Covid 19 Update

Taylor B. Nelson, DO
Asst Prof of Clinical Medicine
Division of Infectious Diseases
10.20.20

Health Care
University of Missouri Health System

MU Updates
Late last night…

MUHC Volumes		
NOTE: Testing volumes will continue to be revised as new		
70,538	5780	41
Visits Tested	Positive Visits	In-house (+)
5518	12.9%	6
Unique + Pts	24 Hr + Rate	In-house (PUI)

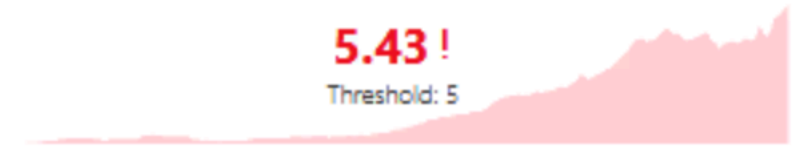
Current Unit	Detected	Pending Results	Pending Symp
CARDIOVASCULAR	1		
CICU 4Tower		1	
EC WEST		1	
EF-AIU		1	
EMER CTR C UH	1	13	4
MED 1		2	
MED 2		1	
MICU3		1	
MICU5	14		
MO YOUTH PSYCH		1	
MPC ADULT 3		2	1
NEURO SCIENCE		2	
NSICU		1	
OBSERVATION		3	
SHORT STAY			
PROGRESSIVE CARE	21		
SICU		1	
Total	41	39	6

2 ED admit
2 at WCH

Active Cases per 1,000 Residents: MUHC Market

5.43 !

Threshold: 5



384

Admitted to Date

Health Care
University of Missouri Health System

MU Updates

- Numbers of Covid admissions consistently highest since pandemic began for the past week [> 40 in house at any given time]
- We do have algorithms for expanding Covid units internally (to different areas of the hospital, cohorting patients in the same room)
- Thus far, resources have been available – PPE, remdesivir, dexamethasone

Case

- Middle age male
- Recent renal transplant, 2 weeks prior to Covid diagnosis
- Gradually improving allograft function post-transplant
- Day 7 post-transplant, got CT abdomen to evaluate fluid collection around transplant kidney
  - Incidentally noted peripheral bilateral lower lobe opacities “consistent with Covid 19”
  - No respiratory symptoms, no further workup done
- Day 14 post-transplant, developed mildly productive cough
  - Covid PCR positive (was negative at time of transplant)

Case

- Room air → 2L → 6L → 45% on 30L/min over the course of 3 days
- Pneumonia PCR panel: + Serratia marscecens (started on ertapenem)
- Sputum culture: + Pseudomonas aeruginosa (switched to meropenem)
- Held mycophenolate (CellCept), increased steroid dose
- Had also received antithymocyte globulin at the time of transplant and was on tacrolimus
- [Heavily immunosuppressed]

Case

- Started remdesivir once renal function was stable with GFR > 30 for two days; GFR then worsened, so stopped RDV
- Prednisone 20 mg → dexamethasone 6 mg
- Improved with treatment of bacterial pneumonia and supportive care for Covid 19

Case

- Special issues to consider in transplant population
  - Donor derived Covid infection? [our donor was negative]
  - Safety of trial medications in transplant population?
    - Specifically – renal transplant patient with slowly improving allograft function, contraindication for remdesivir in GFR < 30 [will touch on this later]
    - Depending upon level of risk, irradiated blood products? (convalescent plasma)
    - Drug-drug interactions with post-transplant medications
  - Risk of other co-occurring infections (based on timeline after transplant, level of immunosuppression, exposure history, prolonged hospitalizations)
  - General increased risk of morbidity/mortality

Covid in Solid Organ Transplant Patients

Health Care
University of Missouri Health System

Donor-Derived SARS-CoV-2 Infection

- To date (to my knowledge and based on my own literature review), no cases of donor-derived Covid 19 have been reported
- Risk is theoretical, based on the fact that we have identified SARS-CoV-2 viral RNA in transplantable organs (lung, heart, kidney, intestines)
- All donors and donor organs should be screened prior to transplant

