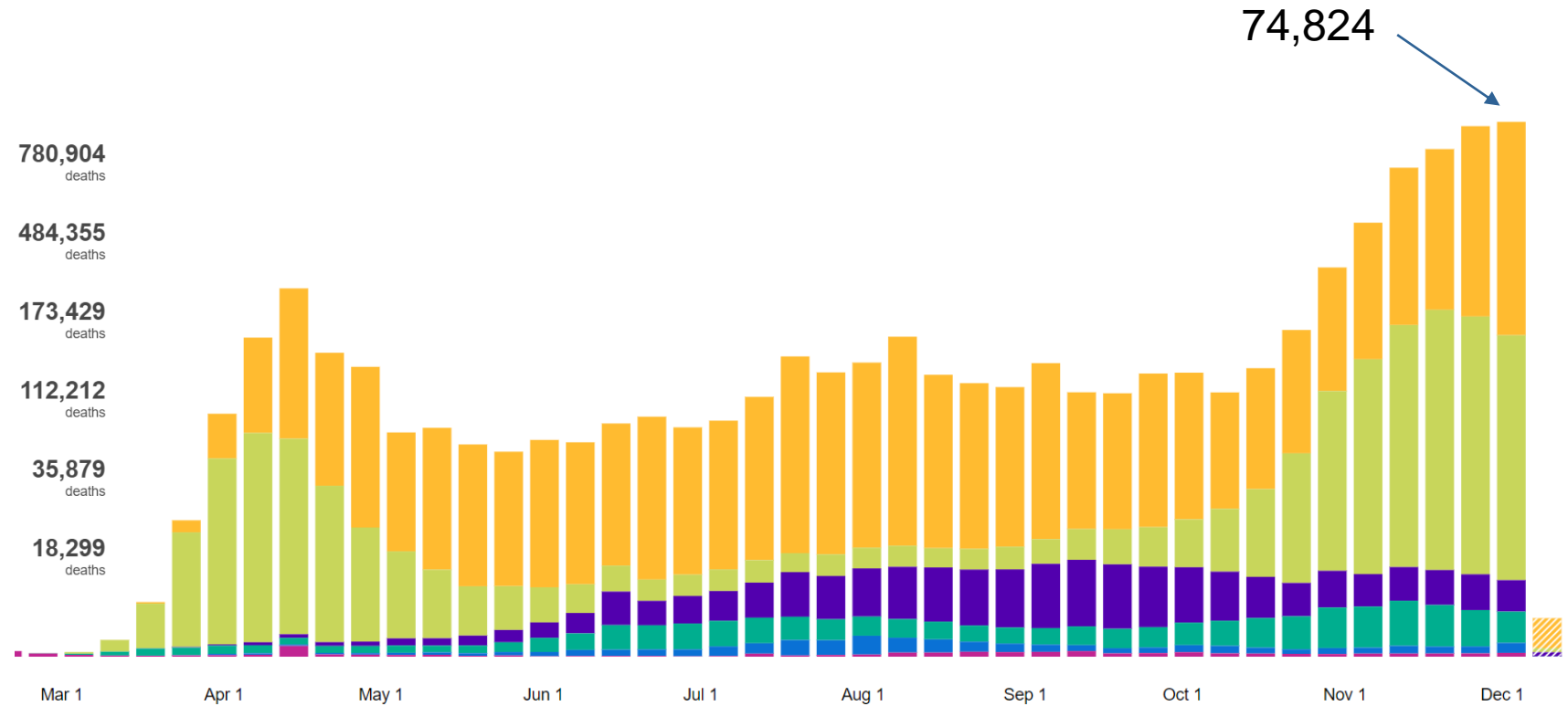
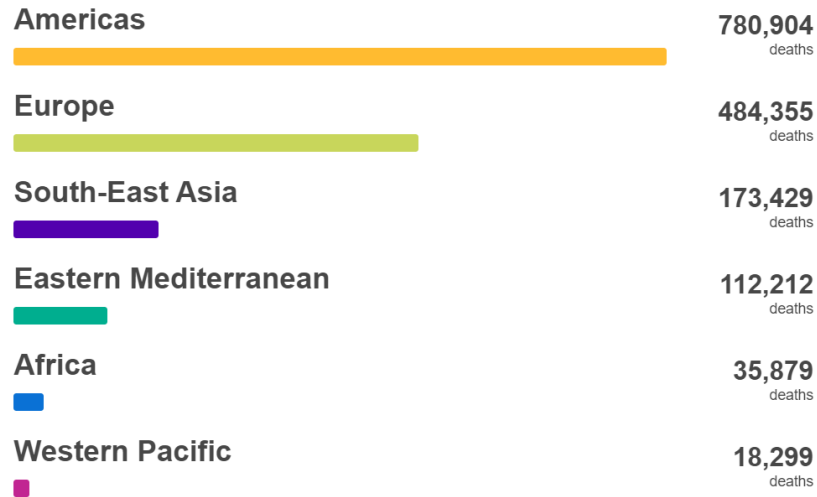
New cases confirmed each day (7-day-average) ▼ DOWN

The first case of COVID-19 in United Kingdom was reported 312 days ago on 1/30/2020. Since then, the country has reported 1,754,911 cases, and 62,130 deaths.



