COVID-19

KRISTIAN TESTERMAN PHARMD

MEDICAL MANAGEMENT MEETINGS 2020

FACTS ABOUT COVID-19

- COVID-19 is a disease caused by a novel coronavirus
- There are many types of coronaviruses; however, COVID-19 is a new disease that has not previously been seen in humans
- The virus that causes COVID-19 is named severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2)
- The name SARS-CoV-2 was chosen, because the virus is genetically similar to the coronavirus that caused the SARS outbreak in 2003
- COVID-19 was first identified in Wuhan, China
- It is likely spread from person to person through respiratory droplets
- It spreads very easily and sustainably [meaning it is very contagious and goes from person to person without stopping]
- It may be spread by people that are currently not showing symptoms

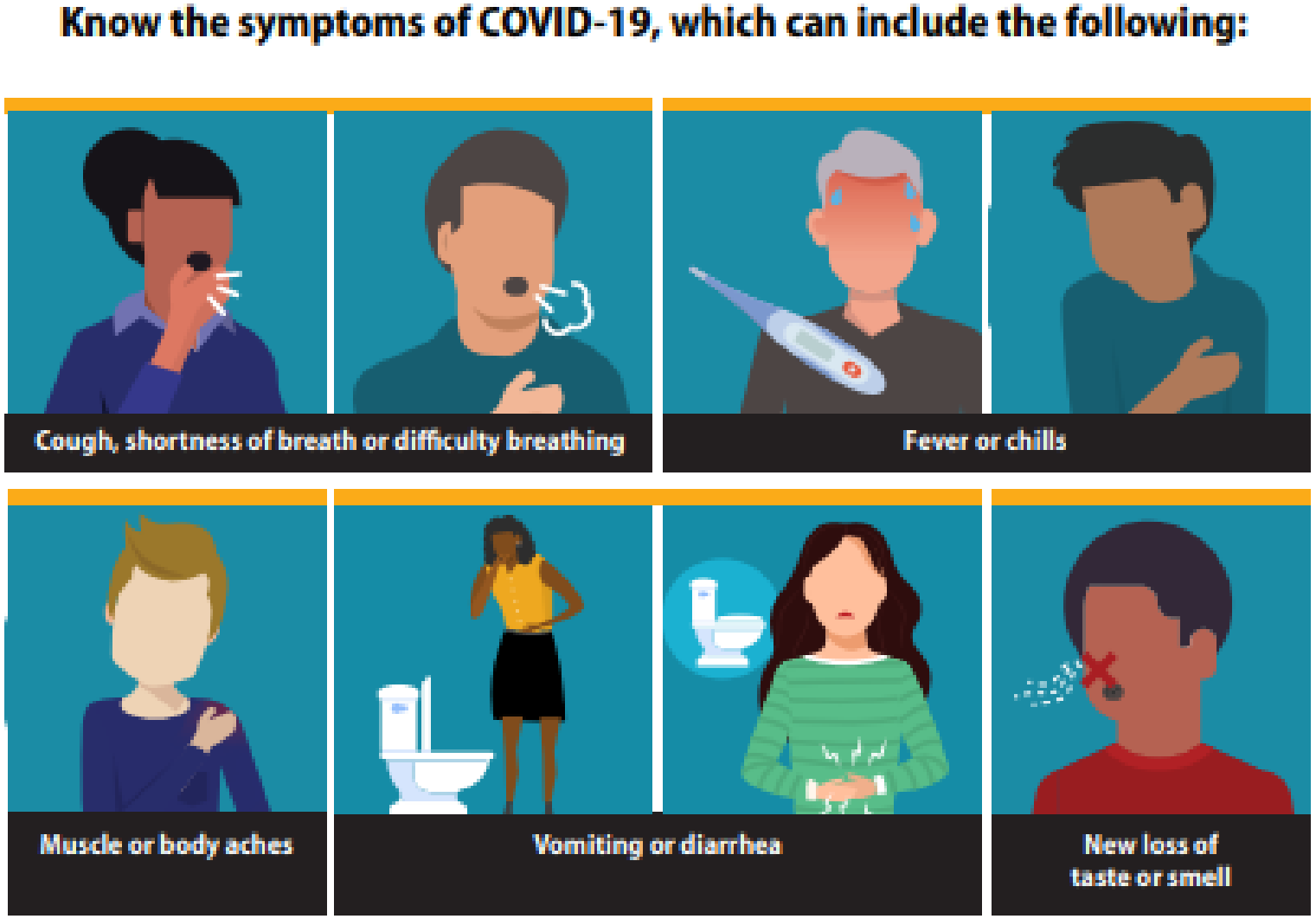
HTTPS://WWW.CDC.GOV/CORONAVIRUS/2019-NCOV/FAQ.HTML
HTTPS://WWW.WHO.INT/EMERGENCIES/DISEASES/NOVEL-CORONAVIRUS-2019/TECHNICAL-GUIDANCE/NAMING-THE-CORONAVIRUS-DISEASE-(COVID-2019)-AND-THE-VIRUS-THAT-CAUSES-IT

PROTECTION AND PREVENTION

Wash	Maintain	Wear	Disinfect	Watch
Wash your hands often with • Soap and Water for 20 seconds • Hand sanitizer with at least 60% alcohol	Maintain social distance of at least 6 feet	Wear a mask	Disinfect high touch surfaces (cell phone, light switches, door-knobs, etc.)	Watch for symptoms