Covid Treatment in Transplant Population

- In general, management approach is similar to non-transplant Covid+ patients
  - Supportive care
  - Consider remdesivir
  - Dexamethasone if appropriate (requiring oxygen/respiratory support)
- In moderate/severe Covid, reduction of immunosuppression should be considered, vs risk of acute rejection
  - Particularly of concern in heart and lung transplants, who typically require higher level of maintenance immunosuppression
- Also concern that Covid itself may increase the risk for acute rejection
- Of note, glucocorticoids are associated with potentially prolonged viral shedding

kidney INTERNATIONAL

ISN INTERNATIONAL SOCIETY OF NEPHROLOGY 60 years 1960-2020

- Looked at prevalence and outcome in renal transplant patients in the Bronx, NY, between March – June
- 132 renal transplant patients tested positive by PCR
  - 80% went on to develop detectable IgG antibodies
- 912 transplant recipients tested for IgG: 16.6% positive
- The prevalence of SARS-CoV-2 infection (diagnosed by PCR or IgG) in 975 renal transplant patients was 23.4%
- Overall mortality 20.5% [37.8% in hospitalized patients]
- 23% of hospitalized patients required renal replacement therapy, and 6.3% lost their allografts

MU Health Care
University of Missouri Health System

Covid in Transplant

- Still a lot of questions to answer
- Very high risk patient population group
- Multi-modal management with input from all teams [surgery, medical, ID] is important

Covid Transmission Precautions

- With increasing cases statewide (nationally, internationally…)
- Remember the importance of PPE/resource preservation
- When can we take patients off precautions? (next slides)
- Conserve the number of staff using PPE to enter Covid patient rooms
- CDC guidelines last updated in August

A test-based strategy is no longer recommended (except as noted below) because, in the majority of cases, it results in prolonged isolation of patients who continue to shed detectable SARS-CoV-2 RNA but are no longer infectious.

Symptom-Based Strategy for Discontinuing Transmission-Based Precautions.

Patients with mild to moderate illness who are not severely immunocompromised:

- At least 10 days have passed *since symptoms first appeared* **and**
- At least 24 hours have passed *since last* fever without the use of fever-reducing medications **and**
- Symptoms (e.g., cough, shortness of breath) have improved

Note: For patients who are **not severely immunocompromised**[1] and who were **asymptomatic** throughout their infection, Transmission-Based Precautions may be discontinued when at least 10 days have passed since the date of their first positive viral diagnostic test.

Patients with severe to critical illness or who are severely immunocompromised[1]:

- At least 10 days and up to 20 days have passed *since symptoms first appeared* **and**
- At least 24 hours have passed *since last* fever without the use of fever-reducing medications **and**
- Symptoms (e.g., cough, shortness of breath) have improved
- Consider consultation with infection control experts

Note: For **severely immunocompromised[1]** patients who were **asymptomatic** throughout their infection, Transmission-Based Precautions may be discontinued when at least 10 days and up to 20 days have passed since the date of their first positive viral diagnostic test.

As described in the Decision Memo, an estimated 95% of severely or critically ill patients, including some with severe immunocompromise, no longer had replication-competent virus 15 days after onset of symptoms; no patients had replication-competent virus more than 20 days after onset of symptoms. The exact criteria that determine which patients will shed replication-competent virus for longer periods are not known. Disease severity factors and the presence of immunocompromising conditions should be considered in determining the appropriate duration for specific patient populations. For example, patients with characteristics of severe illness may be most appropriately managed with at least 15 days of isolation under Transmission-Based Precautions.

Updates on Covid Treatment

Health Care
University of Missouri Health System

Oct 15, 2020

- Study drugs were **Remdesivir, Hydroxychloroquine, Lopinavir/ritonarvir,** and **Interferon-β1a** (mainly subcutaneous; initially with Lopinavir, later not)
- 405 hospitals in 30 countries
  - 11,266 adults were randomized
  - 2750 allocated Remdesivir
  - 954 Hydroxychloroquine
  - 1411 Lopinavir/R
  - 651 Interferon plus Lopinavir
  - 1412 only Interferon
  - 4088 no study drug
- No study drug reduced mortality (in unventilated patients or any other subgroup), initiation of ventilation or hospitalization duration
- The Solidarity Trial is considering evaluating other treatments, to continue the search for effective COVID-19 therapeutics. So far, only corticosteroids have been proven effective against severe and critical COVID-19.

