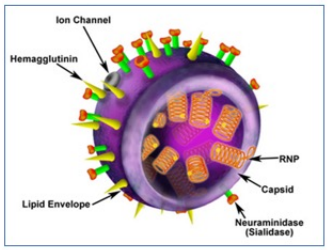
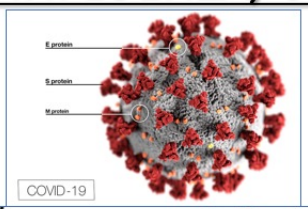
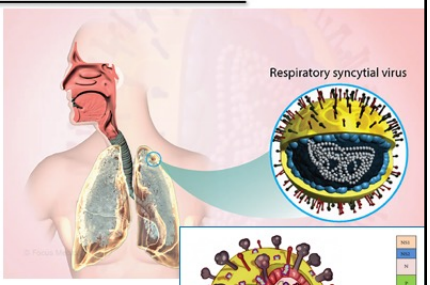
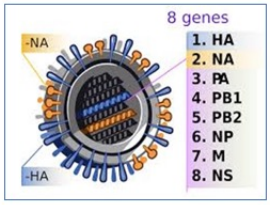
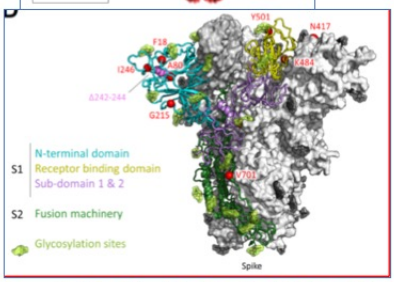
TRIDEMICS OF INFLUENZA, COVID, & RSV 2021

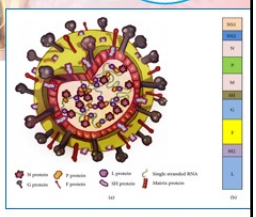












Robert Ball, MD MPH FACP
Assistant Professor: Medical University of South Carolina, USA
Dep't. Medicine: Infectious Diseases & Public Health Sciences
Thanks to CDC, WHO, other colleagues for some slides

R. Ball, MD MPH FACP

Hosted by Paul Webber **www.webbertraining.com** **September 23, 2021**

Objectives

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ATTENDING THIS SESSION WILL ENABLE THE ATTENDEE TO:

1. Outline 3 major factors in Emerging Infectious Diseases

2. Explain several major medical/ scientific similarities and differences in these pandemics

3. Describe several major preventatives re each pandemic and challenges in implementation.

Disclosures:

No university research or pharmaceutical funding
No conflicts of interest
Dr. Ball to receive an honorarium from Webber Training

R. Ball, MD MPH FACP

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Emerging Infectious Diseases ★

Generally, Emerging Infectious Diseases (EIDs) are those in which:

1. A **NEW** "bug" appears (eg, **HIV**, SARS, MERS, etc), or
2. An **OLD** "bug" develops new tricks (eg, **MDR-TB**, **MRSA**, etc)
3. **RESURGENCE** of a microbe thought to have been under ~ complete control (eg, **measles** in US 2014, espec. among vaccine refusers Ebola in ≥3 W. African nations 2013, Zika in 2015…)

There are not (great) case definitions for many of these newer EIDs.
These become a significant global public health threat when:

1. **An epidemic/ pandemic occurs infecting/affecting huge #s of people;**
2. **Health care resources become too scarce to manage the problem , creating geographic, medical, social, ethical, & political dilemmas;**
3. **Worst case scenario: BOTH. (ie, USA needs >5-10K+ epidemiologists.)**

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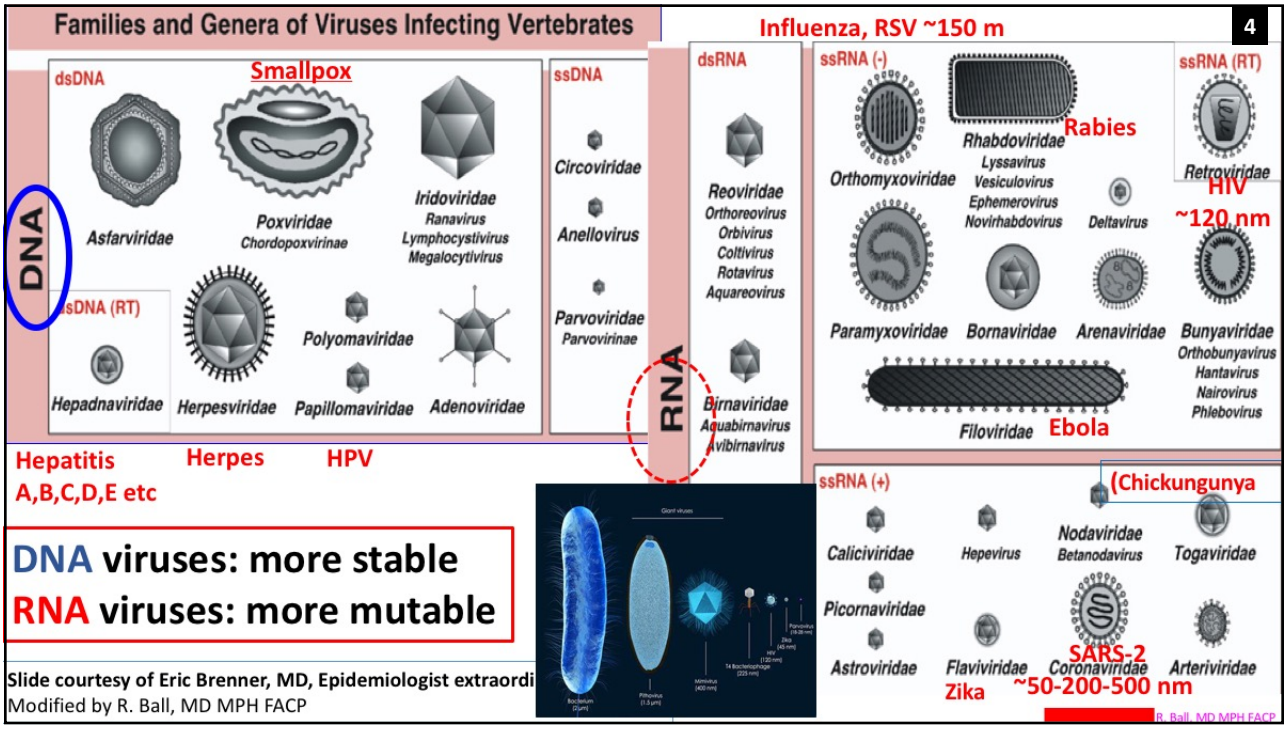

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Herd Immunity Thresholds for Selected Vaccine-Preventable Diseases 9.2021

R_0 (R_t) = mean # of new cases transmitted from 1^0 case

Disease	R_o	Herd Immunity	Immunization Levels 1999 19-35 Months	1997-1998 Pre-School
Diphtheria	6-7	85%*	83%*	9%
Measles	12-18	83-94%	92%	96%
Mumps	4-7	75-86%	92%	97%
Pertussis	12-17	92-94%	83%*	97%
Polio	5-7	80-86%	90%	97%
Rubella	6-7	83-85%	92%	97%
Smallpox	5-7	80-85%		

Attack Rate= # of people infected from 1^0 case in a study

Mean herd immunity level for most VPDs is ~75-80%.

† Modified from *Epid Rev* 1993;15: 265-302, *Am J Prev Med* 2001; 20 (4S): 88-153, *MMWR* 2000; 49 (SS-9); 27-38

CDC

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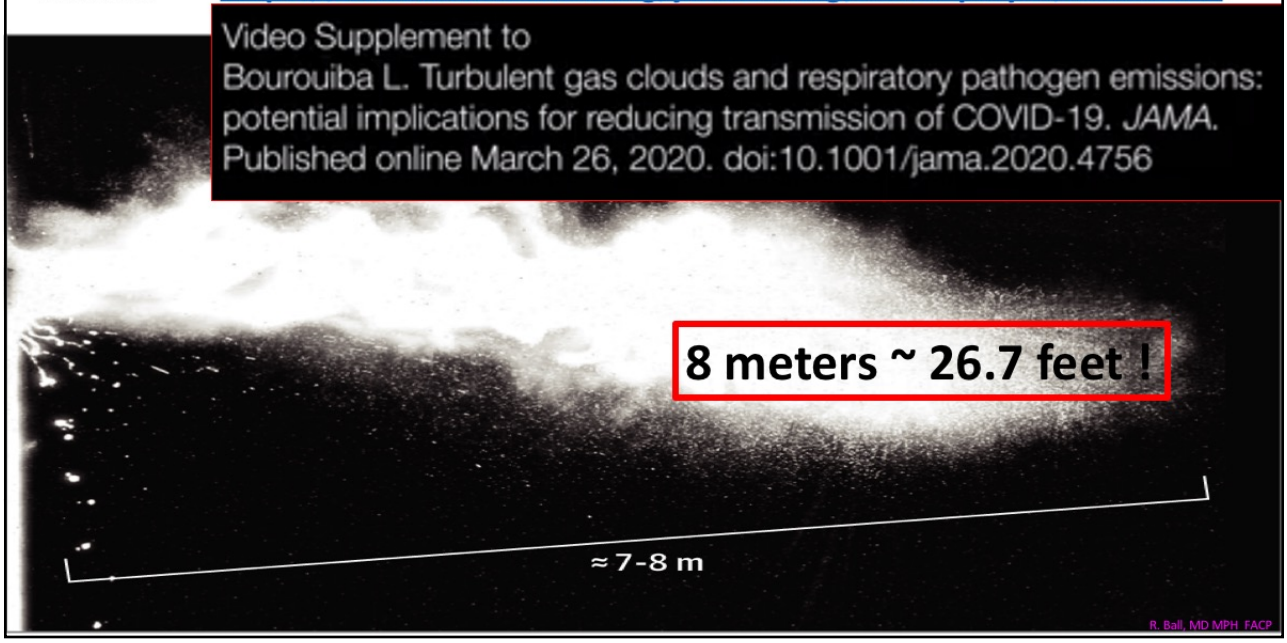
Multiphase Turbulent Gas Cloud From a Human (Sneeze- L. Bourouiba) JAMA video 3.26.20

"A Sneeze" https://edhub.ama-assn.org/jn-learning/video-player/18357411



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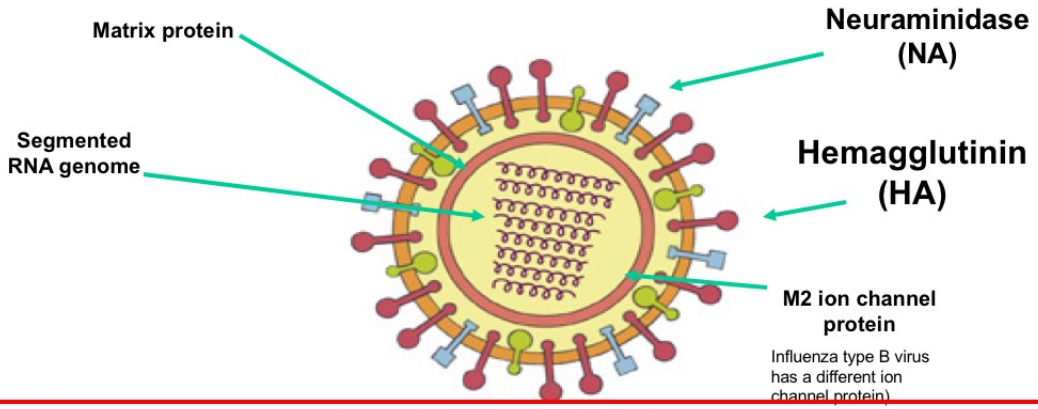
Influenza Virus- Types A, B

Type A: usually either A-H3N2 (worst) or A-H1N1.
Type B occurs early/ late, sl. Less severe



Frequent mutations in either/both **Hemagglutinin** (18 varieties)

or **Neuraminidase** (11 varieties) protein surface "spikes" = **198 possible combos** !

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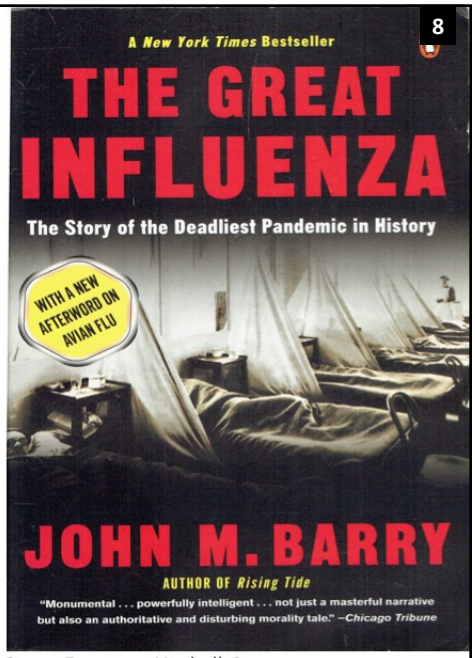
Pandemic Influenza: 1918



Soldiers from Camp (Fort) Riley, KS, ill with Spanish influenza at a hospital ward at Camp Funston, Haskell Co. "Spanish Flu" thought to have also originated in America.