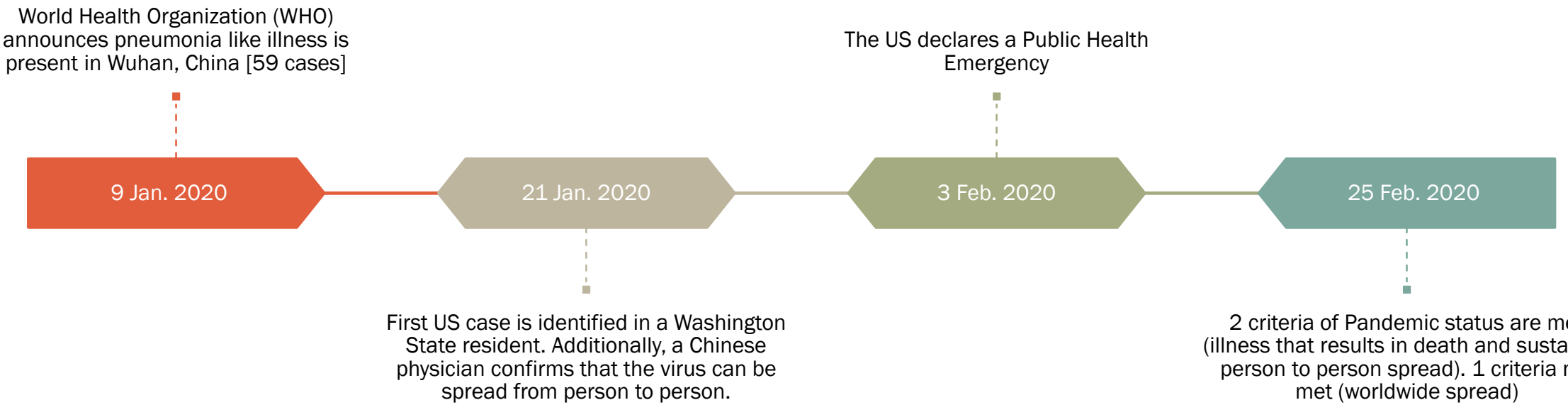
HTTPS://WWW.CDC.GOV/CORONAVIRUS/2019-NCOV/PREVENT-GETTING-SICK/PREVENTION.HTML

SYMPTOMS OF COVID-19



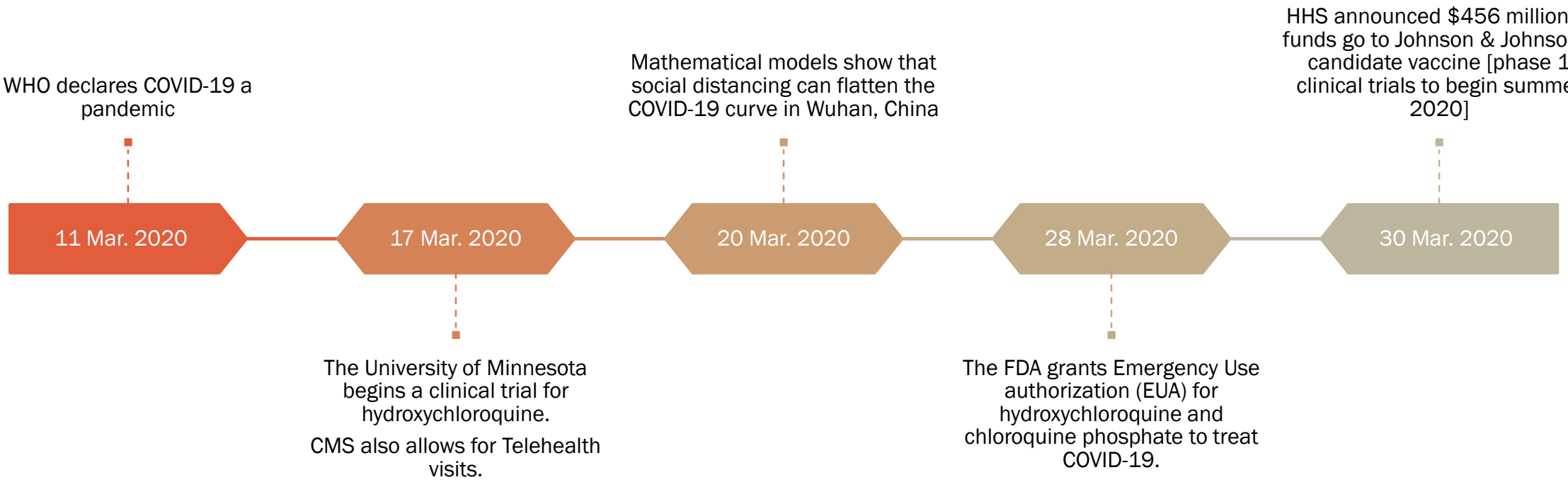
HTTPS://WWW.CDC.GOV/CORONAVIRUS/2019-NCOV/COMMUNICATION/PRINT-RESOURCES.HTML

COVID 19 TIMELINE: JANUARY AND FEBRUARY



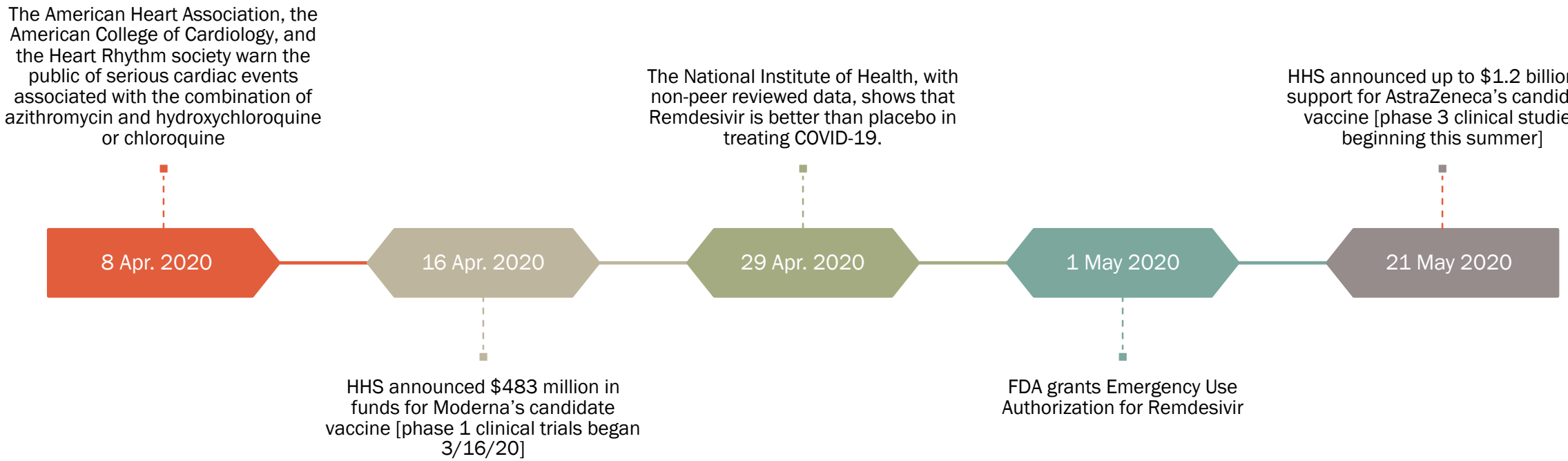