Repurposed antiviral drugs for COVID-19; interim WHO SOLIDARITY trial results

WHO Solidarity Trial Consortium, Hongchao Pan, Richard Peto, Quarraisha Abdool Karim, Marissa Alejandria, Ana Maria Henao Restrepo, Cesar Hernandez Garcia, Marie Paule Kieny, Reza Malekzadeh, Srinivas Murthy, Marie-Pierre Preziosi, Srinath Reddy, Mirta Roses, Vasee Sathiyamoorthy, John-Arne Rottingen, Soumya Swaminathan

doi: https://doi.org/10.1101/2020.10.15.20209817

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Oct 8. 2020

Remdesivir for the Treatment of Covid-19 — Final Report

John H. Beigel, M.D., Kay M. Tomashek, M.D., M.P.H., Lori E. Dodd, Ph.D., Aneesh K. Mehta, M.D., Barry S. Zingman, M.D., Andre C. Kalil, M.D., M.P.H., Elizabeth Hohmann, M.D., Helen Y. Chu, M.D., M.P.H., Annie Luetkemeyer, M.D., Susan Kline, M.D., M.P.H., Diego Lopez de Castilla, M.D., M.P.H., Robert W. Finberg, M.D., et al., for the ACTT-1 Study Group Members*

- Randomized, double-blinded, placebo-controlled, multicenter, multinational study (60 sites)
- Looking at hospitalized patients with Covid 19
- Primary outcome: Time to recovery (defined by discharge, or continued hospitalization ONLY for infection control purposes)
- 1062 patients: RDV group 541, placebo group 521
- RDV: 200 mg on day 1, 100 mg thereafter (up to 10 day course)
- Median time to recover was 10 days in RDV group and 15 days in placebo group ($p < 0.001$)
- Best overall effects were seen in groups with ordinal score 5
  - 4 = no oxygen, 5 = low flow O2, 6 = high flow O2 or non-invasive, 7 = Vent/ECMO

Figure 1. Recommendations for Pharmacologic Management of Patients with COVID-19 Based on Disease Severity

DISEASE SEVERITY	PANEL'S RECOMMENDATIONS *(Recommendations are listed in order of preference in each category below; however, all options are considered acceptable.)*
Not Hospitalized ***or*** **Hospitalized but Does Not Require Supplemental Oxygen**	No specific antiviral or immunomodulatory therapy recommended The Panel **recommends against** the use of **dexamethasone (AI)** See the Remdesivir section for a discussion of the data on using this drug in hospitalized patients with moderate COVID-19.[a]
Hospitalized and Requires Supplemental Oxygen **(but Does Not Require Oxygen Delivery Through a High-Flow Device, Noninvasive Ventilation, Invasive Mechanical Ventilation, or ECMO)**	**Remdesivir** 200 mg IV for one day, followed by remdesivir 100 mg IV once daily for 4 days or until hospital discharge, whichever comes first **(AI)**[b,c,d] ***or*** **Remdesivir** (dose and duration as above) plus **dexamethasone**[e] 6 mg IV or PO for up to 10 days or until hospital discharge, whichever comes first **(BIII)**[f] If **remdesivir** cannot be used, **dexamethasone**[e] may be used instead **(BIII)**
Hospitalized and Requires Oxygen Delivery Through a High-Flow Device or Noninvasive Ventilation	**Dexamethasone**[d] plus **remdesivir** at the doses and durations discussed above **(AIII)**[f] ***or*** **Dexamethasone**[d,e] at the dose and duration discussed above **(AI)**
Hospitalized and Requires Invasive Mechanical Ventilation or ECMO	**Dexamethasone**[d,e] at the dose and duration discussed above **(AI)** ***or*** **Dexamethasone**[e] plus **remdesivir** for patients who have recently been intubated at the doses and durations discussed above **(CIII)**[f]