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A/South Carolina/1/18 H

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Proc. Natl. Acad. Sci. USA
Vol. 96, pp. 1651–1656, February 1999
Microbiology

Proc. NAS Feb. 1999

Origin and evolution of the 1918 "Spanish" influenza virus hemagglutinin gene

ANN H. REID*, THOMAS G. FANNING, JOHAN V. HULTIN, AND JEFFERY K. TAUBENBERGER
Division of Molecular Pathology, Department of Cellular Pathology, Armed Forces Institute of Pathology, Washington, DC 20306-6000

Communicated by Edwin D. Kilbourne, New York Medical College, Valhalla, NY, November 18, 1998 (received for review August 7, 1998)

ABSTRACT The "Spanish" influenza pandemic killed over 20 million people in 1918 and 1919, making it the worst infectious pandemic in history. Here, we report the complete sequence of the hemagglutinin (HA) gene of the 1918 virus. Influenza RNA for the analysis was isolated from a formalin-fixed, paraffin-embedded lung tissue sample prepared during the autopsy of a victim of the influenza pandemic in 1918. Influenza RNA was also isolated from lung tissue samples from two additional victims of the lethal 1918 influenza: one formalin-fixed, paraffin-embedded sample and one frozen sample obtained by *in situ* biopsy of the lung of a victim buried in permafrost since 1918. The complete coding sequence of the A/South Carolina/1/18 HA gene was obtained. The HA1 domain sequence was confirmed by using the two additional isolates (A/New York/1/18 and A/Brevig Mission/1/18). The sequences show little variation. Phylogenetic analyses suggest that the 1918 virus HA gene, although more closely related to avian strains than any other mammalian sequence, is mammalian and may have been adapting in humans before 1918.

Vaughn et al- Epi & Public Health textbook- Vol.1 Respiratory Infections 1922

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Pandemic mortality "U" & "W" curves: 1918

10

Taubenberger. CDC: EID 1.2006
re: 1918 Influenza A-H1N1 (avian)

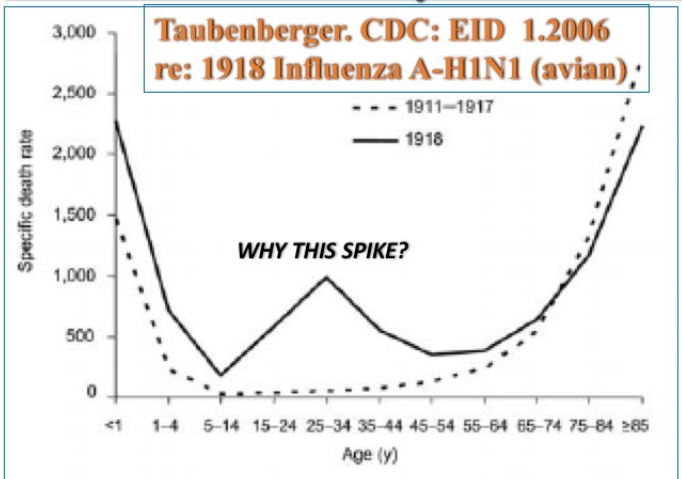

Figure 2. "U-" and "W-" shaped combined influenza and pneumonia mortality, by age at death, per 100,000 persons in each age group, United States, 1911–1918. Influenza- and pneumonia-specific death rates are plotted for the interpandemic years 1911–1917 (dashed line) and for the pandemic year 1918 (solid line) (33,34).

Dr. Mike Osterholm

N ENGL J MED 352;18 WWW.NEJM.ORG MAY 5, 2005

Proposed Mechanism of the Cytokine Storm Evoked by Influenzavirus.
The key element in generating the storm is an uncontrolled exuberant immune response to the virus, in which there is an outpouring of proinflammatory cytokines and chemoattractants. An animated version of this figure is available at www.nejm.org.

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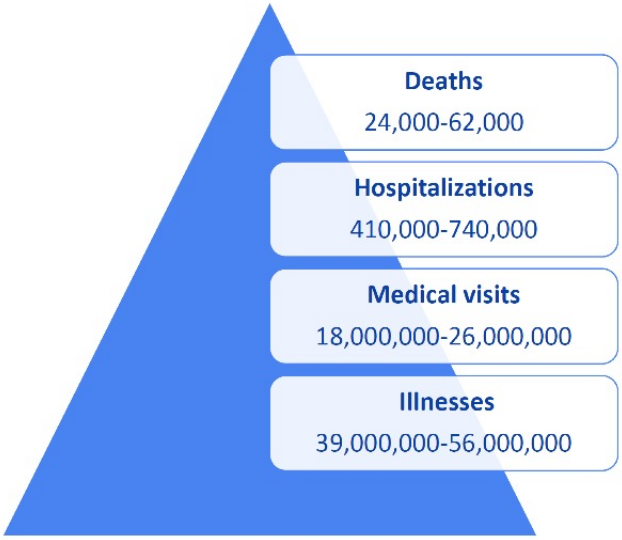
Summary of 2019-2020 influenza season

- Two consecutive waves
  - 1st wave predominantly influenza B/Victoria viruses
  - 2nd wave driven by influenza A (H1N1)
- Pediatric deaths reported to CDC for the 2019-2020 season: **185***



*As of June 13, 2020
https://www.cdc.gov/flu/about/burden/preliminary-in-season-estimates.htm

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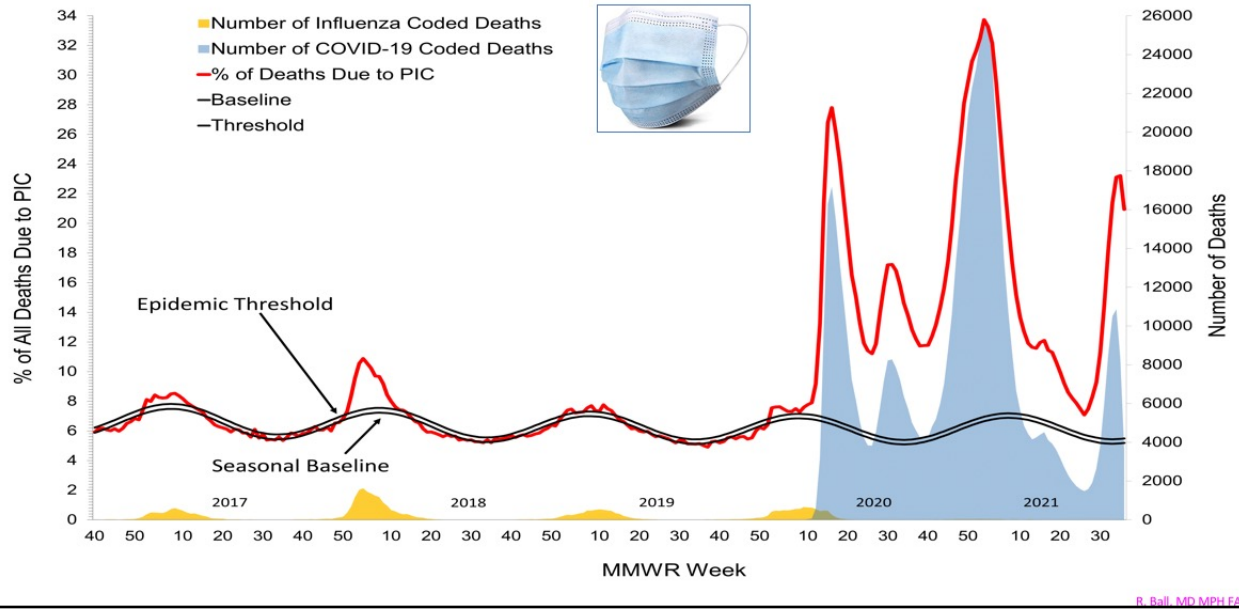
Pneumonia, Influenza, and COVID-19 Mortality from the National Center for Health Statistics Mortality Surveillance System

Data as of September 16, 2021



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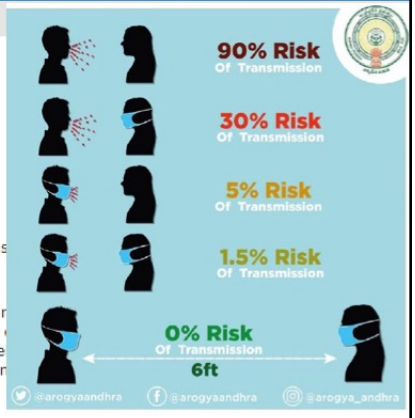
Flu News Europe

Joint ECDC–WHO/Europe weekly influenza update

ecdc

World Health Organization
REGIONAL OFFICE FOR Europe

Weekly overview | Season overview | Primary care data | Hospital data | Virus characteristics | Vaccine | About us | Bulletin archives



Weekly influenza overview

Weeks 33-36/2021 (16 August-12 September 2021)

- Influenza activity remained at interseasonal levels.
- Display of data will be updated on a monthly basis during the interseason period (weeks 21-39).

Qualitative indicators

Information on countries and areas reporting on intensity of activity and geographic spread for this week can be s

Please note:

1. Assessment of the intensity of activity indicator includes consideration of ILI or ARI rates. These ILI or ARI r
   other than influenza, including SARS-CoV-2, leading to observed increases in the absence of influenza virus
2. Assessment of intensity and geographic spread indicators includes consideration of sentinel and non-sentine
   influenza virus detections, often higher, might translate into reporting of elevated geographic spread even ir

EU map layout | WHO map layout

Intensity of influenza | Geographic spread of influenza

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Centers for Disease Control and Prevention

MMWR

Morbidity and Mortality Weekly Report

Recommendations and Reports / Vol. 70 / No. 5 August 27, 2021

- Main influenza vaccine types include:
  - **IIV** = inactivated influenza vaccine
  - **RIV** = recombinant influenza vaccine
  - **LAIV** = live attenuated influenza vaccine
- Numerals following letter abbreviations indicate valency (the number of influenza virus hemagglutinin [HA] antigens represented in the vaccine):
  - **4** for quadrivalent vaccines: one A(H1N1), one A(H3N2), and two B viruses (one from each lineage)
  - **3** for trivalent vaccines: one A(H1N1), one A(H3N2), and one B virus (from one lineage)
- All influenza vaccines expected to be available in the United States for the 2021–22 season are quadrivalent vaccines. However, abbreviations for trivalent vaccines (e.g., IIV3) might be used in this document when discussing information specific to trivalent vaccines.
- Abbreviations for general vaccine categories (e.g., IIV) might be used when discussing information that is not specific to either trivalent or quadrivalent vaccines.
- Prefixes are used when necessary to refer to some specific IIVs:
  - **a** for adjuvanted inactivated influenza vaccine (e.g., aIIV3 and aIIV4)
  - **cc** for cell culture–based inactivated influenza vaccine (e.g., ccIIV3 and ccIIV4)
  - **HD** for high-dose inactivated influenza vaccine (e.g., HD-IIV3 and HD-IIV4)
  - **SD** for standard-dose inactivated influenza vaccine (e.g. SD-IIV3 and SD-IIV4)

Prevention and Control of Seasonal Influenza with Vaccines: Recommendations of the Advisory Committee on Immunization Practices, United States, 2021–22 Influenza Season

R. Ball, MD MPH FACP

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TABLE 1. Influenza vaccines — United States, 2021–22 influenza season*

Trade name (manufacturer)	Presentations	Age indication	µg HA (IIV4s and RIV4) or virus count (LAIV4) for each vaccine virus (per dose)	Route	Mercury (from thimerosal, if present), µg/0.5 mL
IIV4 (standard-dose, egg-based vaccines†)					
Afluria Quadrivalent (Seqirus)	0.25-mL PFS§	6 through 35 mos§	7.5 µg/0.25 mL	IM¶	—
	0.5-mL PFS§	≥3 yrs§	15 µg/0.5 mL	IM¶	—
	5.0-mL MDV§	≥6 mos§ (needle/syringe) 18 through 64 yrs (jet injector)	15 µg/0.5 mL	IM¶	24.5
Fluarix Quadrivalent (GlaxoSmithKline)	0.5-mL PFS	≥6 mos	15 µg/0.5 mL	IM¶	—
FluLaval Quadrivalent (GlaxoSmithKline)	0.5-mL PFS	≥6 mos	15 µg/0.5 mL	IM¶	—
Fluzone Quadrivalent (Sanofi Pasteur)	0.5-mL PFS**	≥6 mos**	15 µg/0.5 mL	IM¶	—
	0.5-mL SDV**	≥6 mos**	15 µg/0.5 mL	IM¶	—
	5.0-mL MDV**	≥6 mos**	15 µg/0.5 mL 7.5 µg/0.25 mL	IM¶	25
cclIV4 (standard-dose, cell culture–based vaccine)					
Flucelvax Quadrivalent (Seqirus)	0.5-mL PFS	≥2 yrs	15 µg/0.5 mL	IM¶	—
	5.0-mL MDV	≥2 yrs	15 µg/0.5 mL	IM¶	25
HD-IIV4 (high-dose, egg-based vaccine†)					
Fluzone High-Dose Quadrivalent # (Sanofi Pasteur)	0.7-mL PFS	≥65 yrs	60 µg/0.7 mL	IM¶	—
aIIV4 (standard-dose, egg-based† vaccine with MF59 adjuvant)					
Fluad Quadrivalent (Seqirus)	0.5-mL PFS	≥65 yrs	15 µg/0.5 mL	IM¶	—
RIV4 (recombinant HA vaccine)					
Flublok Quadrivalent * (Sanofi Pasteur)	0.5-mL PFS	≥18 yrs	45 µg/0.5 mL	IM¶	—
LAIV4 (egg-based vaccine†)					
FluMist Quadrivalent (AstraZeneca)	0.2-mL prefilled single-use intranasal sprayer	2 through 49 yrs	$10^{6.5–7.5}$ fluorescent focus units/0.2 mL	NAS	—

"Quad-quad" vaccine: 4x mcg/ml

* Quad-tri vaccine: 3x mcg/ml

Abbreviations: ACIP = Advisory Committee on Immunization Practices; FDA = Food and Drug Administration; HA = hemagglutinin; IIV4 = inactivated influenza vaccine, quadrivalent; IM = intramuscular; LAIV4 = live attenuated influenza vaccine, quadrivalent; MDV = multidose vial; NAS = intranasal; PFS = prefilled syringe; RIV4 = recombinant influenza vaccine, quadrivalent; SDV = single-dose vial.