Trends Global COVID-19 Deaths

Situation by WHO Region



Vaccines: mRNA 1273 – Moderna

Vaccine: mRNA vaccine using lipid nanoparticle express full-length viral spike protein

Administration: 2 doses 28 days apart

Storage: long-term -20°C, stable 30 days 2-8°C

Population: >30,000 in US – 7,000 age >65

Outcome: Symptomatic COVID-19

Results

- 196 cases
 - 185 in placebo group & 11 in vaccine group
 - **94.1% efficacy**
- 30 severe cases (1 death)
 - All occurred in placebo group
- Severe adverse events
 - Injection site pain – 2.7%
 - Fatigue – 9.7%
 - Myalgias – 8.9%
 - Arthralgia – 5.2%
 - HA – 4.5%

Initial outcomes announced Nov. 16 (95 cases) – updated Nov 30

Vaccines: BNT162b2 – BioNTech & Pfizer

Vaccine: mRNA vaccine using lipid nanoparticle express full-length viral spike protein

Administration: 2 doses 21 days apart

Storage: long-term -70°C +/- 10°C

Population: 41,135 (2 doses) - includes subgroup with prior COVID-19

Outcome: Symptomatic COVID-19

Results

- 170 cases
 - 162 in placebo group & 8 in vaccine group
 - **95% efficacy**
- Efficacy consistent across risk groups (94% in persons >age 65)
- 10 severe cases
 - 9 in placebo group
- 52% efficacy with single dose
- Severe adverse events
 - Injection site pain – 2.7%
 - Fatigue – 3.8%
 - HA – 2%

Initial outcomes announced Nov. 18

Vaccines: ChAdOxnCoV-19/AZD1222 (University of Oxford, AstraZeneca, and the Serum Institute of India)

Vaccine: adenovirus vector expressing spike protein

Design: Interim pooled analysis 2 RCTs – COVID19 vs MenACWY vaccine – safety from 4 single-blind RCTs.

2 dosing regiments

- ½ dose T0 then full dose in 1 month (n=2,741)(LD/SD) – error in measuring dose – 11 days enrollment – no older patients (age >55) – booster added later
- 2 full doses 1 month apart (n= 8895)(SD/SD) – 21% age >55 – more CV disease and DM

Population: 11,636

Storage: 2-8°C 6 months

Outcome: Virologically confirmed symptomatic COVID-19 in seronegative participants >14 days after 2nd dose

- UK & Brazil – Sx prompting assessment - fever >37.°C, cough, SOB, anosmia or ageusia
- South Africa – Above + myalgia, chills, ST, HA, rhinorrhea, diarrhea, fatigue, N/V, anorexia
- Weeks swabs to detect infection in asymptomatics in UK

	Total number of cases	ChAdOx1 nCoV-19		Control		Vaccine efficacy (CI*)
		n/N (%)	Incidence rate per 1000 person-years (person-days of follow-up)	n/N (%)	Incidence rate per 1000 person-years (person-days of follow-up)	
All LD/SD and SD/SD recipients	131	30/5807 (0.5%)	44.1 (248 299)	153/5829 (2.6%)	226.0 (247 228)	70.4% (58.9 to 82.9)†
COV002 (UK)	86	18/3744 (0.5%)	38.6 (170 369)	127/3744 (3.4%)	127.0 (127 000)	72.3% (58.9 to 82.9)†
LD/SD recipients	33	3/1367 (0.2%)	14.9 (73 313)	30/1374 (2.2%)	150.2 (72 949)	90.0% (67.4 to 97.0)‡
SD/SD recipients	53	15/2377 (0.6%)	56.4 (97 056)	38/2430 (1.6%)	142.4 (97 499)	60.3% (28.0 to 78.2)
COV003 (Brazil; all SD/SD)	45	12/2063 (0.6%)	56.2 (77 930)	33/2025 (1.6%)	157.0 (76 780)	64.2% (30.7 to 81.5)‡
All SD/SD recipients	98	27/4440 (0.6%)	56.2 (77 930)	71/4455 (1.6%)	157.0 (76 780)	64.2% (30.7 to 81.5)‡
Other non-primary symptomatic COVID-19 disease¶	18	7/5807 (0.1%)	12.2 (248 299)	10/5829 (0.2%)	16.8 (168 000)	27.3% (-17.2 to 54.9)
Any symptomatic COVID-19 disease	149	37/5807 (0.6%)	56.2 (77 930)	81/5829 (1.4%)	142.4 (97 499)	60.3% (28.0 to 78.2)
Asymptomatic or symptoms unknown (COV002)	69	20/3388 (0.6%)	60.8 (151 673)	40/3350 (1.2%)	106.0 (152 138)	27.3% (-17.2 to 54.9)
LD/SD recipients	24	1/1367 (0.07%)	6.8 (73 313)	10/1374 (0.7%)	100.6 (61 730)	58.9% (1.0 to 82.9)‡
SD/SD recipients	45	19/2377 (0.8%)	92.9 (97 056)	30/2430 (1.2%)	122.9 (90 408)	3.8% (-72.4 to 46.3)
Any NAAT-positive swab	221	68/5807 (1.2%)	100.0 (248 299)	153/5829 (2.6%)	226.0 (247 228)	55.7% (41.1 to 66.7)