Rating of Recommendations: A = Strong; B = Moderate; C = Optional
Rating of Evidence: I = One or more randomized trials with clinical outcomes and/or validated laboratory endpoints; II = One or more well-designed, nonrandomized trials or observational cohort studies; III = Expert opinion

- NIH Covid Treatment Guidelines
- Updated 10/9/20

Health Care
University of Missouri Health System

JASN Journal of the American Society of Nephrology

Remdesivir in Patients with Acute or Chronic Kidney Disease and COVID-19

Meagan L. Adamsick,[1] Ronak G. Gandhi,[1] Monique R. Bidell,[1] Ramy H. Elshaboury,[1] Roby P. Bhattacharyya,[2] Arthur Y. Kim,[2] Sagar Nigwekar,[3] Eugene P. Rhee,[3] and Meghan E. Sise[3]

[1]Department of Pharmacy, Massachusetts General Hospital, Boston, Massachusetts
[2]Division of Infectious Diseases, Department of Medicine, Massachusetts General Hospital, Boston, Massachusetts
[3]Division of Nephrology, Department of Medicine, Massachusetts General Hospital, Boston, Massachusetts

- Concerns about RDV effect on patients with renal dysfunction are due to both remdesivir's mechanism of action as well as its cyclodextrin carrier
  - Potential for mitochondrial toxicity → renal tubular injury
    - This would be exponentially more likely in prolonged exposure, not a 5-10 day course
  - Cyclodextrin, same carrier used for IV voriconazole
    - Concern for accumulation in the kidneys and liver
    - Previous animal studies done with doses 50-100 fold higher than 5-10 day RDV course
- Early studies have excluded patients with renal dysfunction
- It seems likely that short courses of remdesivir would be fairly low risk
- Also keep in mind that there is no proven mortality benefit with RDV
- As always, a risk/benefit scenario

MU Health Care
University of Missouri Health System

Updates on Demographics

Health Care
University of Missouri Health System

Morbidity and Mortality Weekly Report (*MMWR*)