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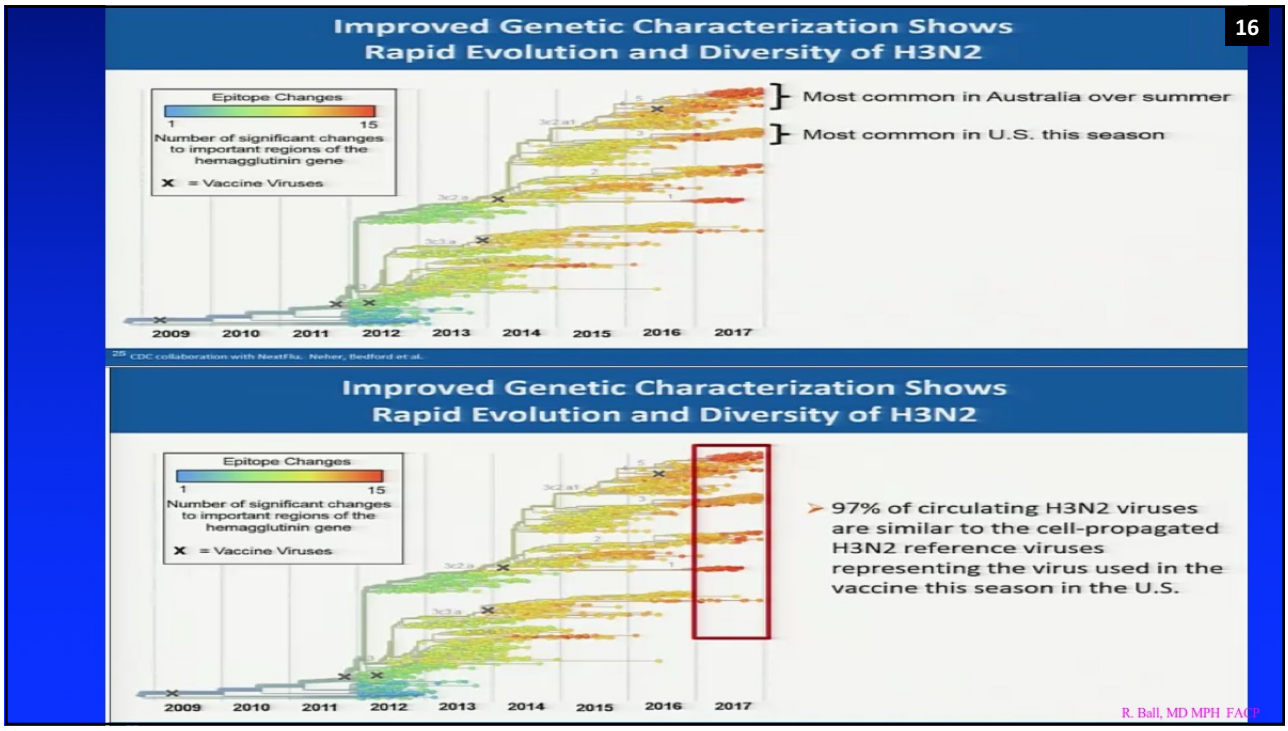

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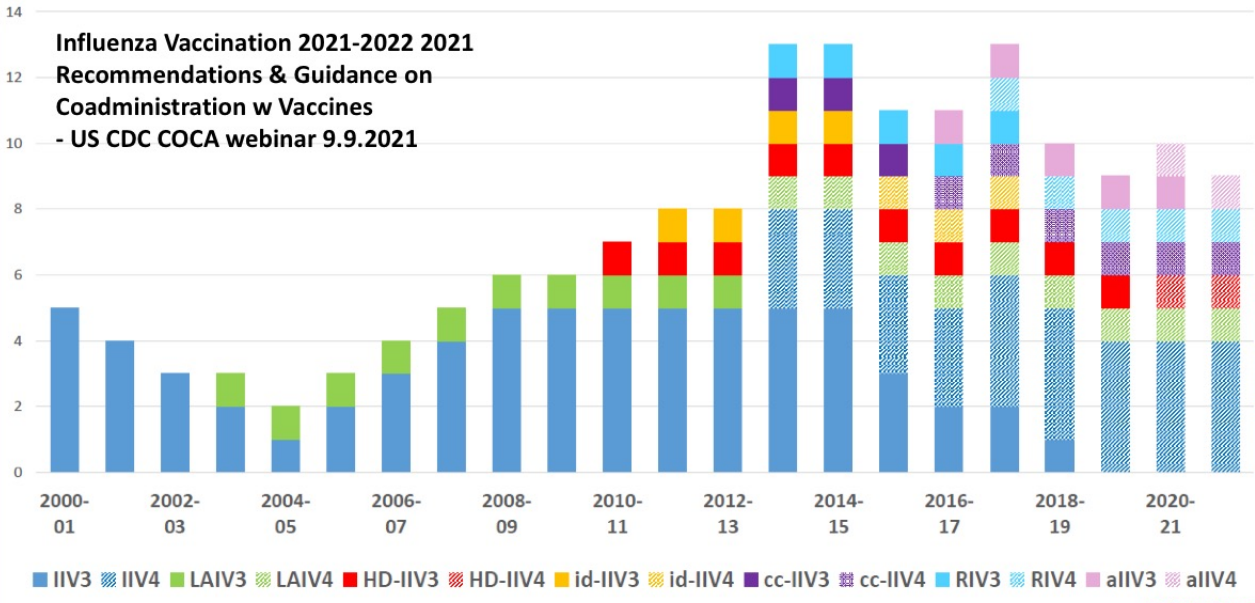
U.S. Seasonal Influenza Vaccines Since 2000-2001

Number of unique products available by season

Influenza Vaccination 2021-2022 2021 Recommendations & Guidance on Coadministration w Vaccines - US CDC COCA webinar 9.9.2021



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Influenza Antiviral Medications

Influenza webinar- CDC COCA 2.5.2019

- Four FDA-approved antivirals are recommended for use in the United States
  - Neuraminidase inhibitors: oral oseltamivir, inhaled zanamivir, and intravenous peramivir
  - Cap-dependent endonuclease inhibitor: oral baloxavir

Drug	Route	Treatment	Chemoprophylaxis	Adverse Events
Oseltamivir	Oral	Any age	≥3 months	Nausea, vomiting, headache*
Zanamivir	Inhaled	≥7 years	≥5 years	Bronchospasm*
Peramivir	Intravenous	≥2 years	N/A	Diarrhea*
Baloxavir	Oral	≥12 years	N/A	(none more common than placebo)

*Post-marketing reports of serious skin reactions and sporadic, transient neuropsychiatric events

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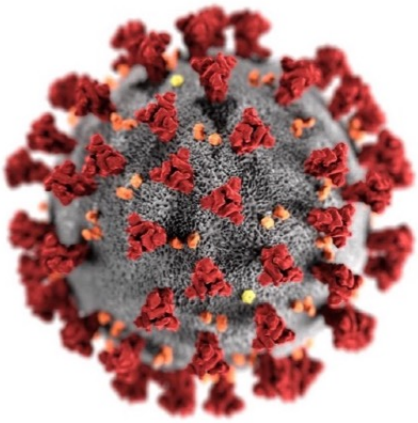
COVID 19 CORONAVIRUS DISEASE

Vaccine Coadministration

Andrew Kroger, MD, MPH
Immunization Services Division, NCIRD, CDC

Clinician Outreach and Communication Activity (COCA) Webinar

September 9, 2021



Influenza Vaccination 2021-2022: Recommendations & Guidance on Coadministration w COVID-19 Vaccines - CDC COCA webinar 9.9.2021

For more information: **www.cdc.gov/COVID19**

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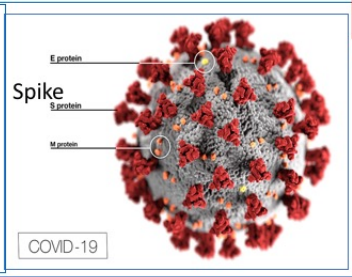
SARS-nCoV-2→ COVID-19: Global Pandemic 2020 → —

Coronavirus Infections—More Than Just the Common Cold

FAMILY of coronaviruses (α,β,γ,δ) (7 strains in humans) cause ~ 1/4 of common colds, but some cause more severe diseases (ie, SARS-1, MERS, & now COVID-19). SARS-nCoV-2 β is in the nidovirus viral order (genus betacoronavirus, subgenus sarbecovirus)



JAMA Published online January 23, 2020

Thanks to many organizations, colleagues for some slides: US CDC, NIH, WHO, JHU, SC DHEC, USC SoM (I.D.), journals, & others TNTC.

Anthony S. Fauci, MD
National Institute of Allergy and Infectious Diseases, National Institutes of Health, Bethesda, Maryland.

SARS-CoV-2, Variants, Vaccines- Update 9.2021

Robert T Ball Jr, MD MPH FACP
Assistant Professor: Medical University of SC/ USA
Department of Medicine,
Division of Infectious Diseases & Dept. Public Health Sciences
(ballrt@musc.edu)

R. Ball, MD MPH FACP

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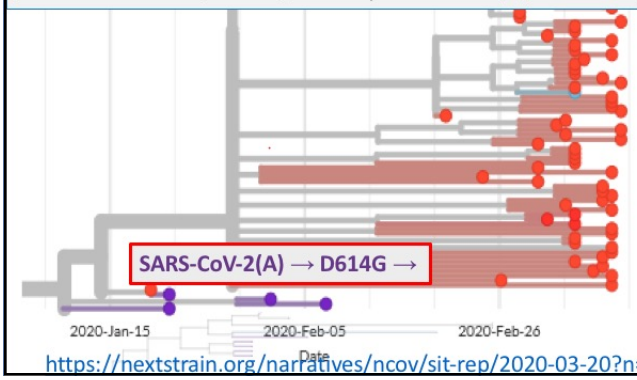
Genomic epidemiology of novel coronavirus

Maintained by the Nextstrain team. Enabled by data from GISAID

2020→2021

Showing 84 of 838 genomes sampled between Jan 2020 and Mar 2020 and comprising 5 recencys, 5 locations, 5 divisions, 5 countries, 5 hosts, 5 re

2020: MAJOR mutations in SARS-CoV-2 spike proteins from wild type Wuhan Hu-1: 1^0= D614G in Spike protein 1 (1.2020). later 2020: more MUTANTS (Variants of Interest/ Concern (VoI/VoC) ie: 20A.EU1/Y453F; 19B=α B.1.1.7 lineage (UK→global, 11.2020 →US). B= L452R (EU), N501Y.V2 So.Africa→Italy, USA. γ Brazil P.1 (20J/501.Y.V3) [B.1.427/429 (CA), B.1.526 (NYC)]. Δ= B.1.617.2 (India) most↑infectivity (30- 50%),↑virulence (20-30%). *Q:Δ shedding/transmission?*



https://nextstrain.org/narratives/ncov/sit-rep/2020-03-20?n=10

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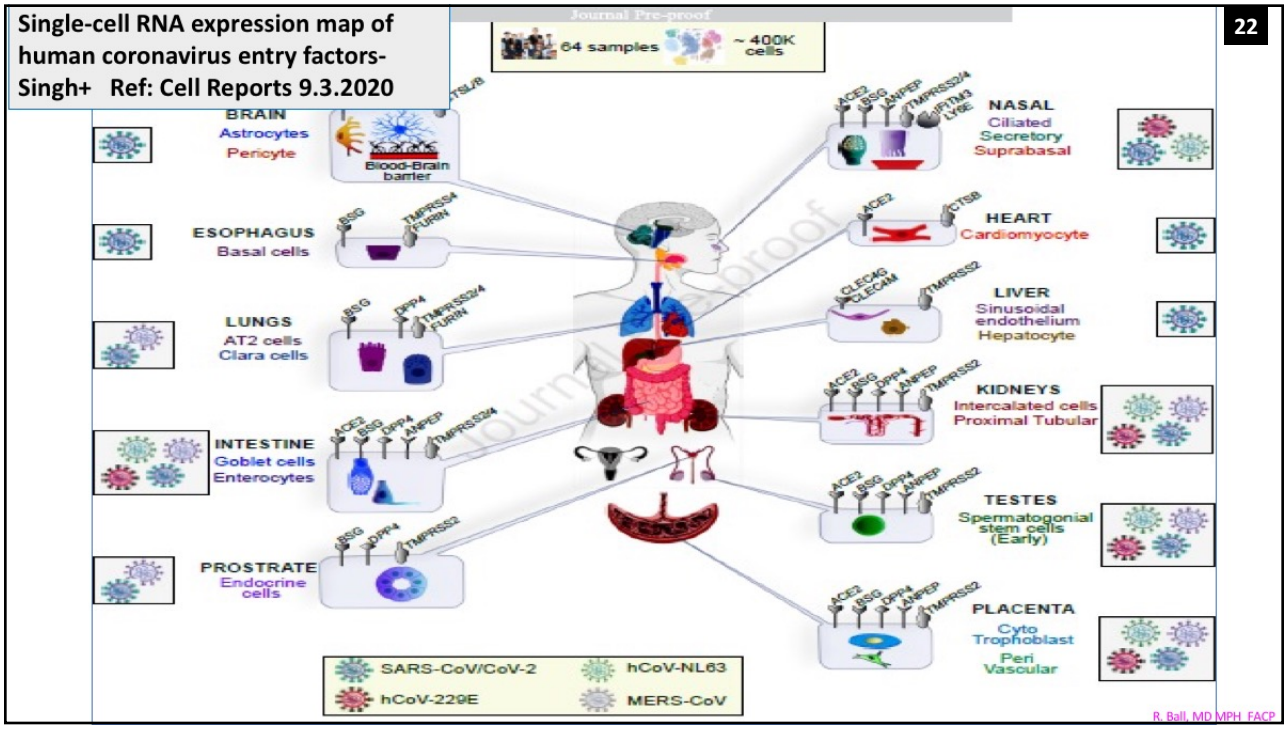
Single-cell RNA expression map of human coronavirus entry factors- Singh+ Ref: Cell Reports 9.3.2020



Some COVID Clinical Sx, Signs: www.cdc.gov et al 2020

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- **1⁰**: fever, cough, dyspnea, fatigue, anorexia, sore throat, headache, odd rashes…
- Loss of **smell (anosmia), taste (ageusia)** [direct infection: NP cells, cranial nerves]
- CNS & peripheral neurologic events, including encephalopathies, meningitis, peripheral neuropathies, psychiatric anomalies (ie, psychosis), "brain fog", others

- **COMPLICATIONS**: severe pneumonia/ "ground-glass" ARDS (~ 1/3 need ventilators, ~ 1/3 never wean off, die); scattered thrombotic/ thromboembolic events in multiple body sites. Examples: cardiac [ie, MIs]; CNS [ie, strokes, incl. large vessel, even in young patients]; pulmonary [eg, pulm. embolism]; renal [ARN, etc]; limbs [eg, "COVID-toes"]; ~MG; diffuse "microthrombi"@ autopsy.