Overall Efficacy=70.4%

**Low Dose Efficacy=90%
Standard Dose Efficacy=62%***

**Over Asymptomatic Efficacy=27%
LD/SD=58.9% (95% CI 1-82.9%)
SD/SD=3.8%**

**10 Severe Cases All Occurred
in Control Group**

*P=.01

Vaccines: ChAdOxnCoV-19/AZD1222 (University of Oxford, AstraZeneca, and the Serum Institute of India)

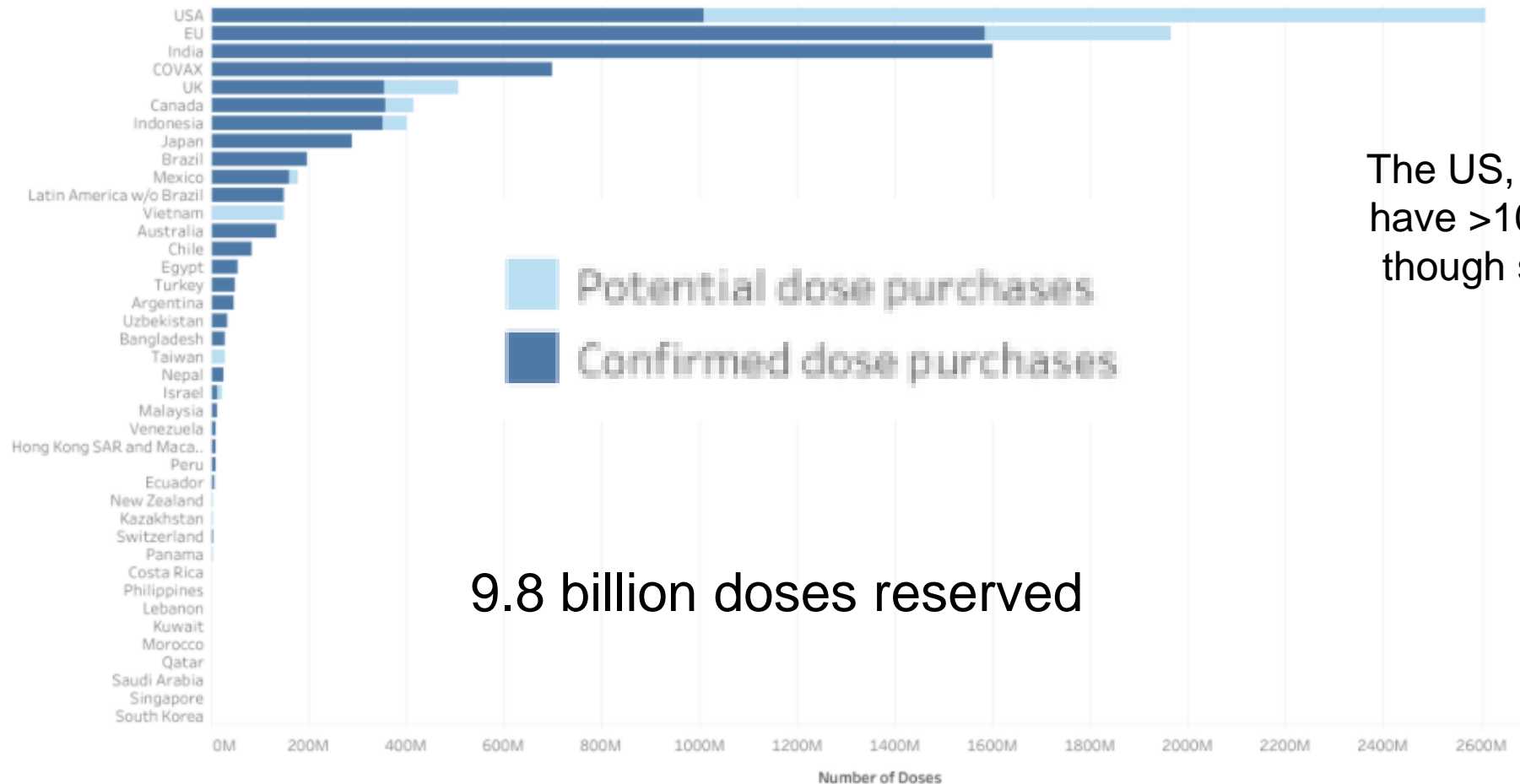
- Adverse events similar in two arms: 79 COVID vs 89 MenACWY – 3 cases transverse myelitis – 2 in COVID arm – 3 of 3 cases not thought to be related
- Why was the lower dose better?
 - Statistical anomaly vs. true difference (i.e. it wasn't better)
 - Differences in populations and vaccine administration
 - SD/SD was older with more CV disease and DM – efficacy was not higher in those aged <55 years
 - LD/SD received second dose at a mean of 69 days vs. 36 days in SD/SD
 - Among SD/SD recipients, efficacy did not differ comparing <6 weeks to 2nd dose to >6 weeks – does not entirely address the issue
 - Immunologic response to vector decreased 2nd dose efficacy
 - Low dose induces more memory T cell response

Vaccine Supply

	2020	2021
Moderna	100-125 million 1 st quarter 2021	500 million-1 billion
BNT162b2	50 million	1.3 billion
AstroZenica	200 million	3 billion