HTTPS://WWW.AJMC.COM/VIEW/A-TIMELINE-OF-COVID19-DEVELOPMENTS-IN-2020

COVID-19 TIMELINE: MARCH



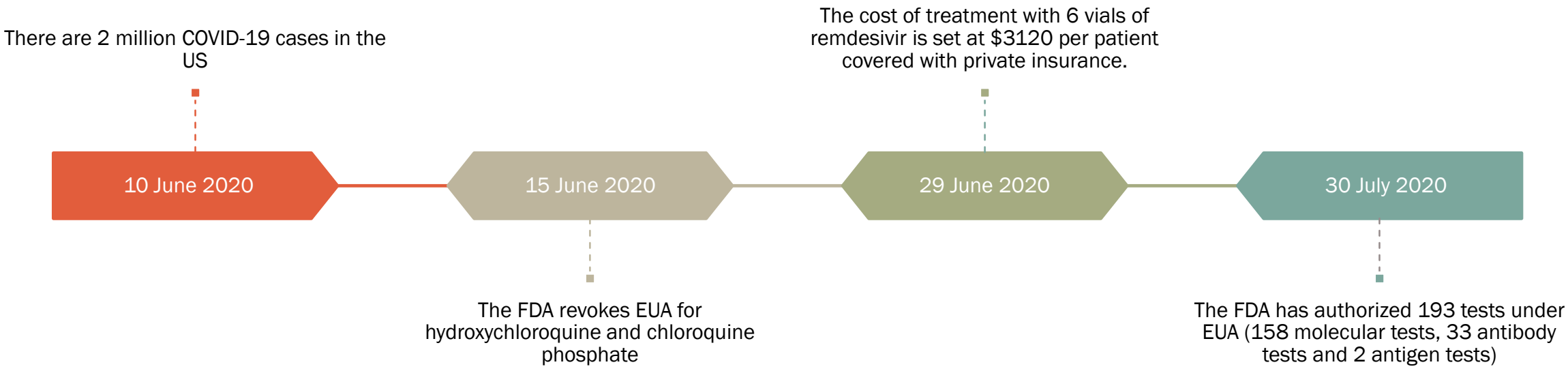
HTTPS://WWW.AJMC.COM/VIEW/A-TIMELINE-OF-COVID19-DEVELOPMENTS-IN-2020

COVID-19 TIMELINE: APRIL AND MAY



HTTPS://WWW.AJMC.COM/VIEW/A-TIMELINE-OF-COVID19-DEVELOPMENTS-IN-2020
HTTPS://WWW.HHS.GOV/ABOUT/NEWS/2020/06/16/FACT-SHEET-EXPLAINING-OPERATION-WARP-SPEED.HTML