- **Others** (rare): multiple Sx: Multisystem Inflammatory Syndrome-Children (**MIS-C**, or MIS-Adults) ~Kawasaki disease (ongoing cytokine storm)→odd focal/ diffuse rashes; myo-pericarditis; peritonitis (abdominal pain+); shock; cardiac arrest.

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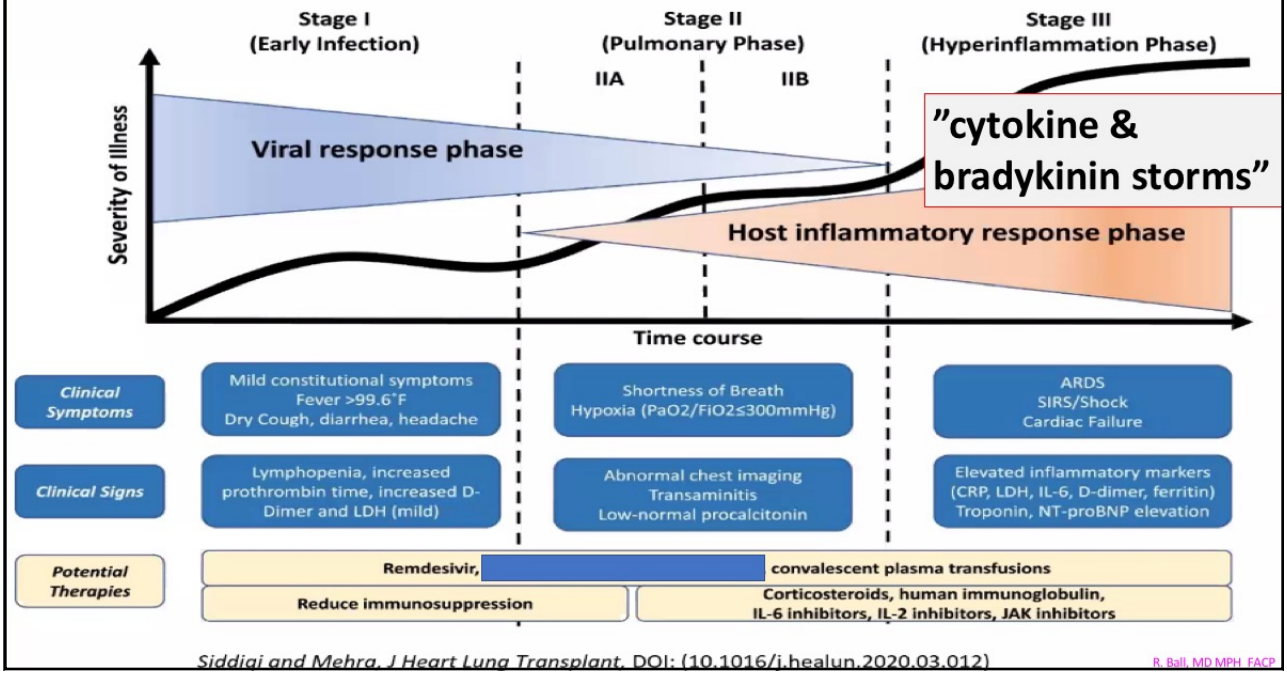

Siddiqi and Mehra, J Heart Lung Transplant. DOI: (10.1016/j.healun.2020.03.012)

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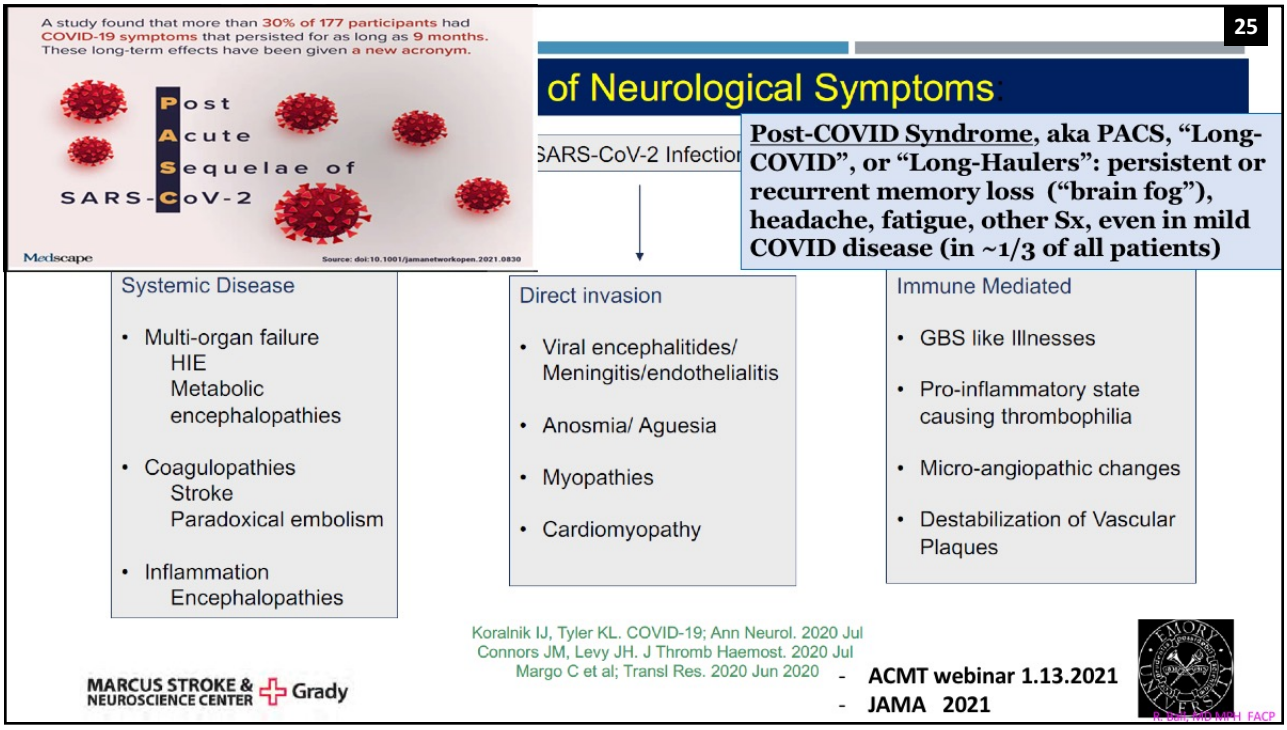
25
A study found that more than 30% of 177 participants had COVID-19 symptoms that persisted for as long as 9 months. These long-term effects have been given a new acronym.
Post Acute Sequelae of SARS-CoV-2
Medscape
of Neurological Symptoms
SARS-CoV-2 Infectio
Post-COVID Syndrome, aka PACS, "Long-COVID", or "Long-Haulers": persistent or recurrent memory loss ("brain fog"), headache, fatigue, other Sx, even in mild COVID disease (in ~1/3 of all patients)
Systemic Disease
• Multi-organ failure
HIE
Metabolic encephalopathies
• Coagulopathies
Stroke
Paradoxical embolism
• Inflammation
Encephalopathies
Direct invasion
• Viral encephalitides/ Meningitis/endothelialitis
• Anosmia/ Aguesia
• Myopathies
• Cardiomyopathy
Immune Mediated
• GBS like Illnesses
• Pro-inflammatory state causing thrombophilia
• Micro-angiopathic changes
• Destabilization of Vascular Plaques
Koralnik IJ, Tyler KL. COVID-19; Ann Neurol. 2020 Jul
Connors JM, Levy JH. J Thromb Haemost. 2020 Jul
Margo C et al; Transl Res. 2020 Jun 2020
- ACMT webinar 1.13.2021
- JAMA 2021
MARCUS STROKE & NEUROSCIENCE CENTER Grady
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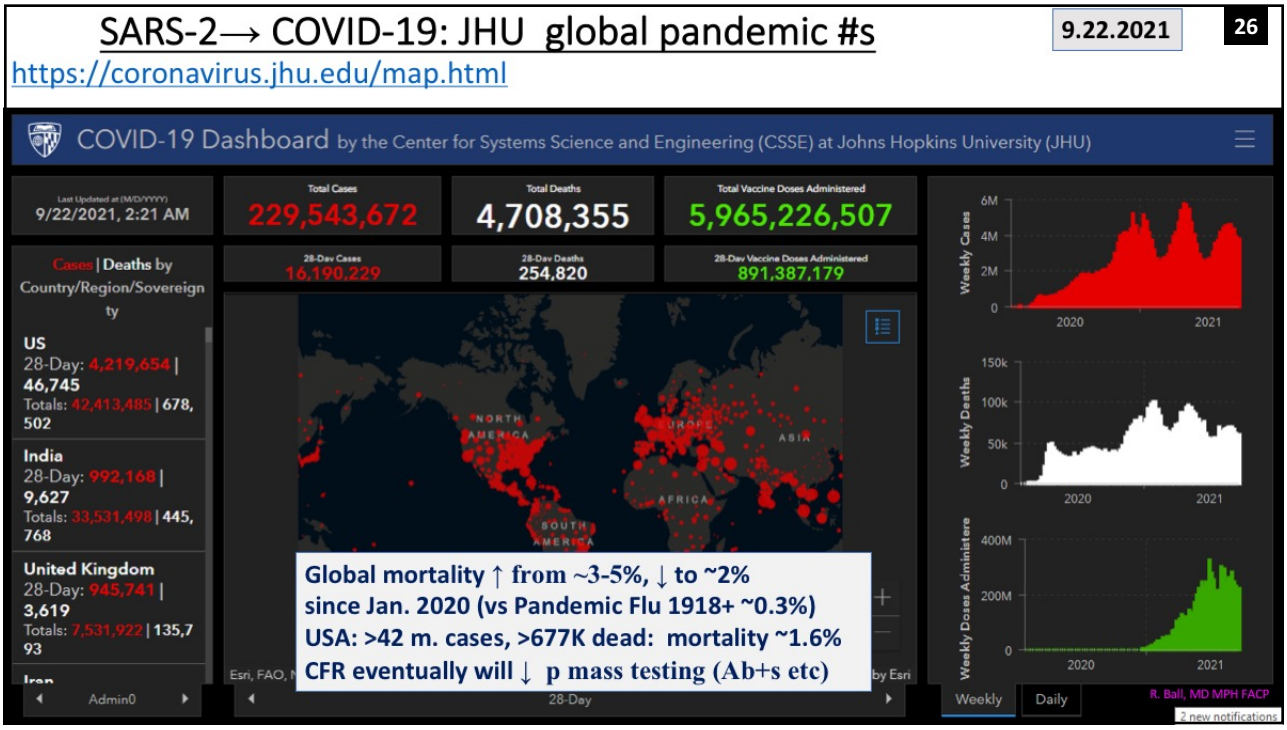
SARS-2→ COVID-19: JHU global pandemic #s
9.22.2021
26
https://coronavirus.jhu.edu/map.html
COVID-19 Dashboard by the Center for Systems Science and Engineering (CSSE) at Johns Hopkins University (JHU)
Last Updated at (M/D/YYYY)
9/22/2021, 2:21 AM
Total Cases
229,543,672
Total Deaths
4,708,355
Total Vaccine Doses Administered
5,965,226,507
28-Day Cases
16,190,229
28-Day Deaths
254,820
28-Day Vaccine Doses Administered
891,387,179
Cases | Deaths by Country/Region/Sovereignty
US
28-Day: 4,219,654 | 46,745
Totals: 42,413,485 | 678,502
India
28-Day: 992,168 | 9,627
Totals: 33,531,498 | 445,768
United Kingdom
28-Day: 945,741 | 3,619
Totals: 7,531,922 | 135,793
Admin0
28-Day
Weekly Cases
Weekly Deaths
Weekly Doses Administered
2020
2021
Weekly
Daily
Global mortality ↑ from ~3-5%, ↓ to ~2%
since Jan. 2020 (vs Pandemic Flu 1918+ ~0.3%)
USA: >42 m. cases, >677K dead: mortality ~1.6%
CFR eventually will ↓ p mass testing (Ab+s etc)
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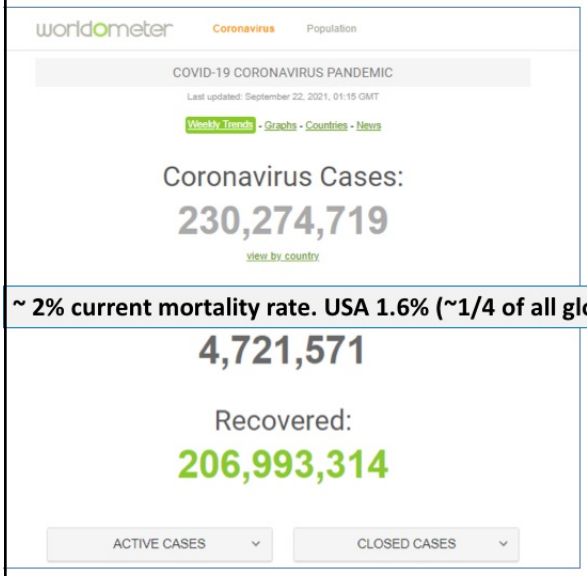
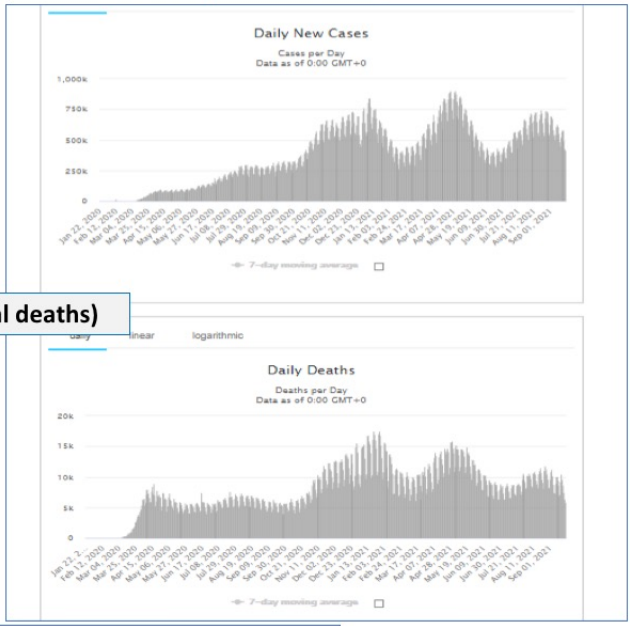
https://www.worldometers.info/coronavirus/coronavirus-cases/#total-cases **9.22.2021** **27**



~ 2% current mortality rate. USA 1.6% (~1/4 of all global deaths)



US CDC estimates 2-5x as many COVID cases as reported (+) tests.