Bilateral Vaccine Purchase Agreements

COVID-19 Vaccine Advance Market Commitments by Country



The US, UK, EU, and Canada all have >100% coverage reserved, though some vaccines may not work

Vaccine Prioritization: US National Academy Sciences

Phase 1	Phase 2	Phase 3	Phase 4
<p>Phase 1a: High-risk health workers & first responders</p> <p>Phase 1b:</p> <ul style="list-style-type: none">- Older persons living in congregate or over crowded settings- Persons with comorbidities that place them at significantly high risk for severe disease	<ul style="list-style-type: none">• K-12 teachers and staff & child care workers• Critical workers high risk settings• Persons with comorbidities that place them at moderate risk• Homeless shelters and groups homes• Prisons/jails• Older adults not in phase 1	<ul style="list-style-type: none">• Young adults• Children• Workers at increased risk not in phases 1-2	<ul style="list-style-type: none">• Everyone else

In each group, prioritize geographic areas based on social vulnerability index

Vaccine Prioritization: WHO COVID-19 Vaccines Global Access (COVAX)

Goal

Protect public health and minimize societal and economic impact by reducing COVID-19 mortality

Indicative
Target
groups

Frontline workers in health and social care settings

All countries receive doses to cover 3% of their population.
This would be enough to cover all workers involved in health and social care work in most countries.

High-risk adults

All countries receive additional doses to cover a total of 20% of their population (in tranches)
This could include the elderly, adults with comorbidities or others depending on locally relevant risk factors

Further priority groups

Countries receive doses to cover more than 20% of their population.
This would cover additional priority populations.

Timing

← **Phase 1:** Countries receive doses proportionally to their total population* →

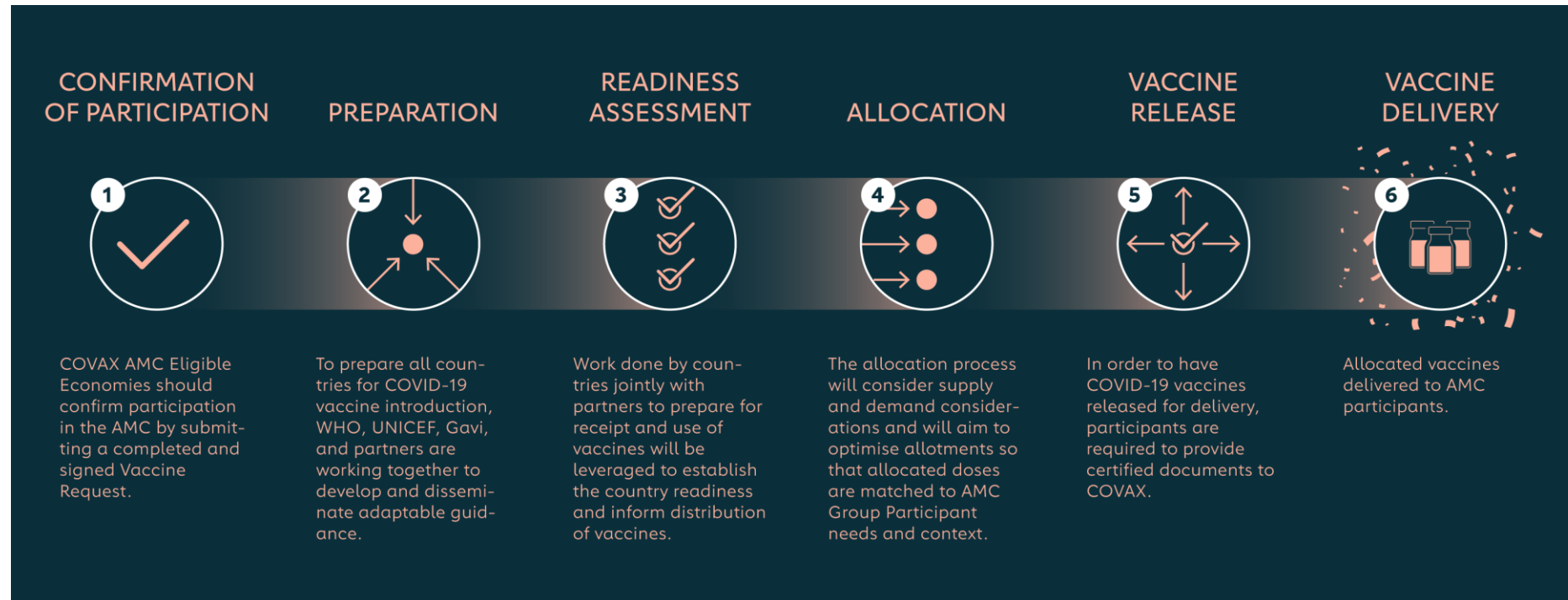
← **Phase 2:** Timing may be based on consideration of country need, vulnerability and COVID-19 threat →

A buffer will also be set aside for humanitarian deployment

*The fundamental principle applies that all countries receive doses at the same rate to the extent possible, notwithstanding likely practical limitations to be further worked out (e.g. minimum delivery volumes)