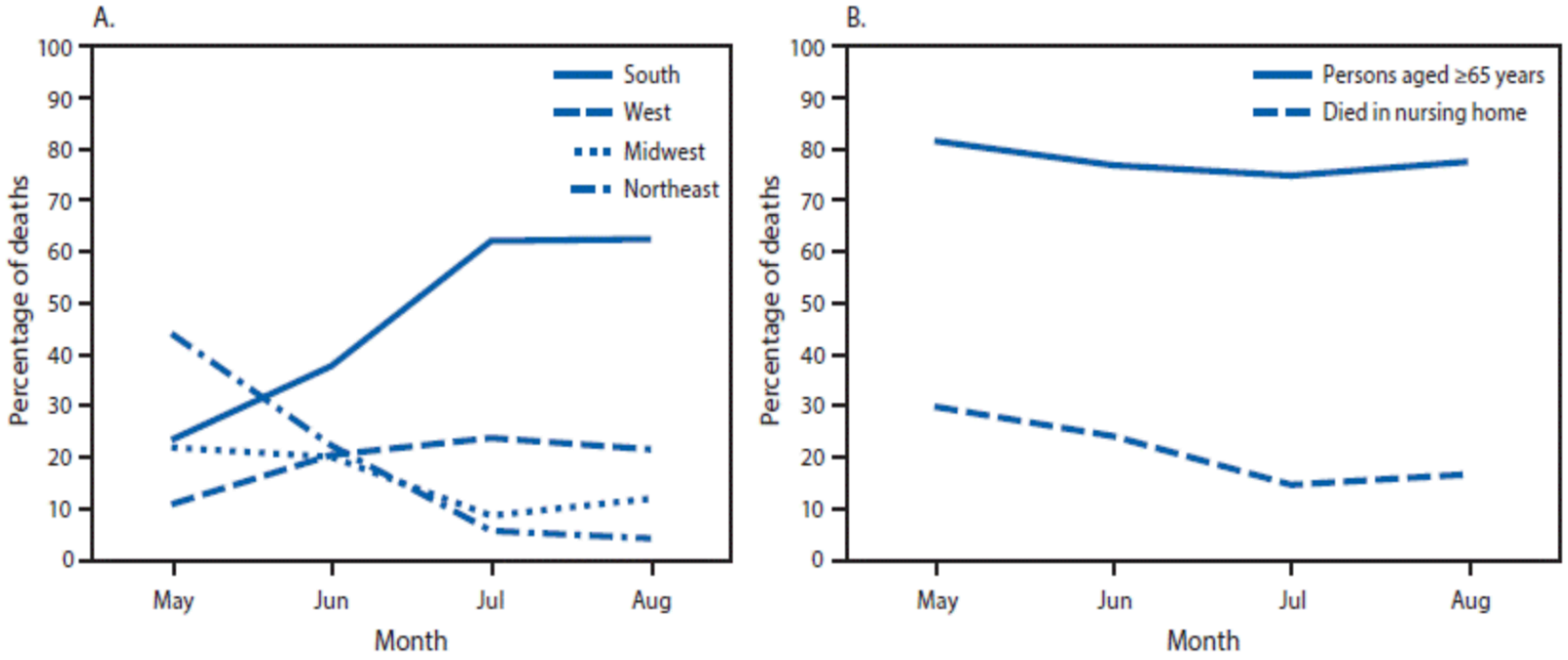
CDC

Race, Ethnicity, and Age Trends in Persons Who Died from COVID-19 — United States, May–August 2020

Early Release / October 16, 2020 / 69

Jeremy A.W. Gold, MD[1,2]; Lauren M. Rossen, PhD[3]; Farida B. Ahmad, MPH[3]; Paul Sutton, PhD[3]; Zeyu Li, MPH[4]; Phillip P. Salvatore, PhD[1,2]; Jayme P. Coyle, PhD[1]; Jennifer DeCuir, MD, PhD[1,2]; Brittney N. Baack, MPH[1]; Tonji M. Durant, PhD[1]; Kenneth L. Dominguez, MD[1]; S. Jane Henley, MSPH[1]; Francis B. Annor, PhD[1]; Jennifer Fuld, PhD[1]; Deborah L. Dee, PhD[1]; Achuyt Bhattarai, MD[1]; Brendan R. Jackson, MD[1] (View author affiliations)