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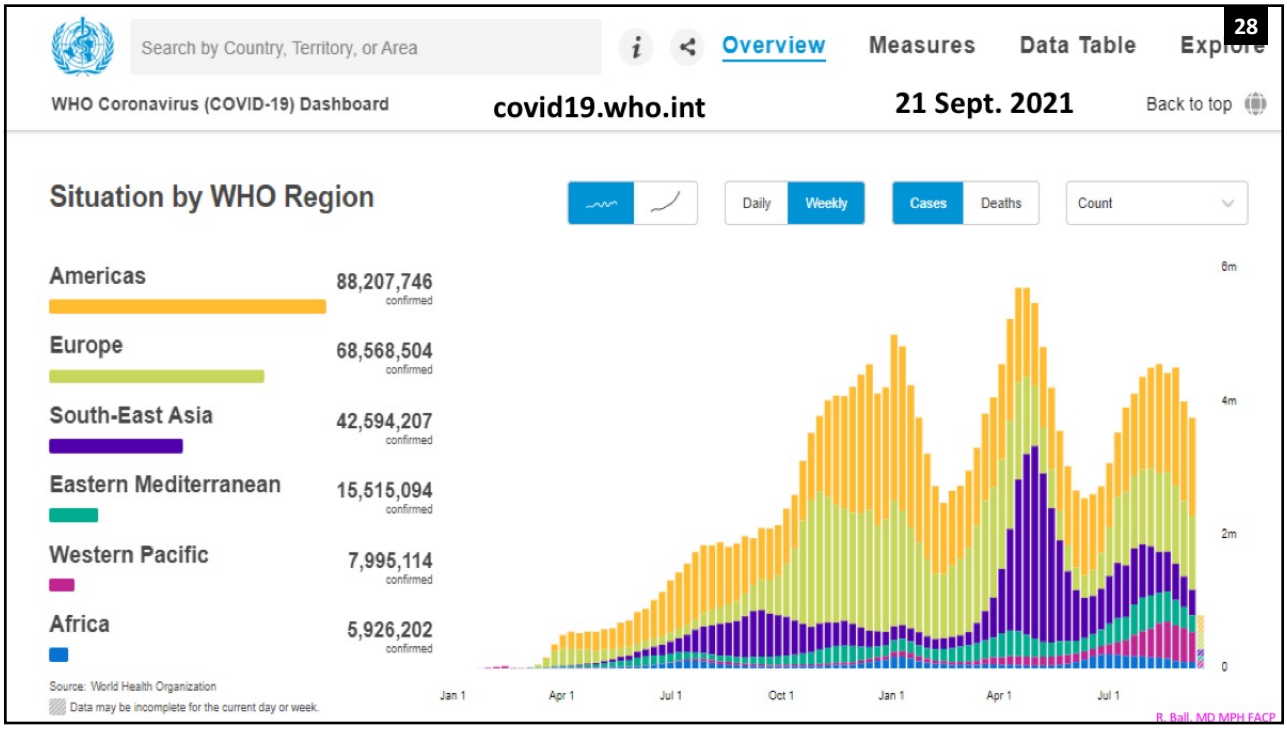

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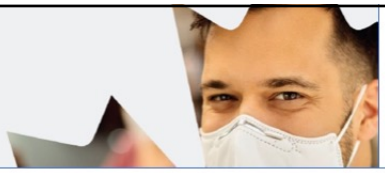
Update on COVID-19 in Canada: Epidemiology and Modelling



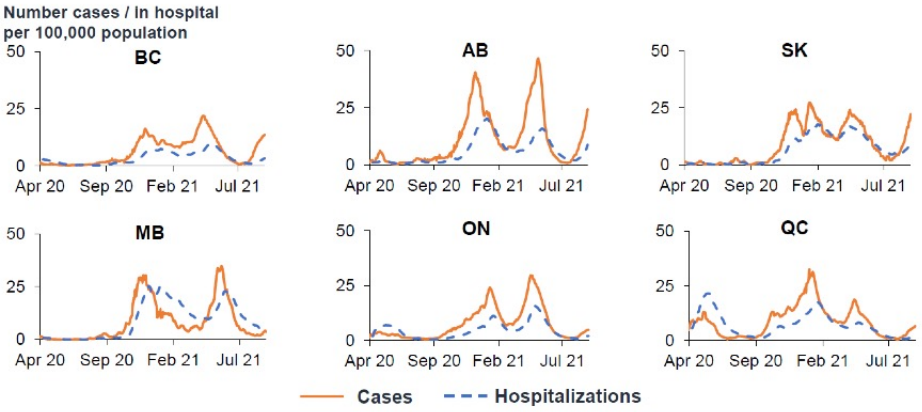
September 3, 2021

Canada.ca/coronavirus

Public Health Agency of Canada | Agence de la santé publique du Canada

Great epidemiologic metrics !

Regional COVID-19 trends show hospital and ICU occupancy increasing, following weeks of rapidly increasing cases in some jurisdictions



Data as of September 1, 2021
***Note:** Daily cases trend lines reflect 7-day moving averages. Total number in hospitals include all people in hospital on that day.*

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Modern US Pandemics: Mortality comparison

- The COVID-19 pandemic has become the deadliest disease event in American (no other country) history, now with a death toll surpassing that of the 1918 Spanish flu.
- The "Spanish Flu" was previously the disease event that caused the biggest loss of life in the United States; the CDC estimates that **675,000** Americans died during the 1918 pandemic, in waves of illness that stretched out over ~2 years in this country.
- COVID deaths as of 9.21.2021 in USA per STATNews.com Covid-19 Tracker **>675,400+**; Worldometer: **696,853+**; JHU: **678,502**. These #s will >1 million soon.
- Most experts predict: multiple mutations (variants) and COVID waves yearly through the next few years, requiring annual updated booster vaccines, multiple other mitigation measures, with multiple coronaviruses becoming endemic globally for years/ decades to come.

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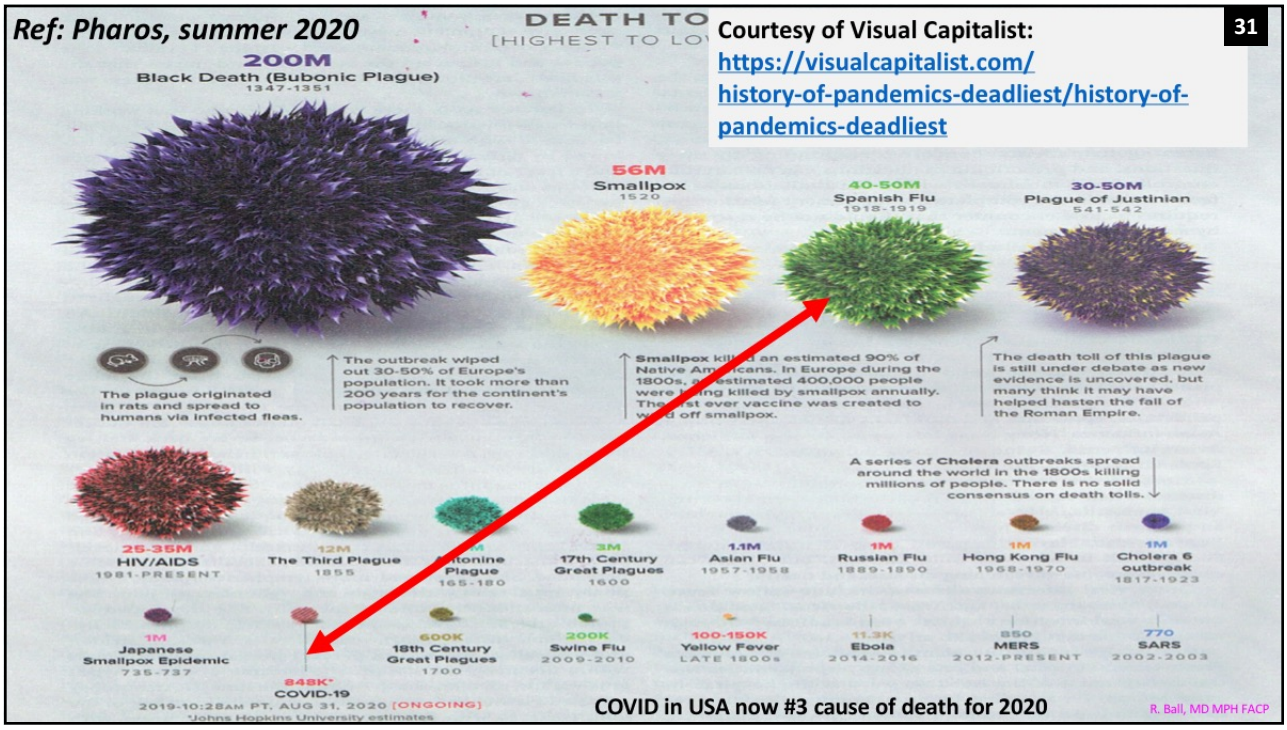
Ref: Pharos, summer 2020
31
Courtesy of Visual Capitalist:
https://visualcapitalist.com/history-of-pandemics-deadliest/history-of-pandemics-deadliest
200M
Black Death (Bubonic Plague)
1347-1351
56M
Smallpox
1520
40-50M
Spanish Flu
1918-1919
30-50M
Plague of Justinian
541-542
The plague originated in rats and spread to humans via infected fleas.
The outbreak wiped out 30-50% of Europe's population. It took more than 200 years for the continent's population to recover.
Smallpox killed an estimated 90% of Native Americans. In Europe during the 1800s, an estimated 400,000 people were being killed by smallpox annually. The first ever vaccine was created to ward off smallpox.
The death toll of this plague is still under debate as new evidence is uncovered, but many think it may have helped hasten the fall of the Roman Empire.
A series of Cholera outbreaks spread around the world in the 1800s killing millions of people. There is no solid consensus on death tolls.
25-35M
HIV/AIDS
1981-PRESENT
12M
The Third Plague
1855
3M
17th Century Great Plagues
1600
1.1M
Asian Flu
1957-1958
1M
Russian Flu
1889-1890
1M
Hong Kong Flu
1968-1970
1M
Cholera 6 outbreak
1817-1923
1M
Japanese Smallpox Epidemic
735-737
848K*
COVID-19
2019-10:28AM PT, AUG 31, 2020 (ONGOING)
*Johns Hopkins University estimates
600K
18th Century Great Plagues
1700
200K
Swine Flu
2009-2010
100-150K
Yellow Fever
LATE 1800s
11.3K
Ebola
2014-2016
850
MERS
2012-PRESENT
770
SARS
2002-2003
COVID in USA now #3 cause of death for 2020
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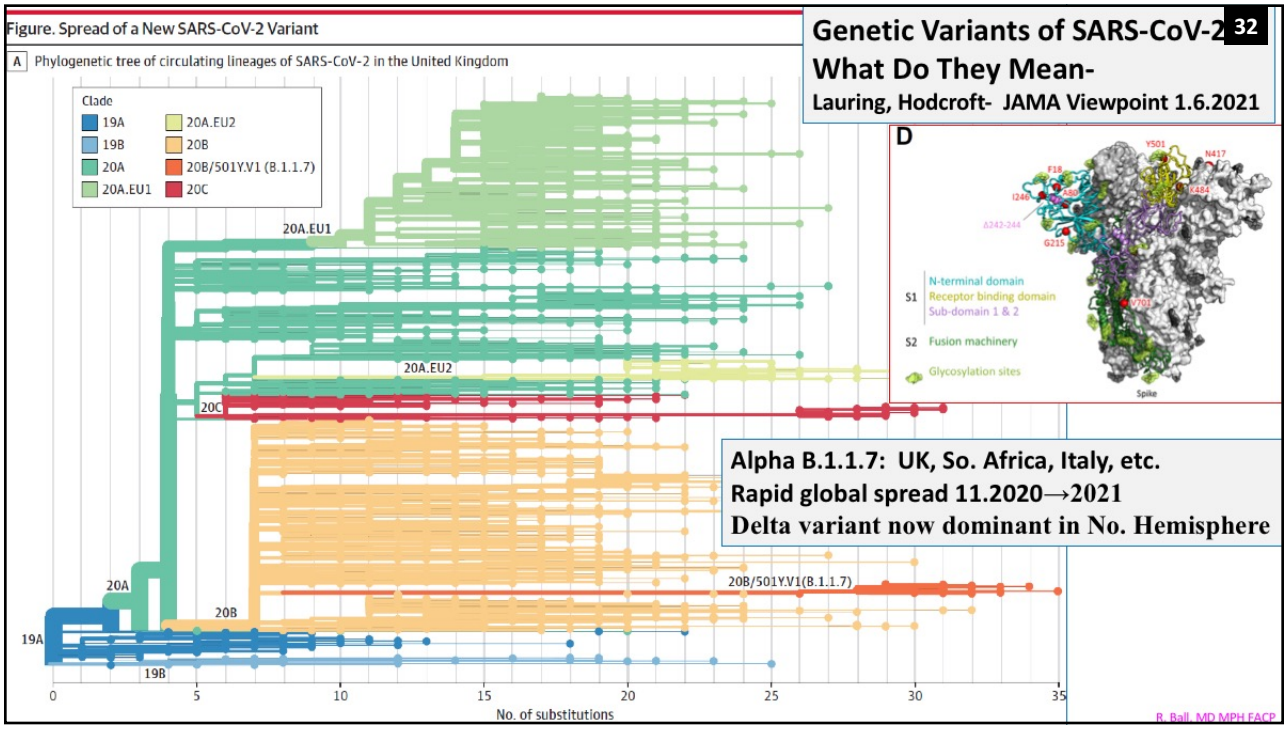
Figure. Spread of a New SARS-CoV-2 Variant
A Phylogenetic tree of circulating lineages of SARS-CoV-2 in the United Kingdom
Clade
19A
19B
20A
20A.EU1
20A.EU2
20B
20B/501Y.V1 (B.1.1.7)
20C
Genetic Variants of SARS-CoV-2
32
What Do They Mean-
Lauring, Hodcroft- JAMA Viewpoint 1.6.2021
D
N-terminal domain
S1 Receptor binding domain
Sub-domain 1 & 2
S2 Fusion machinery
Glycosylation sites
Spike
Alpha B.1.1.7: UK, So. Africa, Italy, etc.
Rapid global spread 11.2020→2021
Delta variant now dominant in No. Hemisphere
No. of substitutions
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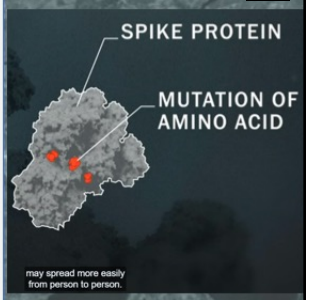
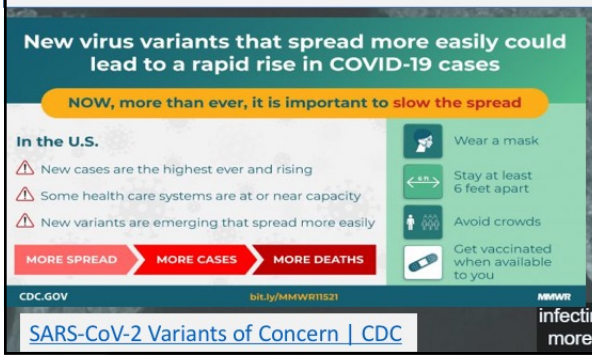
11.2020: U.K. variant is B.1.1.7, 20I/501Y.V1 (now Alpha), and a VoC (Variants of high Concern) 202012/01 (has E484K mutation). ***NERVTAG note 1.21.2021 on B.1.1.7:*** ***↑ transmission (50-70%) & probably increased disease severity, even death.***