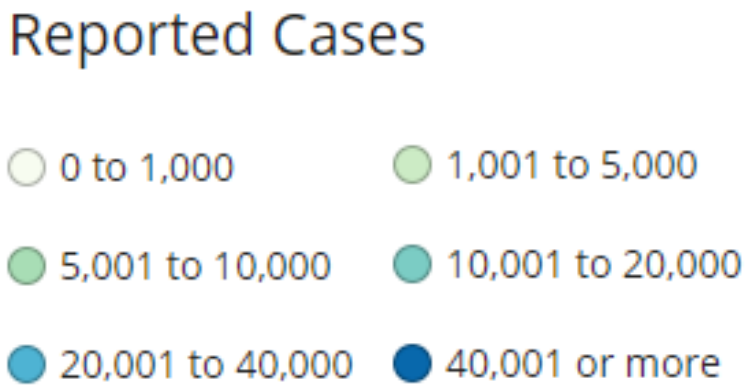
COVID-19 TIMELINE: JUNE AND JULY

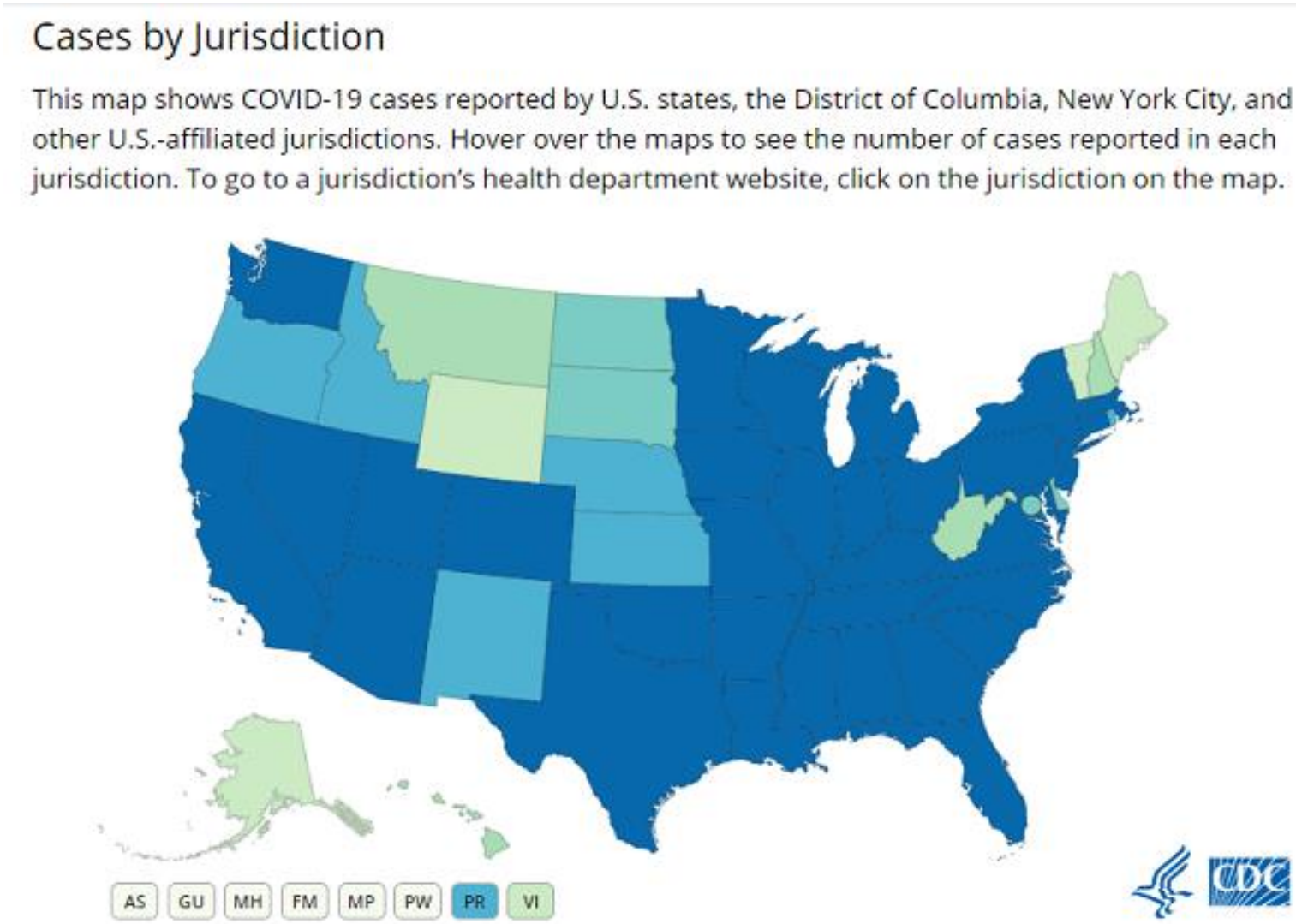


HTTPS://WWW.HHS.GOV/ABOUT/NEWS/2020/05/15/TRUMP-ADMINISTRATION-ANNOUNCES-FRAMEWORK-AND-LEADERSHIP-FOR-OPERATION-WARP-SPEED.HTML