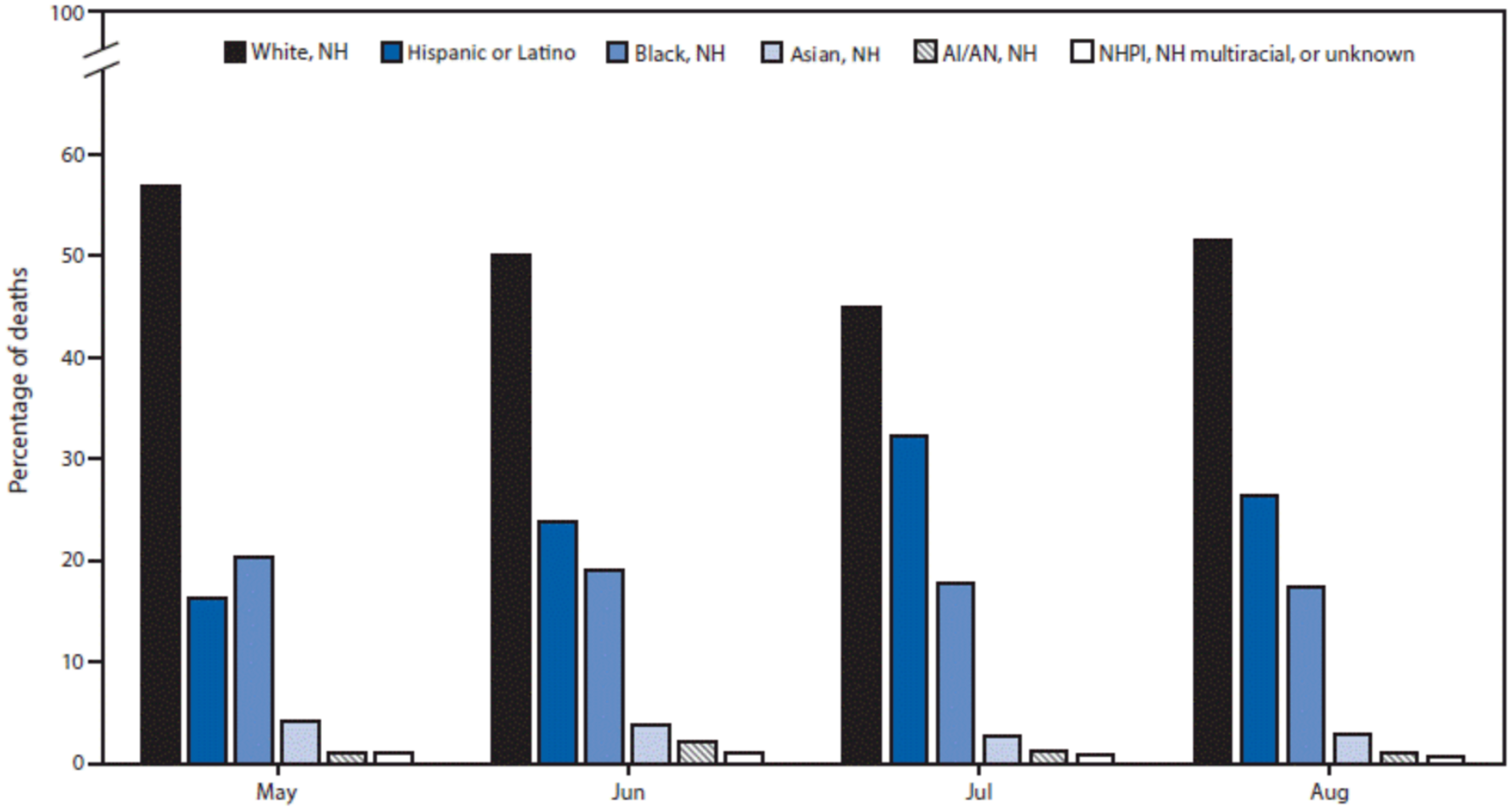
FIGURE 1. Monthly COVID-19–associated deaths* as a percentage of all deaths, by U.S. Census region, all ages (A), and for persons aged ≥65 years or persons of any age who died in a nursing home or long-term care facility (B) (N = 114,411) — National Vital Statistics System, United States, May 1–August 31, 2020



Downtrending numbers in elderly and institutionalized patients reflects higher numbers of young patients that we have seen

Health Care
University of Missouri Health System

FIGURE 2. Monthly deaths, by race/ethnicity* as a percentage of all COVID-19–associated deaths (N = 114,411) — National Vital Statistics System, United States, May 1–August 31, 2020



US population by race/origin:
From USCensus

White: 86%
Hispanic: 19%
Black: 13%
Asian: 6%
Alaskan Native/American Indian: 1.2%
Native Hawaiian or other Pacific Islander: 0.2%