South Africa variant is B.1.351 or 20C/501Y.V2 (now Beta). Has major mutations that blunt the effects of neutralizing antibodies that recognize 2 key regions of spike: its receptor-binding and N-terminal domains.

Brazil/Japan variant: P.1 or 20J/501Y.V3- now Gamma
India variant is B.1.617.1 & 2 (Pango lineage)- now Delta

"Immune escape" from current vaccines is possible, but thus far vaccines prevent death, severe disease from most VoIs/ VoCs.





SARS-CoV-2 Variants of Concern | CDC

SOUTH AFRICA

Delta variant (B.1.617.1) mutation: P681R (transforms proline into arginine) in a region of the spike protein called the furin cleavage site (for faster virion entry into new cells).
- BioRxiv 8.13.2021

infecting younger people more this time around.

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Britain's MHRA gave EUA to Pfizer, Moderna, & Oxford/AZ vaccines 12.30.2020

Israel's COVID vaccine rollout fastest & more complete in the world; & UK, UAE, Bahrain, others…

As of 9.20.2021, ≥ 100 countries have (multiple) mutants.
more in 2021: B.1.427/429 in California (1.17.2021), NYC B.1.526 (1/2 of cases).
3.2021: Japan (B.1.1.248) & variant (P.3) from the Philippines prob 2nd- and 3rd-generation descendants of P.1 (per ISID ProMed Post 3.20.2021)

2021: most SARS-CoV-2 variants were deemed ≥ 50% more transmissible & ~30% more virulent.

The Canberra Times
TO SERVE THE NATIONAL CITY

Australia Therapeutic Goods Administration (TGA) authorized Pfizer vaccine 01.2021

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SARS-CoV-2 Variants of Concern and Variants of Interest, updated 31 May 2021

Variants of Concern

A SARS-CoV-2 variant that meets the definition of a VOI (see below) and, through a comparative assessment, has been demonstrated to be associated with one or more of the following changes at a degree of global public health significance:

- Increase in transmissibility or detrimental change in COVID-19 epidemiology; or
- Increase in virulence or change in clinical disease presentation; or
- Decrease in effectiveness of public health and social measures or available diagnostics, vaccines, therapeutics.

WHO label	Pango lineage	GISAID clade/lineage	Nextstrain clade	Earliest documented samples	Date of designation
Alpha	B.1.1.7	GRY (formerly GR/501Y.V1)	20I/S:501Y.V1	United Kingdom, Sep-2020	18-Dec-2020
Beta	B.1.351	GH/501Y.V2	20H/S:501Y.V2	South Africa, May-2020	18-Dec-2020
Gamma	P.1	GR/501Y.V3	20J/S:501Y.V3	Brazil, Nov-2020	11-Jan-2021
Delta	B.1.617.2	G/452R.V3	21A/S:478K	India, Oct-2020	VOI: 4-Apr-2021 VOC: 11-May-2021

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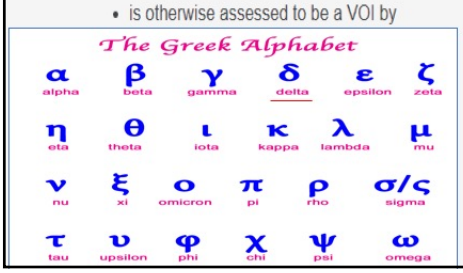
Variants of Interest

A SARS-CoV-2 isolate is a Variant of Interest (VOI) if, compared to a reference isolate, its genome has mutations with established or suspected phenotypic implications, and either:

- has been identified to cause community transmission/multiple COVID-19 cases/clusters, or has been detected in multiple countries; OR
- is otherwise assessed to be a VOI by



WHO label	Pango lineage	GISAID clade/lineage	Nextstrain clade	Earliest documented samples	Date of designation
Epsilon	B.1.427/B.1.429	GH/452R.V1	20C/S.452R	United States of America, Mar-2020	5-Mar-2021
Zeta	P.2	GR	20B/S.484K	Brazil, Apr-2020	17-Mar-2021
Eta	B.1.525	G/484K.V3	20A/S484K	Multiple countries, Dec-2020	17-Mar-2021
Theta	P.3	GR	20B/S:265C	Philippines, Jan-2021	24-Mar-2021
Iota	B.1.526	GH	20C/S:484K	United States of America, Nov-2020	24-Mar-2021
Kappa	B.1.617.1	G/452R.V3	21A/S:154K	India, Oct-2020	4-Apr-2021

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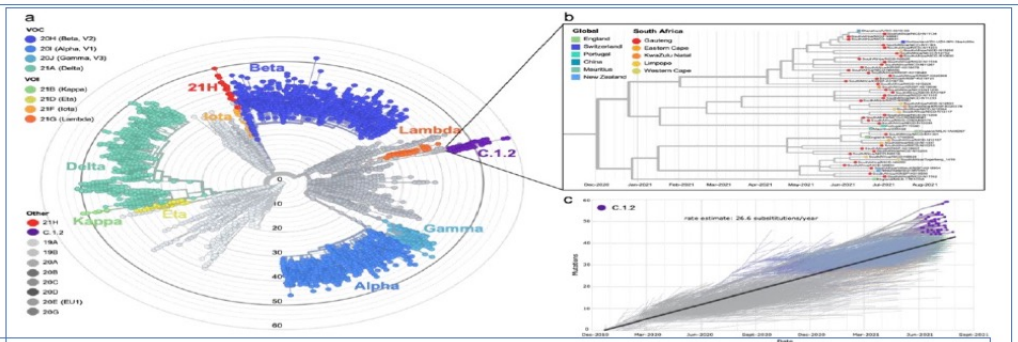
posted 8.26.2021

GISAID (www.gisaid.org): the global reference database for SARS-CoV-2 viral genomes

The continuous evolution of SARS-CoV-2 in South Africa: a new lineage with rapid accumulation of mutations of concern and global detection

"C.1.2 is highly mutated beyond C.1 and all other VOCs and VOIs globally with between 44-59 mutations away from the original Wuhan Hu-1 virus (**Fig. 1a**). While the VOI Lambda (C.37) is phylogenetically closest to C.1.2, the latter has distinct lineage-defining mutations."



Phylogenetic Assignment of Named Global Outbreak Lineages' (PANGOLIN) software suite (https://github.com/hCoV-2019/pangolin)

Fig. 1 | Global phylogenetic distribution of C.1.2

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SARS-nCoV-2/COVID testing(3 types)

1) current **NP PCR (nasal swab, or even saliva) detects RNA fragments** of SARS-CoV-2, whether in high or low concentrations (# of PCR cycles= Cn). Is **THE** diagnostic test ("gold standard") to detect (+) virus in folk for several months; it's still necessary (for now). ~ 99% sensitive, specific.

2) 3) New nasal swab tests for **Antigen (Ag) got EUA approval by US FDA 5.2020**, detect some CoV-2 proteins & can be done rapidly (like the flu nasal swab for influenza A&B Ag), with a result within an hour or less. Currently Quidel's Sofia2 & Abbott's ***BINAX-NOW***, IDNOW have suboptimal sensitivity but decent specificity. These rapid tests, some now validated, are likely to become commonplace.

3) ≥ 85 new FDA+ Antibody (Ab) tests: (ie, Abbott Labs & others). FDA EUA: blood- fingerstick or venipuncture; detect neutralizing (+) IgG Ab ("G" for Geriatric/ older Ab, which last months/years, indicating older/past infection), BUT recent articles show that some COVID patients have trace IgG Ab and still harbor the virus (small amounts). & some data prove binding Ab are fully or even partially "protective", but if so, for how long (months/ years/ ?). IgM Ab occurs sooner but w shorter duration. FDA gave GenScript USA EUA for the cPass SARS-CoV-2 Neutralization Antibody Detection Kit. And only research labs test T-cell subsets…

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Journal Pre-proof

Comparing the diagnostic accuracy of rapid antigen detection tests to real time polymerase chain reaction in the diagnosis of SARS-CoV-2 infection: A systematic review and meta-analysis

Jonghoo Lee MDPhD , Jae-Uk Song MDPhD , Sung Ryul Shim MDPhD

PII: S1386-6532(21)00252-3
DOI: https://doi.org/10.1016/j.jcv.2021.104985
Reference: JCV 104985

To appear in: *Journal of Clinical Virology*

Received date: 14 April 2021
Revised date: 19 August 2021
Accepted date: 8 September 2021

online 9.16.2021

"Comparing the diagnostic accuracy of rapid antigen detection tests (RADTs) to real time polymerase chain reaction in the diagnosis of SARS-CoV-2 infection: A systematic review and meta-analysis" **CONCLUSIONS:**

- **RADTs showed low sensitivity of 0.68 compared to those of RT-PCR.**
- **The pooled sensitivity of tests was higher in patients with high viral loads.**
- **These tests were more sensitive in patients within 5 days of symptoms onset.**

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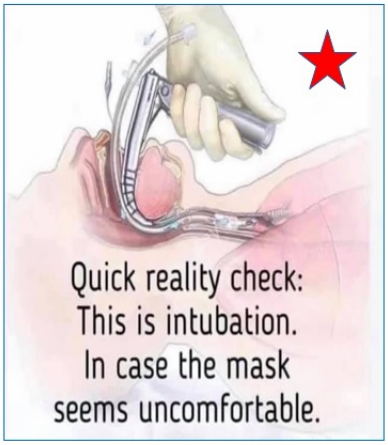
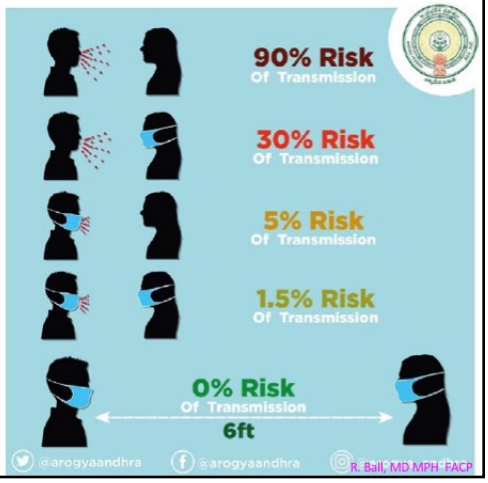
GEN. PREVENTIVE MEASURES: VACCINES & MASKS!

cloth OK, but…



HCWs: medical N95 "respirators" filter ~95% (large) droplets

"surgical masks": cheap, commonly worn by public & general HCWs



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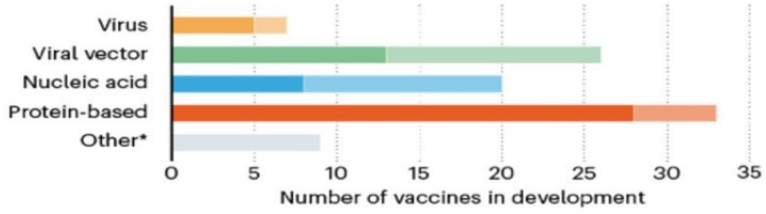
How modern vaccines work

COVAX Accelerator, led by the World Health Organization (WHO) and other global health groups including Gavi obtain & distribute COVID vaccines to many poor countries.