Gavi COVAX Advanced Market Commitment

- Goal is to assure equitable access during initial phase of immunization through advance purchase of vaccine for low and middle income nations
 - Goal 1 billions doses by the end of 2021
- >\$2 billion pledged so far - \$5 billion needed (November 15, 2020)
- All vaccine manufactures have expressed support
 - AstraZeneca – 64% of vaccine will go to low and middle income nations



Herd Immunity

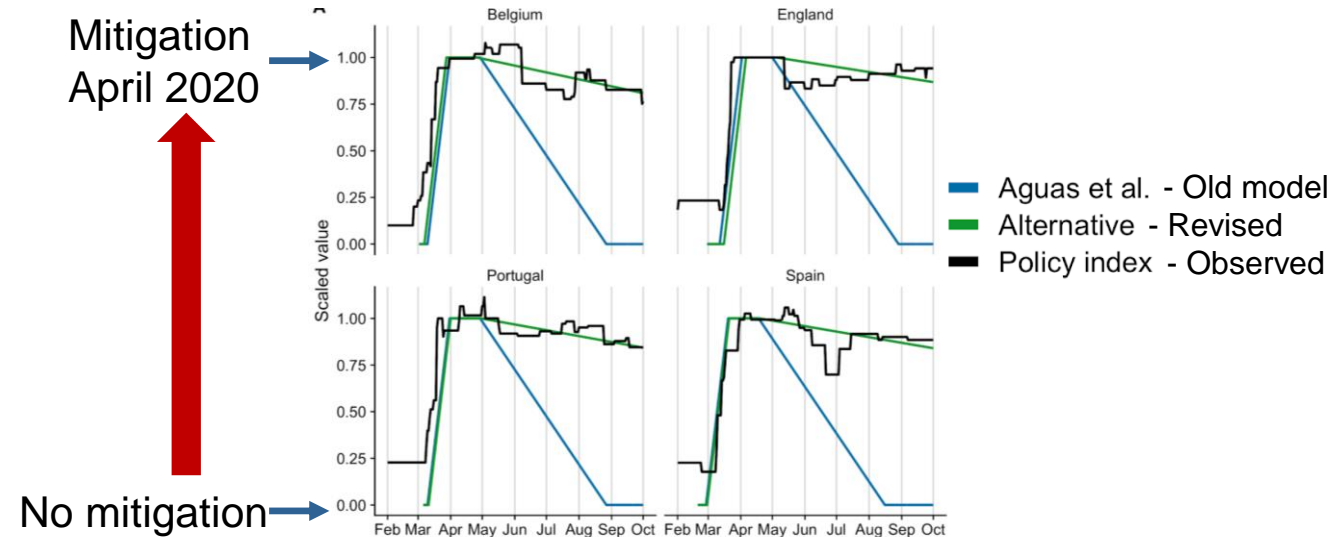
- Approximately 10% of the world's population is thought to have already had COVID-19.
- Estimates of the point where herd immunity will control the virus vary from 6-60%
- Great Barrington Declaration – “Focused Protection”
 - “Allow those who are at minimal risk of death to live their lives normally to build up immunity to the virus through natural infection, while better protecting those who are at highest risk.”

October 4 2020

- Based on model suggesting 10-20% infection would lead to herd immunity

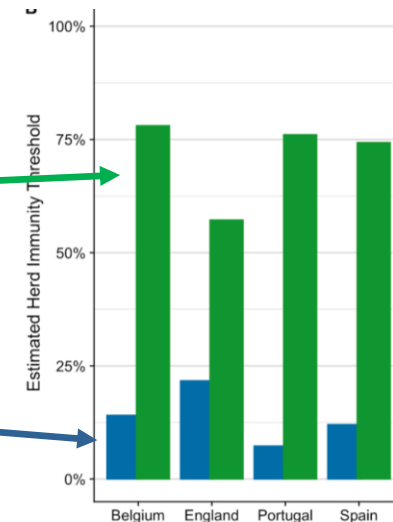
Herd Immunity

- Study objective: reevaluate model on which Barrington Declaration was based
 - Model fitted to observed data
 - Original model assumed that initial decline in COVID-19 in Europe resulted from social distancing, masks, etc., but then population returns to normal behavior.
 - Revision parameterized to observed levels of mitigation



Revised model suggests 60-75% infection would induce immunity

Original model suggested 10-20% infection would induce immunity



Should People Who Have Had COVID-19 Be Immunized?

Natural Infection Better than Vaccine	Vaccine Better than Natural Infection
Measles	Tetanus
Mumps	H. Flu type b
	VZV
	HPV

- Antibody levels to SARS-CoV-2 wane over time – may not matter – memory T & B cells persist
 - H1N1 flu in 1918 resulted in protected until the 9th decade of life
- Small number of case reports of recurrent infection – proven by new strains
- Vaccines may induce higher levels of antibody than natural infection
- AstraZenica – Efficacy among SARS-CoV-2 seropositive persons at baseline similar – no data
- Conclusion:
 - Lots of uncertainty and would be good to see data
 - I favor getting immunized