Health Care
University of Missouri Health System

Herd Immunity

Health Care
University of Missouri Health System

JAMA Insights

ONLINE FIRST FREE

October 19, 2020

Herd Immunity and Implications for SARS-CoV-2 Control

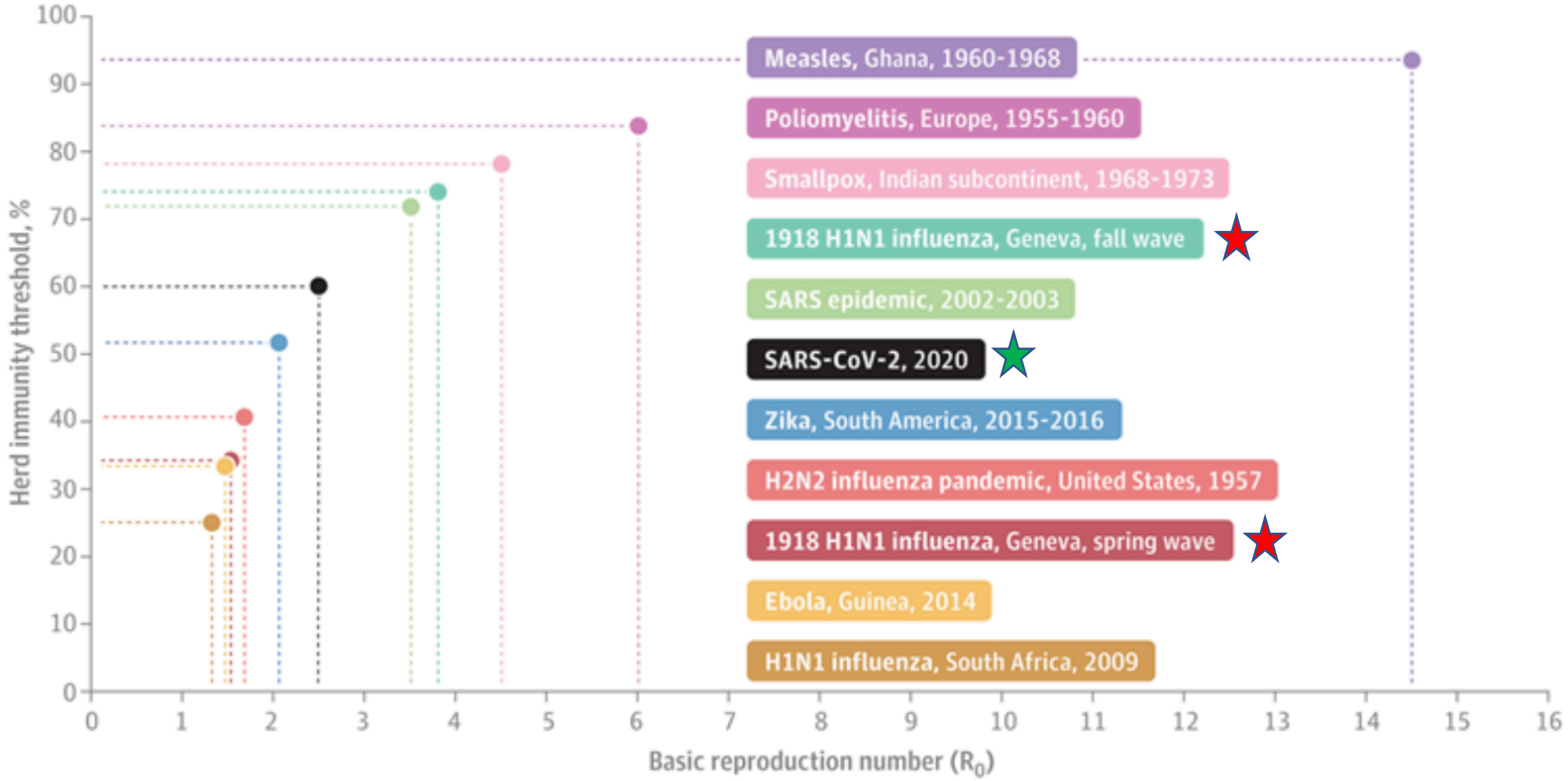
Saad B. Omer, MBBS, MPH, PhD[1,2]; Inci Yildirim, MD, PhD, MSc[1,3]; Howard P. Forman, MD, MBA[4,5]

» Author Affiliations | Article Information

JAMA. Published online October 19, 2020. doi:10.1001/jama.2020.20892

- Herd immunity – what is it?
  - When enough of the population is immune to a disease (either by natural infection or vaccination), protection is provided to those who are susceptible
- Herd immunity threshold
  - The threshold at which enough people are immune to extinguish an ongoing outbreak, and to interrupt endemic transmission of a pathogen
  - More highly communicable pathogen (higher R_0) requires higher herd immunity threshold
- Based on what we know of SARS-CoV-2, herd immunity threshold in the absence of any other interventions would be approximately 60%

Figure. Herd Immunity Thresholds by Disease



★ Something to think about

Health Care
University of Missouri Health System

JAMA Insights

ONLINE FIRST FREE

October 19, 2020

Herd Immunity and Implications for SARS-CoV-2 Control

Saad B. Omer, MBBS, MPH, PhD[1,2]; Inci Yildirim, MD, PhD, MSc[1,3]; Howard P. Forman, MD, MBA[4,5]