AN ARRAY OF VACCINES

Virus	Viral vector	Nucleic acid	Protein-based
Inactivated	Replicating	DNA	Protein subunit
Weakened	Non-replicating	RNA	Virus-like particles

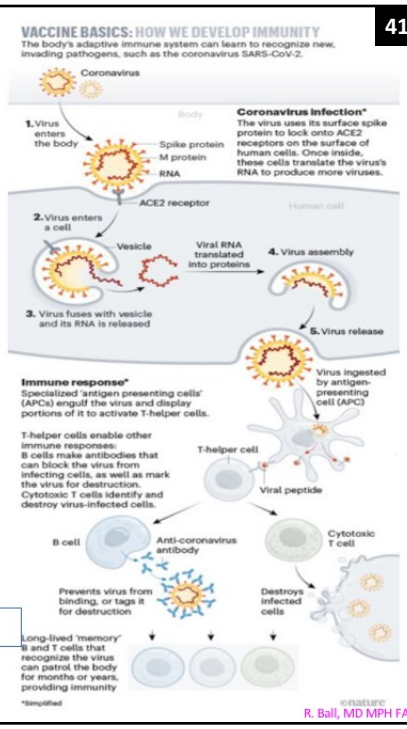


* Other efforts include testing whether existing vaccines against poliovirus or tuberculosis could help to fight SARS-CoV-2 by eliciting a general immune response (rather than specific adaptive immunity), or whether certain immune cells could be genetically modified to target the virus.

©nature

Coronavirus mRNA Vaccine Safety and Efficacy - YouTube

slide courtesy of Carlos del Rio MD, Emory Univ.



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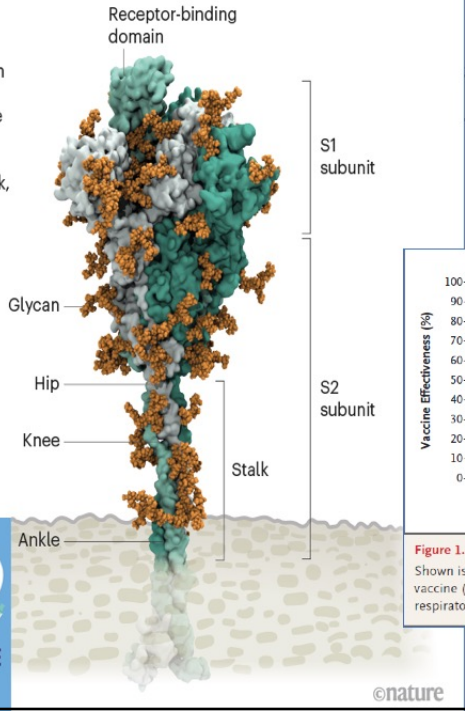
A HIDDEN SPIKE

The spike protein of SARS-CoV-2 is coated in sugar molecules, or glycans, which disguise it from the immune system. It can hinge at three points on the stalk, giving it flexibility.



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The NEW ENGLAND JOURNAL of MEDICINE

NEJM 7.21.2021

ORIGINAL ARTICLE

Effectiveness of Covid-19 Vaccines against the B.1.617.2 (Delta) Variant

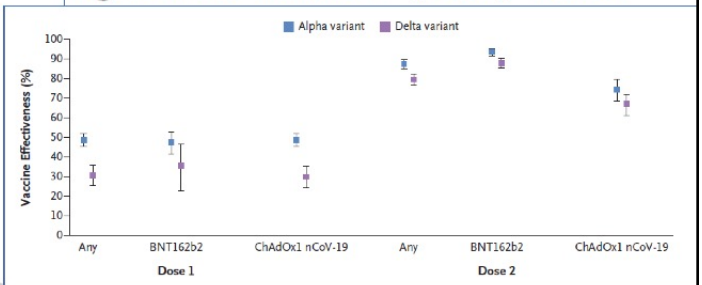

Figure 1. Vaccine Effectiveness against the Alpha and Delta Variants, According to Dose and Vaccine Type.

Shown is the effectiveness of one dose and two doses of the BNT162b2 and ChAdOx1 nCoV-19 vaccines, or either vaccine ("any"), against symptomatic disease with the B.1.1.7 (alpha) or B.1.617.2 (delta) variant of the severe acute respiratory syndrome coronavirus 2. I bars indicate 95% confidence intervals.

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FDA (Fri. 9.17.2021): Vaccines & Related Biological Products Advisory Committee (VRBPAC) voted 16:2 to deny a 3rd dose of the **Pfizer-BioNTech** vaccine for all 16+ yo Americans ~8 months after their second one. Then VRBPAC voted 18:0 to offer a booster to those 65+ yo, as well as to immunocompromised individuals at high risk of developing severe COVID, HCWs+

Centers for Disease Control and Prevention
MMWR
Morbidity and Mortality Weekly Report
Early Release / Vol. 70
September 17, 2021

Comparative Effectiveness of Moderna, Pfizer-BioNTech, and Janssen (Johnson & Johnson) Vaccines in Preventing COVID-19 Hospitalizations Among Adults Without Immunocompromising Conditions — United States, March–August 2021

Summary

What is already known about this topic?

Two 2-dose mRNA COVID-19 vaccines (from Pfizer-BioNTech and Moderna) and a 1-dose viral vector vaccine (from Janssen [Johnson & Johnson]) are currently used in the United States.

What is added by this report?

Among U.S. adults without immunocompromising conditions, vaccine effectiveness against COVID-19 hospitalization during March 11–August 15, 2021, was higher for the Moderna vaccine (93%) than the Pfizer-BioNTech vaccine (88%) and the Janssen vaccine (71%).

What are the implications for public health practice?

Although these real-world data suggest some variation in levels of protection by vaccine, all FDA-approved or authorized COVID-19 vaccines provide substantial protection against COVID-19 hospitalization.

J&J reports second dose of COVID-19 vaccine boosts protection to 94% (phase 3 ENSEMBLE 2 study). Data not presented to FDA but to news media.

A second shot of the Johnson & Johnson COVID-19 vaccine given 56 days after the first provided:

100%	94%	75%
protection against severe or critical COVID-19 after at least 14 days	protection against symptomatic (moderate to severe/ critical) COVID-19 in the U.S.	protection against symptomatic (moderate to severe/ critical) COVID-19 globally

Healio

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COVID Monoclonal Antibody Therapies

- McCreary EK, et al. *medRxiv*. 2021;doi:10.1101/2021.09.03.21262551

Since USA lags behind many 1st world countries re: % of population vaccinated, "community immunity" is unrealistic. We also depend on various therapies.

Estimating Herd Immunity Thresholds for SARS-CoV-2

- Estimates of herd immunity threshold for SARS-CoV-2 use various assumptions of R_0 varying rates of heterogenous contact[1,2]
- Various epidemiological models of the herd immunity threshold for SARS-CoV-2 currently range from 50% to 75% of the population[1,2]
  - Assume that infection provides lasting protection against reinfection
  - This equates to 200 million people in the US and 5.6 billion people worldwide[1]

1. Bloom. NEJM. 2020;(Epub). 2. Britton. Science. 2020;369:846.

Slide credit: clinicaloptions.com

Compared with combination therapy, the probability of inferiority of bamlanivimab was:

Bamlanivimab/etesevimab		Casirivimab/imdevimab
91%	VS	94%

Healio www.news-medical.net/health

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USA: "Mandates May Be The Only Way Out of This"

Professor Larry Gostin JD in a conversation of where America as a country stands today, almost two years into Covid-19. Human ingenuity and scientific gains have been "astounding," while our preparedness, in the face of such a "wily enemy," has too often been "abysmal." We experienced shock when the first wave that began in Wuhan landed at our shores; CDC bungled tests; the Trump administration stoked anti-Asian hatred and politicized essential tools– masks, vaccines, and temporary lockdowns. Public health messaging too often has been "appalling," as CDC's scientific leadership has stumbled. Now, in late 2021, we face the danger of dividing our society into two opposing camps, the vaccinated versus the unvaccinated. The Biden administration has refused to take up vaccine credentialing, a significant mistake. It has also shown remarkable leadership in trying to overcome vaccine hesitancy and refusal, and now must turn increasingly to mandates.

- **CSIS Global Health Policy Center 9.2.2021**

VIEWPOINT

An International Agreement on Pandemic Prevention and Preparedness JAMA 9.15.2021

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Weekly Operational Update on COVID-19

20 September 2021

Issue No. 72

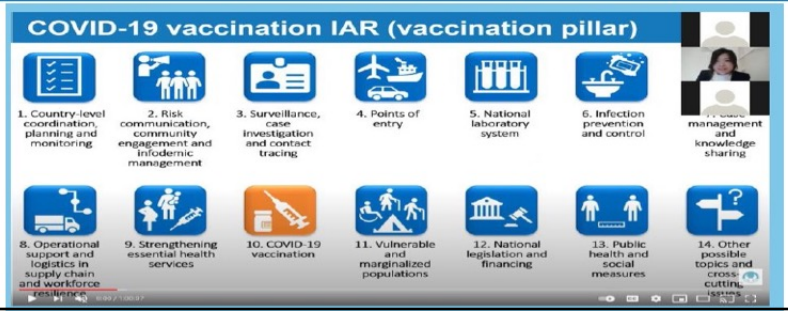
As of 19 September 2021

For all other latest data and information, including trends and current incidence, see the WHO COVID-19 Dashboard and Situation Reports

Confirmed cases **227 940 972**

Confirmed deaths **4 682 899**

www.who.int



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Home / News / Leaders Make Urgent Call To Accelerate Vaccination Globally And In Africa

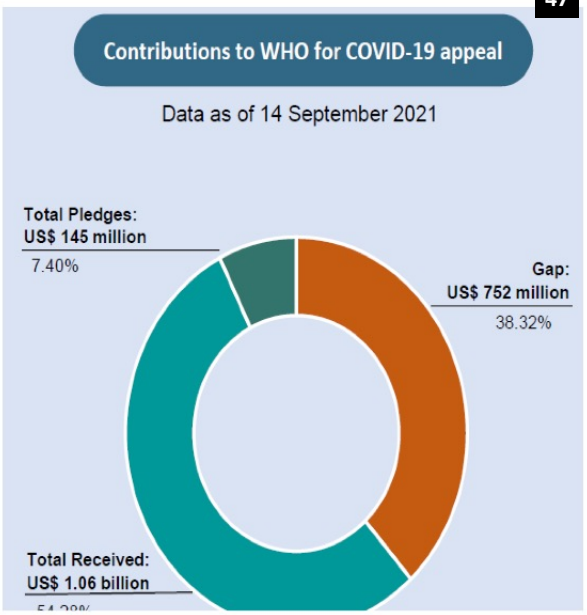
Leaders Make Urgent Call To Accelerate Vaccination Globally And In Africa

14 September 2021 | News release | Geneva | Reading time: 4 min (1119 words)

WHO-Director-General Dr Tedros Adhanom Ghebreyesus and a group of global health leaders today issued an urgent call for vaccine equity globally and in Africa in particular. The leaders stressed that the worst pandemic in the last hundred years will not end unless and until, there is genuine global cooperation on vaccine supply and access. They also reiterated the WHO's global vaccination target for 70% of the population of all countries to be vaccinated by mid- 2022.

Dr Tedros was joined by Dr Seth Berkley, CEO Gavi, Strive Masiyiwa, AU Special Envoy for COVID- 19, Dr John Nkengasong, Africa CDC Director, Professor Benedict Oramah, President and Chairman of the Board of Directors, Afreximbank, Dr Vera Songwe, UN Under- Secretary- General and Executive Secretary of the Economic Commission For Africa and Dr Matshidiso Moeti, WHO Regional Director for Africa.

The press conference followed two days of meetings among the leaders, with Richard Hatchett, Chief Executive Officer of CEPI joining the meetings as well.



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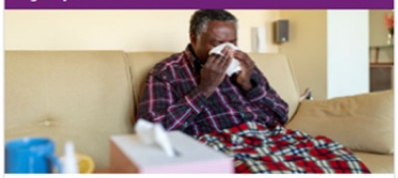
Respiratory Syncytial Virus Infection (RSV)

Respiratory syncytial (sin-SISH-uhl) virus, or RSV, is a **common respiratory virus that usually causes mild, cold-like symptoms**. Most people recover in a week or two, but RSV can be serious, especially for infants and older adults. RSV is the most common cause of bronchiolitis (inflammation of the small airways in the lung) and pneumonia (infection of the lungs) in children younger than 1 year of age in the United States.

Symptoms & Care



Know the symptoms to look for and how to care for people with RSV.

Symptoms & Care

Infants & Children

RSV can be dangerous for some infants and young children.

Infants & Children

Transmission

Help protect yourself and your loved ones from RSV infection.