HTTPS://WWW.FDA.GOV/NEWS-EVENTS/PRESS-ANNOUNCEMENTS/CORONAVIRUS-COVID-19-UPDATE-DAILY-ROUNDUP-JULY-30-2020

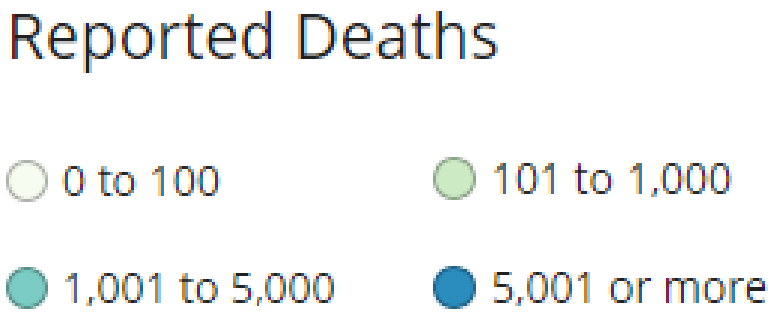
8/27/20:
US MAP OF CASES

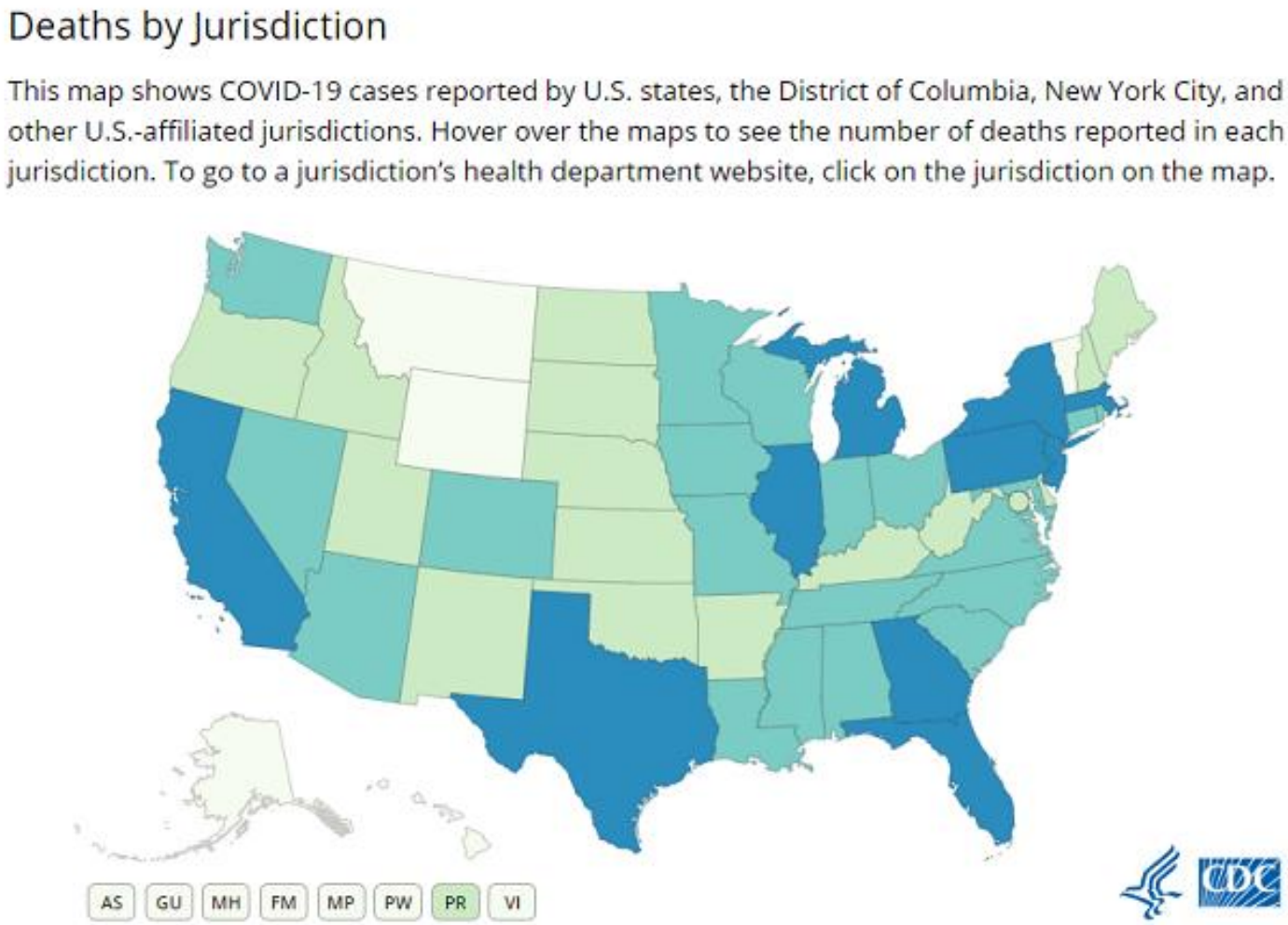




HTTPS://WWW.CDC.GOV/CORONAVIRUS/2019-NCOV/CASES-UPDATES/CASES-IN-US.HTML

8/27/20:
US MAP OF DEATHS

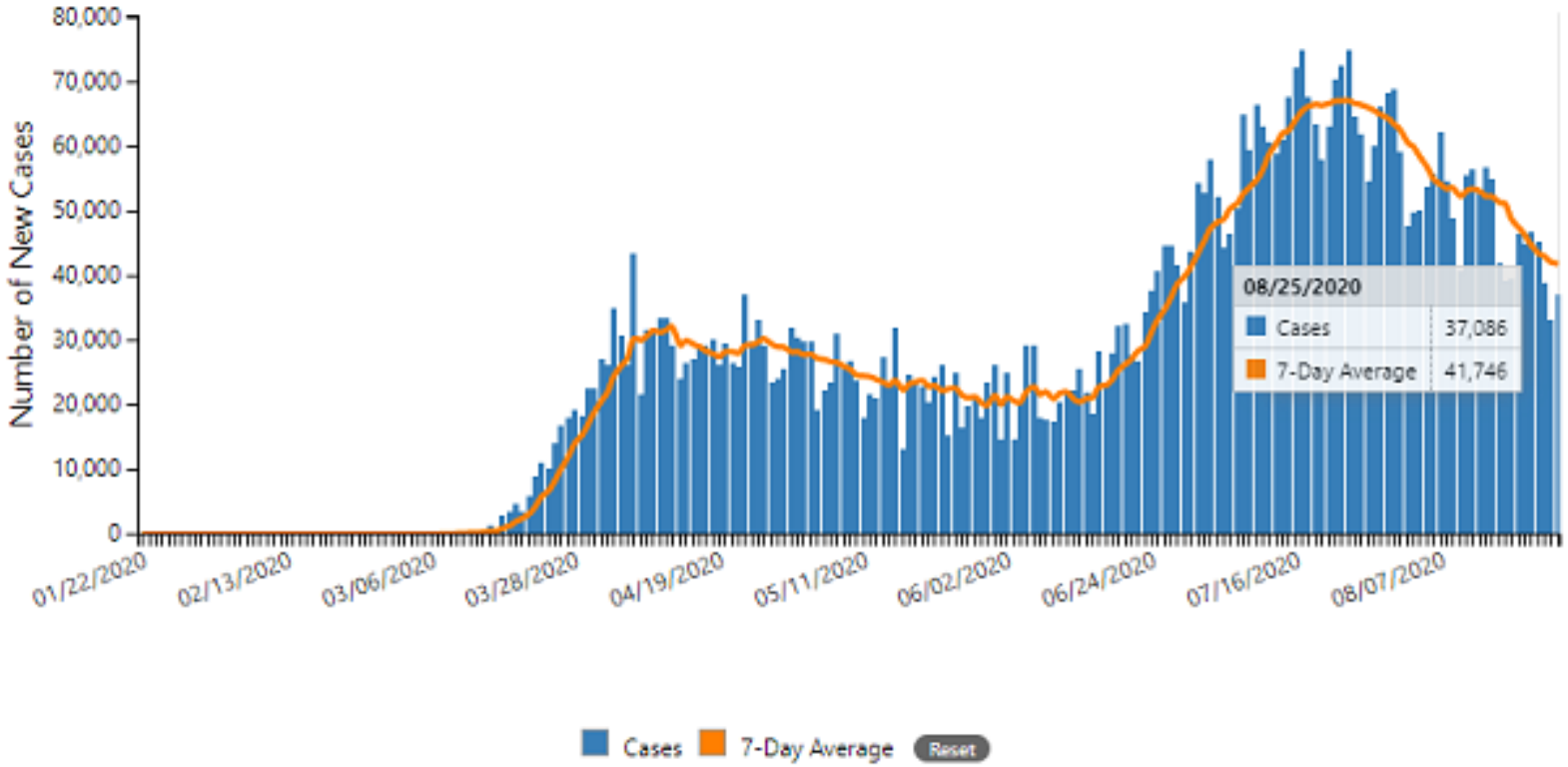




HTTPS://WWW.CDC.GOV/CORONAVIRUS/2019-NCOV/CASES-UPDATES/CASES-IN-US.HTML

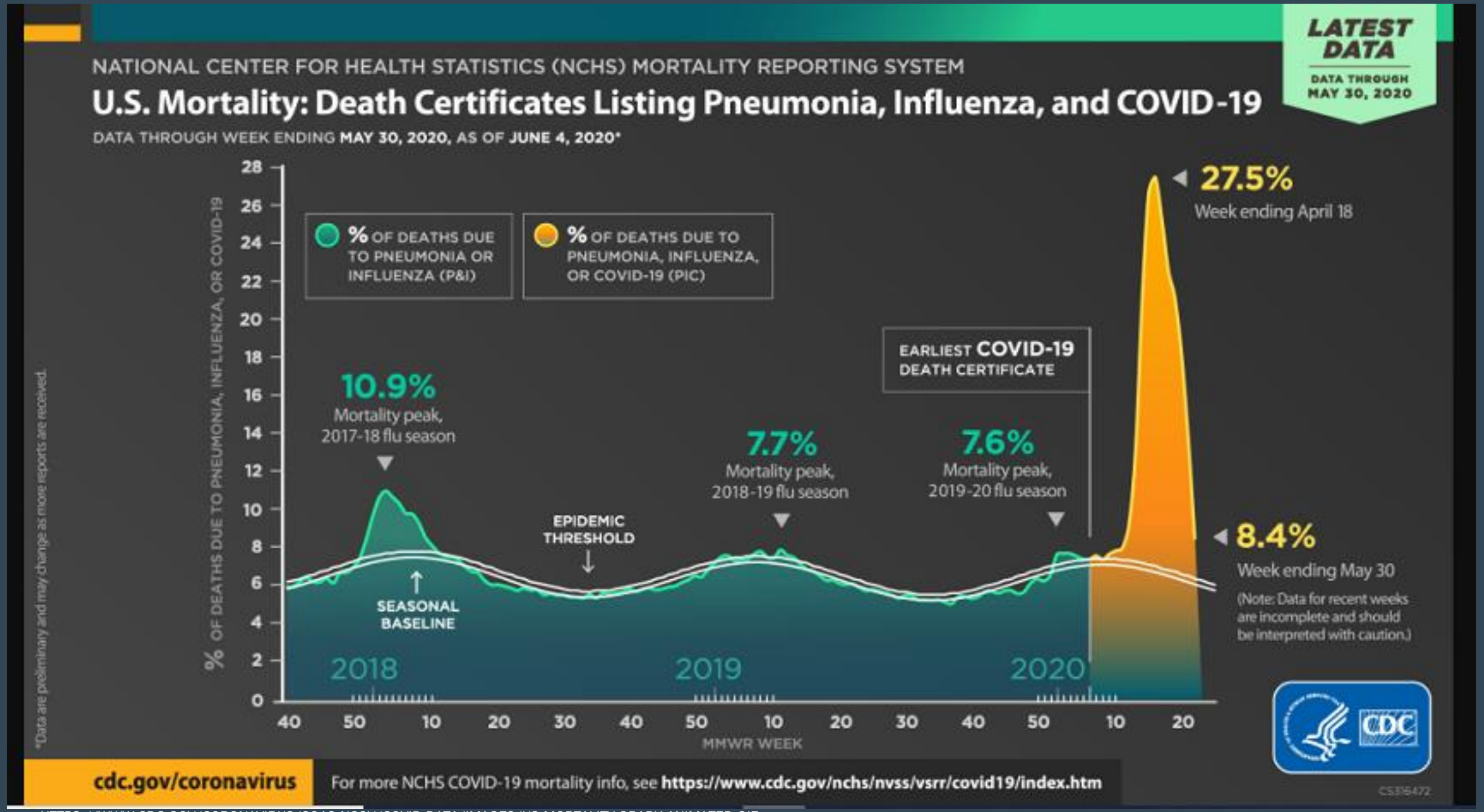
New Cases by Day

The following chart shows the number of new COVID-19 cases reported each day in the U.S. since the beginning of the outbreak. Hover over the bars to see the number of new cases by day.



The 7-Day moving average of new cases (current day + 6 preceding days / 7) was calculated to smooth expected variations in daily counts.

HTTPS://WWW.CDC.GOV/CORONAVIRUS/2019-NCOV/CASES-UPDATES/CASES-IN-US.HTML