» Author Affiliations | Article Information

JAMA. Published online October 19, 2020. doi:10.1001/jama.2020.20892

- Duration of immunity
  - Durability of immune memory is critical to sustaining herd immunity
  - Measles, rubella, varicella - long-term immunity achieved with both natural infection and immunization
  - Seasonal coronaviruses – no such luck
  - When natural immunity is not durable, successful immunization (even if required periodically) can sustain herd immunity

JAMA Insights

ONLINE FIRST FREE

October 19, 2020

Herd Immunity and Implications for SARS-CoV-2 Control

Saad B. Omer, MBBS, MPH, PhD[1,2]; Inci Yildirim, MD, PhD, MSc[1,3]; Howard P. Forman, MD, MBA[4,5]

» Author Affiliations | Article Information

JAMA. Published online October 19, 2020. doi:10.1001/jama.2020.20892

- T-Cell Cross-Reactivity
  - Some reports have suggested cross reactivity with other coronaviruses may confer immunity to SARS-CoV-2
  - It is not clear whether this could provide sterilizing immunity (host cannot carry or transmit the virus) as opposed to reducing severity of SARS-CoV-2 infection

JAMA Insights

ONLINE FIRST FREE

October 19, 2020

Herd Immunity and Implications for SARS-CoV-2 Control

Saad B. Omer, MBBS, MPH, PhD[1,2]; Inci Yildirim, MD, PhD, MSc[1,3]; Howard P. Forman, MD, MBA[4,5]

» Author Affiliations | Article Information

JAMA. Published online October 19, 2020. doi:10.1001/jama.2020.20892

- Infection-based herd immunity as an approach to the pandemic
  - Letting “low risk” groups become infected while sequestering “high risk” groups
  - Lots of problems with this proposed method
  - Even with modest infection fatality ratios, 100% of us are susceptible at baseline (new pathogen) – so there will be substantial mortality
  - Sequestering high risk populations is impractical, and infection in low risk population will eventually spread to high risk population

JAMA Insights

ONLINE FIRST FREE

October 19, 2020

Herd Immunity and Implications for SARS-CoV-2 Control

Saad B. Omer, MBBS, MPH, PhD[1,2]; Inci Yildirim, MD, PhD, MSc[1,3]; Howard P. Forman, MD, MBA[4,5]

» Author Affiliations | Article Information

JAMA. Published online October 19, 2020. doi:10.1001/jama.2020.20892

- We have no large-scale examples where infection-based herd immunity works
  - The authors cited
  - Sweden attempted this early in the pandemic (Feb-March)
  - In April, population seroprevalence was reported to be < 8%, similar to other cities which had undertaken more restrictions

JAMA Insights

ONLINE FIRST FREE

October 19, 2020

Herd Immunity and Implications for SARS-CoV-2 Control

Saad B. Omer, MBBS, MPH, PhD[1,2]; Inci Yildirim, MD, PhD, MSc[1,3]; Howard P. Forman, MD, MBA[4,5]

» Author Affiliations | Article Information

JAMA. Published online October 19, 2020. doi:10.1001/jama.2020.20892

- US: population 330 million
- WHO Infection fatality rate: 0.5%
- 198 million Americans would need to become immune to reach the 60% herd immunity threshold
  - This would result in at least several hundred thousand more deaths
- Assuming < 10% of the US population has been infected thus far, and with uncertain durability of immunity, infection-induced herd immunity is not realistic
- Efficacy of vaccines is yet to be seen

JAMA Insights

ONLINE FIRST FREE

October 19, 2020

Herd Immunity and Implications for SARS-CoV-2 Control

Saad B. Omer, MBBS, MPH, PhD[1,2]; Inci Yildirim, MD, PhD, MSc[1,3]; Howard P. Forman, MD, MBA[4,5]

» Author Affiliations | Article Information

JAMA. Published online October 19, 2020. doi:10.1001/jama.2020.20892

- So…
  - Herd immunity is important
  - Even small deviations from protective herd immunity levels can allow for significant outbreaks (e.g. Measles)
  - Vaccines are critical for herd immunity in SARS-CoV-2, if it can be achieved
  - They must be effected and broadly administered

Questions?

Thanks!

Feel free to email me at **nelsontb@health.missouri.edu**.

Health Care
University of Missouri Health System