Transmission

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RSV Testing traditionally not done (no specific Tx yet)

Clinicians occasionally get upper and/or lower respiratory specimens

The most common types of RSV clinical laboratory tests used are:

- Real-time reverse transcriptase-polymerase chain reaction (rRT-PCR), which is more sensitive than culture or antigen testing
- Antigen testing, which is highly sensitive in children but not very sensitive in adults
- Less commonly used tests include viral culture & serology (which is usually only used for research and surveillance studies)

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Respiratory Syncytial Virus Infection in Elderly and High-Risk Adults

CONCLUSIONS

RSV infection is an important illness in elderly and high-risk adults, with a disease burden similar to that of nonpandemic influenza A in a population in which the prevalence of vaccination for influenza is high. An effective RSV vaccine may offer benefits for these adults.

N ENGL J MED 352;17 WWW.NEJM.ORG APRIL 28, 2005

R_0 (R_t) for RSV is ~5-25 !

Table 3. Diagnostic Tests.

Test	RSV Infection	Influenza A	Influenza B
	no. of patients with positive test/total no. tested (%)		
Viral culture	64/2356 (3)	80/2356 (3)	18/2356 (<1)
RT-PCR*	163/2355 (7)	154/2354 (7)	Not done
Serologic test	183/2058 (9)	120/2051 (6)	29/2051 (1)
Total infections diagnosed by any method	244/2514 (10)	198/2514 (8)	35/2514 (1)

* RT-PCR denotes reverse-transcriptase polymerase chain reaction.

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RSV Impact espec on older adults & children

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Respiratory syncytial virus (RSV) is a seasonally circulating virus that predominantly affects children, but there a growing recognition of the effects of RSV among older adults (age ≥65 years). Annual estimates of US deaths due to RSV in older adults are approximately 14,000, with more than 177,000 inpatient admissions at a cost of more than $1 billion.

Given older adults' high incidence of multimorbidity and susceptibility to adverse infection-related sequelae, RSV infections are particularly burdensome. In particular, infection with influenza and RSV commonly result in cardiorespiratory events that include acute myocardial infarction, stroke, and exacerbation of asthma and chronic obstructive pulmonary disease (COPD).

The impact of circulating RSV can be seen from the results of a 2005 landmark study, which estimated the relationship between lab-confirmed RSV infection and cardiopulmonary events in older adults and high-risk individuals admitted to several hospitals during 4 respiratory seasons. In their findings, RSV accounted for proportion of hospital admissions: 10.6% (pneumonia,) 11.4% (COPD), 5.4% (heart failure), & 7.2% (asthma)

LTCF Setting and Risk for Respiratory Infections

Residents of long-term care facilities (LTCFs) are among the most susceptible to respiratory infections:

1) older adults are at high risk for influenza and RSV infection as a result of age-related physiologic changes such as reduced chest wall compliance, decreased cough strength, and impaired immune function due to cellular senescence.

2) the risk of infection is increased owing to the institutional nature of LTCFs- this risk is influenced by frequent resident exposure to coresidents, visitors, volunteers, and staff, all of whom may transmit viruses.

3) frail residents with decreased functional capacity experience the most severe forms of illness, requiring transfer to the hospital for supportive care and services that are not often provided in the LTCF setting.

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Recognizing RSV Among Older Adults

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RSV infections among older adults can have variable presentations. Most infections present with no symptoms or mild symptoms lasting up to 5 days and include: cough, headache, fatigue, runny nose, and throat ache. Fever may be present but is not always a reliable marker of infection in older adults. Older adults with cardiovascular illnesses, such as heart failure or acute coronary syndrome, and respiratory illnesses, such as asthma and COPD, are at risk of severe illness. Infection with RSV may also result in pneumonia. Greater attention should be paid to older adults at highest risk of severe illness from RSV infection.

Preventing RSV Infection

There are currently no approved vaccinations for RSV, although several are in development. In preparation for the potential availability of a vaccine, education on the benefits of such a vaccination should be targeted toward LTCF staff and residents.

Currently, however, the best approach to preventing RSV infection is to take precautions when RSV is circulating. Precautions relate to RSV's airborne and surface contact routes of transmission. In LTCFs, mask wearing among residents, staff, and visitors is a standard preventive measure. In addition, RSV can persist on hard surfaces for several hours, making handwashing and sanitization of surfaces effective measures. Furthermore, eating and drinking utensils should not be shared. Taken together, these steps present effective ways to prevent the transmission of RSV, and potentially severe illness, among older adults.

Credit: Elliott Bosco, PharmD, PhD, Department of Health Sciences, Policy, and Practice
Brown University School of Public Health, Providence, Rhode Island

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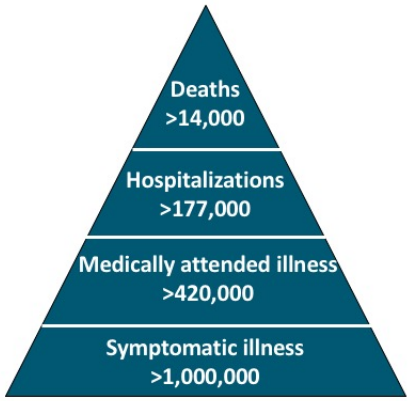
Although RSV is Often Considered a Childhood Disease, RSV Poses a Serious Threat to Older Adults

Estimated Annual RSV Cases in Adults Aged ≥65 Yr in the US[1]



- Annual attack rates in the US[2]
  - 2%-10% in older adults within the community
  - As high as 5%-10% in older adults within congregate settings
- Compared with their younger adult counterparts, older adults with RSV more likely to become hospitalized and die[3]
- Disease burden expected to increase considering the aging population

1. cdc.gov/rsv/high-risk/older-adults.html. 2. Branche. Drugs Aging. 2015;32:261. 3. Pastula. Open Forum Infect Dis. 2017;4:ofw270.

Slide credit: clinicaloptions.com

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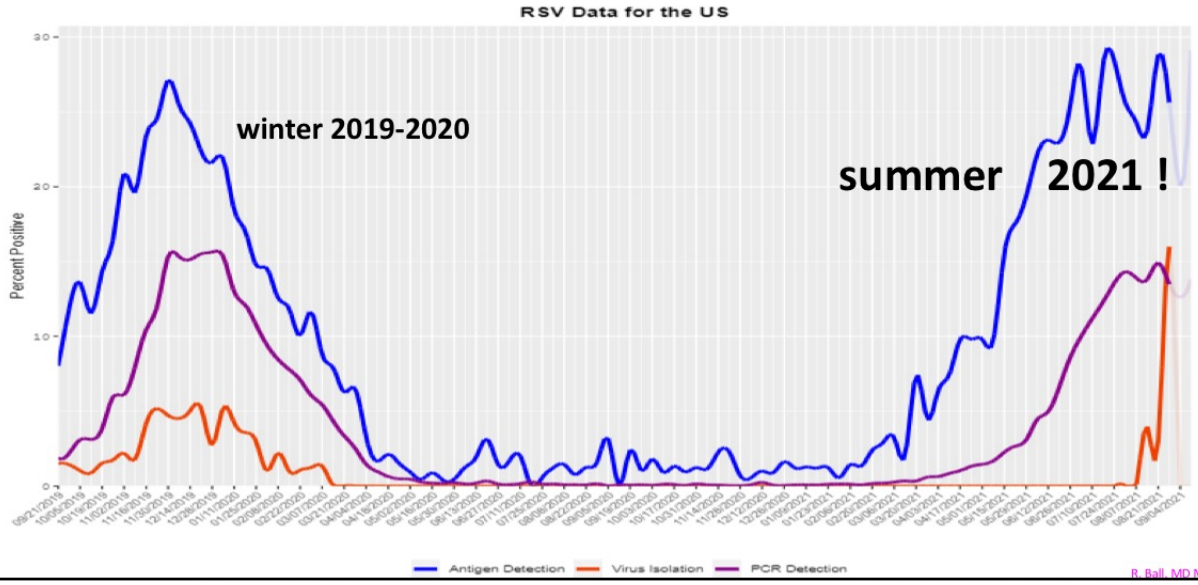
RSV is usually a winter virus in children, elderly. Why this US summer upsurge?

Percent Positive https://www.cdc.gov/surveillance/nrevss/rsv/natl-trend.html



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Older Adults More Susceptible to RSV Infection vs Younger Adult Counterparts

Interconnected Factors

- Atypical and delayed presentation
- Chronic diseases and multi-morbidities
- Aging/dysregulated immune system
- Frailty
- Contact with HCPs
- Malnutrition
- Polypharmacy
- Lung structure and physiology
- Decreased physiologic reserve
- LTCF resident
- Immobility and decreased physical activity

Interconnected Outcomes

- Increased susceptibility
- Increased morbidity and mortality
- Prolonged hospital stay
- Increased transmission
- Increased healthcare costs

https://www.clinicaloptions.com/infectious-disease/programs/2021/adult-rsv

Watson. Ther Adv Respir Dis. 2021;15:1753466621995050.

Slide credit: clinicaloptions.com

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CDC: RSV Treatment, Vaccine future:

"Researchers are working to develop RSV vaccines, but none are available yet. A drug called palivizumab is available to prevent severe RSV illness in certain infants and children who are at high risk for severe disease."

RSV: WHO activities

- **A three-year pilot project (2016-18) successfully tested the feasibility of implementing RSV surveillance based on the Global Influenza Surveillance and Response System (GISRS) in 14 countries across all six WHO regions.**

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Current types of RSV vaccines in research:

particle-based, attenuated, protein subunit , or vector-based

The DS-Cav1 vaccine for RSV, a protein subunit vaccine, was shown to be safe and to elicit "a robust boost in RSV F-specific antibodies and neutralising activity that was sustained above baseline for at least 44 weeks" in a phase 1 clinical trial, according to a study published in April 2021 in The Lancet Respiratory Medicine.

A vaccine using this antigen, called GSK3888550A, developed by GlaxoSmithKline (GSK), is currently in phase 3 clinical trials, which began in November 2020 (NIAID VRC) & University of Texas at Austin. The vaccine's antigen, a stabilized version of the virus' F protein, was developed using structure-based vaccine design.

August 2021: Moderna received US FDA fast track designation for Respiratory Syncytial Virus Vaccine **(mRNA-1345)** clinical trials.

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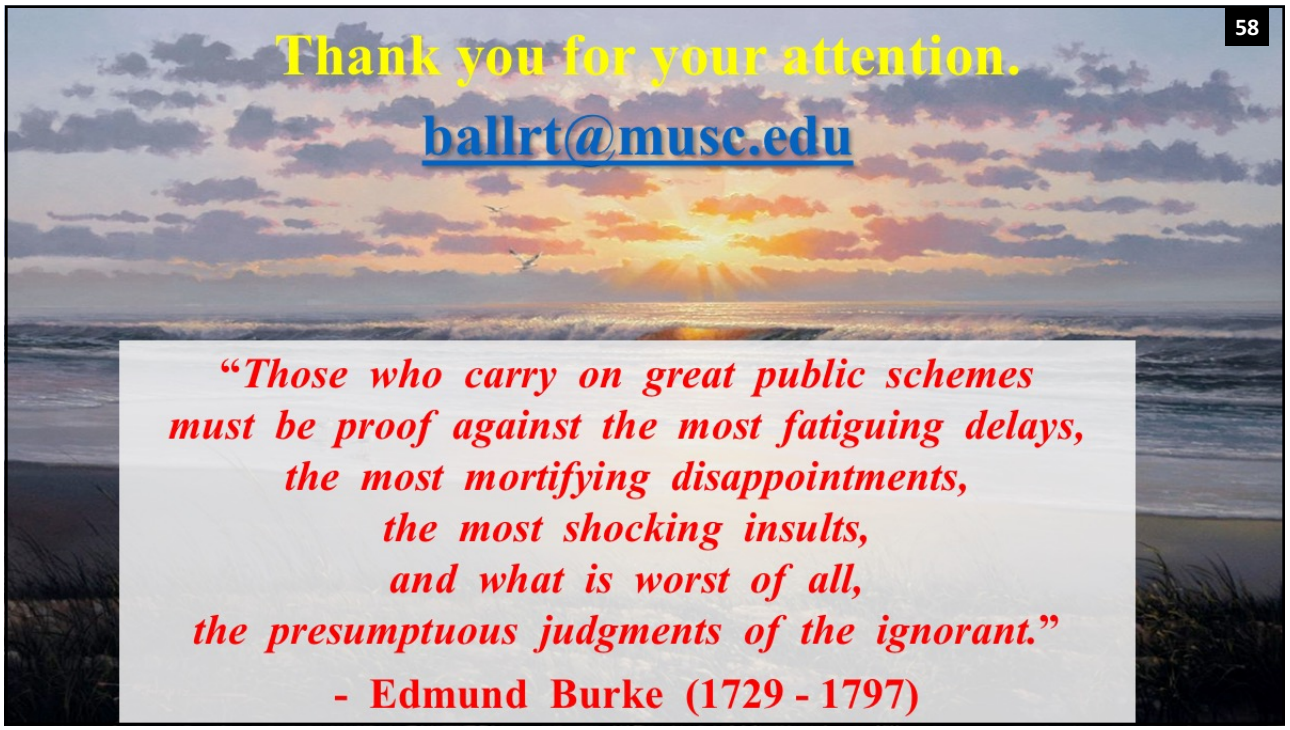

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September 29, 2021	*(FREE European Teleclass - Broadcast live from the Infection Prevention Society conference)* **Ayliffe Lecture ... PAST, PRESENT AND FUTURE** Speaker: **Peter Hoffman**, Public Health England
October 7, 2021	**INFECTION CONTROL AND PREVENTION IN LONG-TERM CARE FACILITIES AND HEALTHCARE LAUNDRY** Speaker: **John Scherberger**, Healthcare Risk Mitigation, Spartanburg, SC
October 14, 2021	**COMMON FEATURES OF WATERBORNE PATHOGENS IN HEALTHCARE FACILITIES: WHY ARE THEY SO CHALLENGING?**

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