HTTPS://WWW.CDC.GOV/CORONAVIRUS/2019-NCOV/COVID-DATA/IMAGES/US-MORTALITY-GRAPH-ANIMATED.GIF

PHARMACOLOGIC INTERVENTIONS

- Antiviral Agents
- Immune Based Agents
- Corticosteroids
- Empiric Broad-Spectrum Antimicrobial Agents

HTTPS://WWW.ASHP.ORG/-/MEDIA/8CA43C674C6D4335B6A19852843C4052.ASHX

HTTPS://FILES.COVID19TREATMENTGUIDELINES.NIH.GOV/GUIDELINES/COVID19TREATMENTGUIDELINES.PDF

ANTIVIRAL AGENTS UNDER INVESTIGATION

- Remdesivir
- Hydroxychloroquine
- Chloroquine Phosphate
- HIV Protease Inhibitors

HTTPS://WWW.ASHP.ORG/-/MEDIA/8CA43C674C6D4335B6A19852843C4052.ASHX
HTTPS://FILES.COVID19TREATMENTGUIDELINES.NIH.GOV/GUIDELINES/COVID19TREATMENTGUIDELINES.PDF

REMDESIVIR (VEKLURY)

- Pharmacologic Category: Antiviral Agent, Nucleoside RNA polymerase inhibitor
- Mechanism of Action: It competes for incorporation into SARS-CoV-2 chains at the site of the RNA-dependent RNA polymerase. It inhibits viral replication by terminating RNA transcription.
- It is an investigational IV drug with no currently FDA approved indications
- Most promising antiviral for COVID-19
- Potential Adverse Effects: elevated LFTs, mild and reversible PT prolongation, renal toxicity, nausea, vomiting
- Not covered by Medicaid

HTTPS://ONLINE.LEXI.COM/LCO/ACTION/HOME
HTTPS://WWW.MEDICAID.ALABAMASERVICES.ORG/ALPORTAL/NDC%20LOOK%20UP/TABID/39/DEFAULT.ASPX
HTTPS://WWW.ASHP.ORG/-/MEDIA/8CA43C674C6D4335B6A19852843C4052.ASHX

REMDESIVIR: EMERGENCY USE AUTHORIZATION

- May 1, 2020 the FDA issued an Emergency Use Authorization (EUA) for the use of Remdesivir in patients that met specified criteria
- This was in response to the preliminary results of the Adaptive Covid-19 Treatment Trial (ACTT-1)
  - Study included 1000 severely ill hospitalized patients
  - Patients that received remdesivir instead of placebo recovered 31% faster
  - Time of hospitalization was 11 days (remdesivir) versus 15 days (placebo)