Rationale for Changing Guidance

- Current quarantine guidelines are hard for people to follow
 - Particularly difficult for people who need to go to work in order to live and those with small homes or many people in their households
 - If we ask too much of people, do we decrease adherence?
- Scientific advances suggest that the current 14 day quarantine period may not be necessary in all instances
 - There continues to be substantial uncertainty about how safe a shorter period of quarantine is
 - New CDC guidance is based on mathematical models that seek to estimate how much transmission might occur if people leave quarantine early - Not real data
 - Model is driven by 3 main issues – None precisely known
 - Length of the incubation period – Time from infection to symptoms
 - Test sensitivity – What percentage of infected people have a positive test when?
 - Relationship between the timing of infection to infectiousness



Risk of Transmission Based on CDC Model

- Implications of model need to be interpreted based on the absolute risk of transmission

Days Quarantine	Residual Risk as a Percent of Baseline Risk				Absolute Risk Resulting from Approach Among 200 Infected People (Assume 2 Transmissions if Nothing is Done)
	No Testing		RT-PCR Testing Before Leaving Quarantine		
	Median	Range	Median	Range	Median
7	10.7	10.3-22.1	4.0	2.3-8.6	400->16 (upper estimate=34)
10	1.4	0.1-10.6	0.3	0.0-2.4	400->6 (upper estimate=42)
14	0.1	0.0-3.0	0.0	0.0-1.2	400->4 (upper estimate=12)



New CDC Quarantine Guidance

OLD CDC GUIDANCE

- Quarantine 14 days from last exposure
- Ongoing exposure (households)
 - 14 day quarantine starts when isolation ends for case
 - If multiple people in household with COVID-19, quarantine starts on latest day of isolation of any infected person in the house

NEW CDC GUIDANCE: 3 OPTIONS

- **14 day** quarantine from last exposure - **PREFERRED**
 - No test timed to decrease duration of quarantine
 - No symptoms of COVID-19*
- **OR**
- **10 day** quarantine from last exposure
 - No test timed to decrease duration of quarantine
 - No symptoms of COVID-19*
 - Continue symptoms monitoring and masks through day 14
- **OR**
- **7 day** quarantine from last exposure
 - Requires all of the following:
 - Negative test 5 days or more after last exposure
 - No symptoms of COVID-19*
 - Continue symptom monitoring and masks through day 14

* Persons with new symptoms should retest and stay in isolation as probably cases for 10 days after onset of symptoms



Quarantine Guidelines Internationally

Organization	Quarantine Recommendation	Last Update
WHO	14 days	August 2020
UK	14 Days	November 5, 2020
South Africa	14 days	May 2020
Australia	14 days	October 13, 2020
South Korea	14 days	February 2020
Denmark	Test 4 days after exposure and retest 2 days later (Contact can leave isolation if 1 st test is negative)	December 9, 2020
Netherlands	10 days*	?
France	7 days	September 14, 2020
Germany	"The period of isolation does not end automatically but only once it has been lifted by the responsible authority"	November 30, 2020

* Not explicit – based on guidance on stated incubation period

UW COVID Treatment Guidelines

DISEASE SEVERITY

PANEL'S RECOMMENDATIONS

Not Hospitalized,
Mild to Moderate COVID-19

There are insufficient data to recommend either for or against any specific antiviral or antibody therapy. SARS-CoV-2 neutralizing antibodies (**bamlanivimab** or **casirivimab plus imdevimab**) are available through EUAs for outpatients who are at high risk of disease progression.^a These EUAs do not authorize use in hospitalized patients.

Dexamethasone should not be used (**AIII**).

Hospitalized^a But Does Not Require Supplemental Oxygen

Dexamethasone should not be used (**AIIa**).

There are insufficient data to recommend either for or against the routine use of **remdesivir**. For patients at high risk of disease progression, the use of remdesivir may be appropriate.

Hospitalized^a and Requires Supplemental Oxygen

(But Does Not Require Oxygen Delivery Through a High-Flow Device, Noninvasive Ventilation, Invasive Mechanical Ventilation, or ECMO)

Use one of the following options:

- **Remdesivir**^{b,c} (e.g., for patients who require minimal supplemental oxygen) (**BIIa**)
- **Dexamethasone**^d plus **remdesivir**^{b,c} (e.g., for patients who require increasing amounts of supplemental oxygen) (**BIII**)^{e,f}
- **Dexamethasone**^d (e.g., when combination therapy with remdesivir cannot be used or is not available) (**BI**)

Hospitalized^a and Requires Oxygen Delivery Through a High-Flow Device or Noninvasive Ventilation

Use one of the following options:

- **Dexamethasone**^{d,f} (**AI**)
- **Dexamethasone**^d plus **remdesivir**^{b,c} (**BIII**)^{e,f}

Hospitalized^a and Requires Invasive Mechanical Ventilation or ECMO

Dexamethasone^d (**AI**)^g

Screenshot

Category/Grade

Definition

Strength of recommendation

A	Good evidence to support a recommendation for or against use.
B	Moderate evidence to support a recommendation for or against use.
C	Poor evidence to support a recommendation.

Quality of evidence

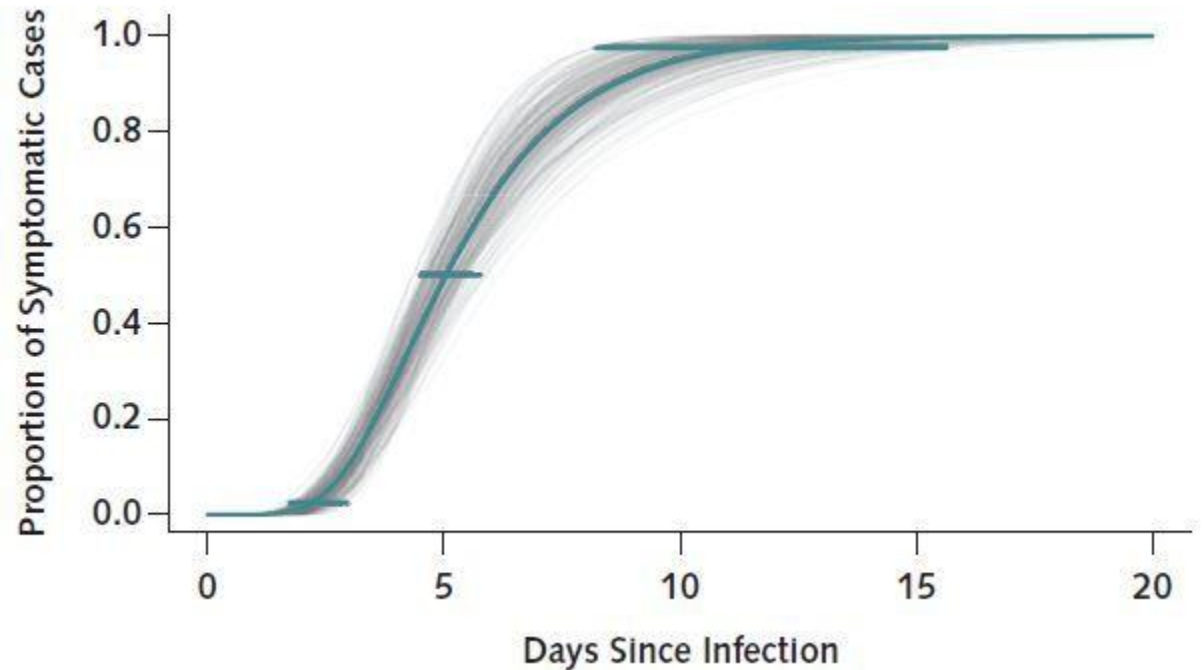
I	Evidence from >1 properly randomized, controlled trial.
II	Evidence from >1 well-designed clinical trial, without randomization; from cohort or case-controlled analytic studies (preferably from >1 center); from multiple time-series; or from dramatic results from uncontrolled experiments.
III	Evidence from opinions of respected authorities, based on clinical experience, descriptive studies, or reports of expert committees.

<https://www.covid19treatmentguidelines.nih.gov/>

Questions and Comments

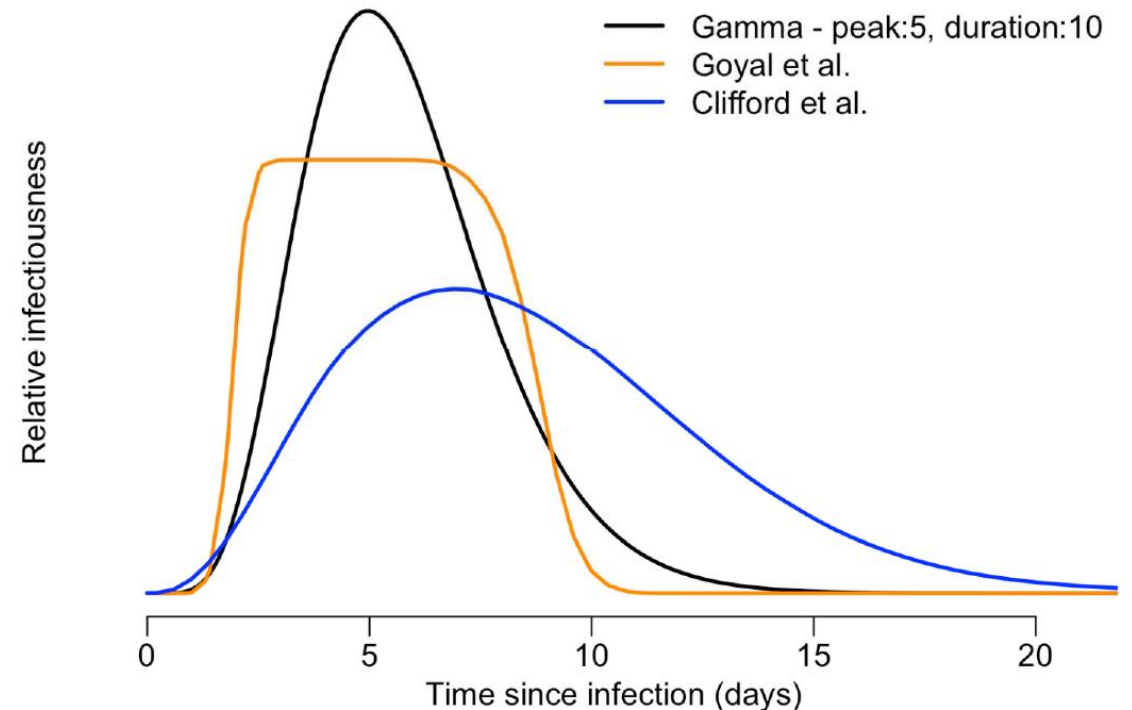
Incubation Period for COVID-19

- Incubation estimated from 181 cases with identified exposure
- Median 5.1 days – half of cases that develop symptoms have done so by this time
- 97.5% develop symptoms within 11.5 days
- This is not precise
 - Another study estimated a median of 7.8 days with 5-10% of cases developing symptoms >14 days after exposure (Qin J. Aci And 2020)



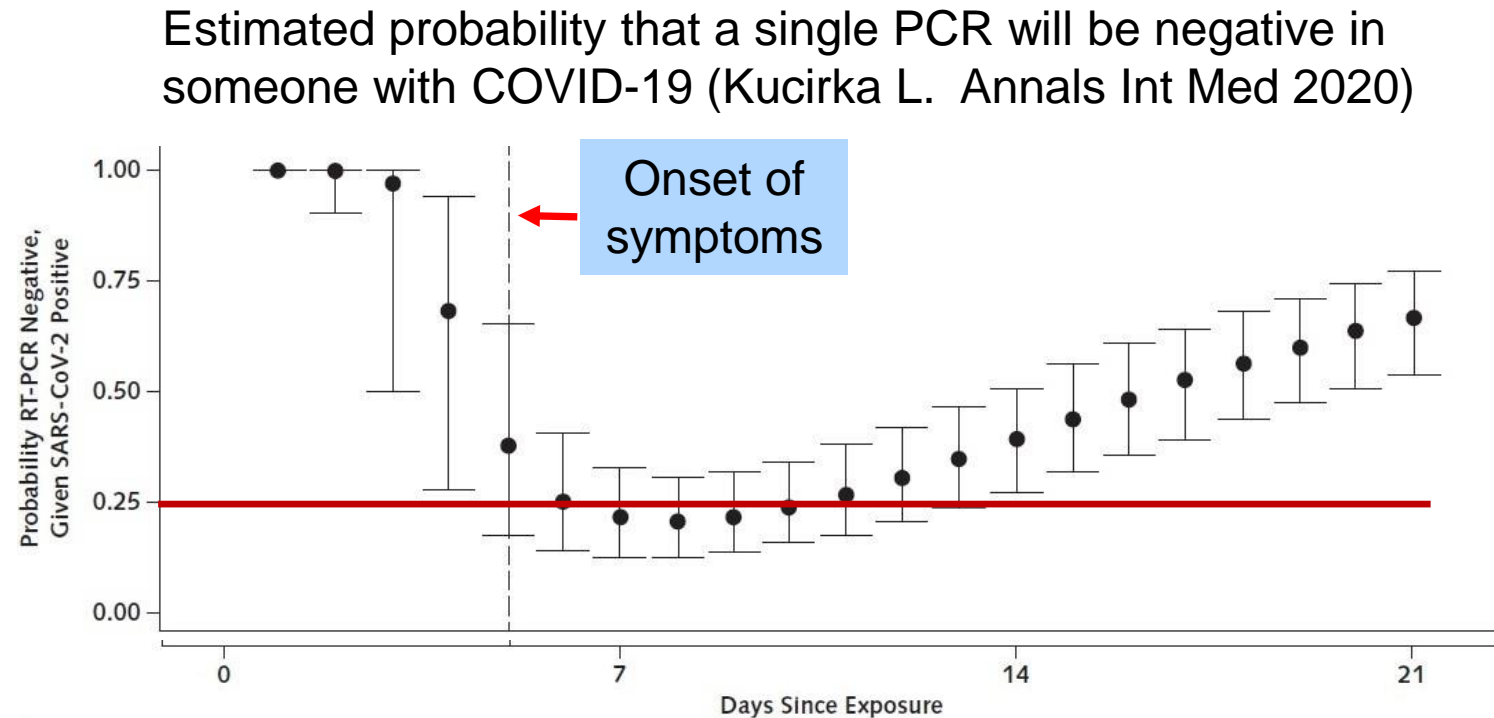
How Does Infectiousness Vary Over the Course of Infection?

- Risk of transmission varies over the course of infection.
- Peak near the time of symptom onset
- This affects whether early discontinuation of quarantine will prevent transmission
 - If infectiousness peaks early, we need to get people into quarantine faster, but can let them out earlier
 - If infectiousness lasts longer, we need a longer period of quarantine
- Relationship is not precisely known



Testing for COVID-19: Sensitivity

- PCR is not 100% sensitive – it misses infection
- Sensitivity (proportion of infected persons who test positive) is highest in the first days after symptom onset
- Sensitivity is low prior to onset of symptoms



Implications:

- 1) A negative test does NOT mean a person does not have COVID-19
- 2) Model – What testing of quarantined people buys depends on when one tests – never 100% in identifying who is infected



Trends Global COVID-19 Cases

Situation by WHO Region

Americas 30,416,759 confirmed

Europe 21,910,729 confirmed

South-East Asia 11,398,927 confirmed

Eastern Mediterranean 4,515,045 confirmed

Africa 1,622,096 confirmed

Western Pacific 965,555 confirmed

Source: World Health Organization

▨ Data may be incomplete for the current day or week.