HTTPS://WWW.FDA.GOV/MEDIA/137564/DOWNLOAD
HTTPS://WWW.FDA.GOV/MEDIA/137565/DOWNLOAD
HTTPS://WWW.NIAID.NIH.GOV/NEWS-EVENTS/NIH-CLINICAL-TRIAL-SHOWS-REMDESIVIR-ACCELERATES-RECOVERY-ADVANCED-COVID-19

REMDESIVIR: EUA GUIDELINES

- Can be used in hospitalized children and adults with suspected or confirmed COVID-19
- Patients must have severe disease:
  - Oxygen saturation (SpO2) less than or equal to 94% on room air OR
  - Require supplemental oxygen
  - Require mechanical ventilation
  - Require Extracorporeal Membrane Oxygenation (ECMO)
- Must be administered at EUA recommended dosages via an IV infusion in an inpatient setting

HTTPS://WWW.FDA.GOV/MEDIA/137565/DOWNLOAD
HTTPS://WWW.GILEAD.COM/-/MEDIA/FILES/PDFS/REMDESIVIR/EUA-FACT-SHEET-FOR-HCPS.PDF

REMDESIVR: EUA GUIDELINES

- Providers must comply with record keeping and reporting requirements
  - Distribution records
  - Adverse event reports (FDA MedWatch)
    - Must be reported within 7 calendar days from event onset
  - Medication error reports
- Providers must review EUA fact sheets
  - Fact sheet for health care providers
  - Fact sheet for patients and parent/caregivers
    - Must be distributed prior to treatment
    - Patients must also be informed of other treatment alternatives and that remdesivir is an unapproved drug

HTTPS://WWW.GILEAD.COM/-/MEDIA/FILES/PDFS/REMDESIVIR/EUA-FACT-SHEET-FOR-HCPS.PDF

REMDESIVIR: MONITORING AND PRECAUTIONS

Renal function must be determined before treatment

Liver function testing should be performed prior to treatment and daily while receiving treatment

Patients with known hypersensitivity to Remdesivir ingredients must not receive treatment

Concomitant use with Chloroquine (CQ) or Hydroxychloroquine (HCQ) is not recommended

In vitro evidence that CQ may antagonize intracellular metabolic activation and antiviral activity of remdesivir

Concomitant use with inducers of cytochrome P-450 isoenzymes is not recommended

Remdesivir plasma concentrations may be reduced (clinical relevance unknown)

HTTPS://WWW.GILEAD.COM/-/MEDIA/FILES/PDFS/REMDESIVIR/EUA-FACT-SHEET-FOR-HCPS.PDF
HTTPS://WWW.ASHP.ORG/-/MEDIA/8CA43C674C6D4335B6A19852843C4052.ASHX

NIH GUIDELINE RECOMMENDATIONS: REMDISIVIR

- Prioritize use in a specific population (patient is hospitalized and requires supplement oxygen, BUT is not utilizing high-flow oxygen, ventilation, or ECMO)
  - Use for 5 days or until hospital discharge, whichever comes first
  - If no clinical improvement after 5 days, then some experts recommend extending treatment to 10 days
- No recommendations from the NIH for patients that require high-flow oxygen, ventilation, or ECMO due to insufficient data
  - The manufacturer recommends treatment for 10 days in this adult patient population
- No recommendations for mild to moderate disease

HTTPS://FILES.COVID19TREATMENTGUIDELINES.NIH.GOV/GUIDELINES/COVID19TREATMENTGUIDELINES.PDF
HTTPS://WWW.GILEAD.COM/-/MEDIA/FILES/PDFS/REMDESIVIR/EUA-FACT-SHEET-FOR-HCPS.PDF

HYDROXYCHLOROQUINE (PLAQUENIL)

- Pharmacologic Category: Aminoquinoline, Antimalarial
- Labeled Uses: Lupus erythematosus, malaria, rheumatoid arthritis
- Early observations showed decreased viral shedding in COVID-19
- 3/28/20: FDA issued Emergency Use Authorization (EUA) with specified guidelines for COVID-19 treatment
- Often used in combination with azithromycin
- Both Hydroxychloroquine and azithromycin have a risk of QT prolongation
- 6/15/20: FDA revoked the EUA citing that the benefits no longer outweighed the risks of treatment for COVID-19

HTTPS://ONLINE.LEXI.COM/LCO/ACTION/HOME
HTTPS://WWW.FDA.GOV/MEDIA/138945/DOWNLOAD

CHLOROQUINE PHOSPHATE

- Pharmacologic Category: Aminoquinoline, Antimalarial
- Labeled Uses: Treatment of malaria and extra-intestinal amebiasis
- Early observations showed decreased viral shedding in COVID-19
- 3/28/20: FDA issues Emergency Use Authorization (EUA) with guidelines for COVID-19 treatment
- 6/15/20: The FDA revoked the EUA for chloroquine due to benefits no longer outweighing risks of treatment. Risks included reports of serious adverse cardiac events and methemoglobinemia.

HTTPS://ONLINE.LEXI.COM/LCO/ACTION/HOME
HTTPS://WWW.FDA.GOV/MEDIA/138945/DOWNLOAD

HYDROXYCHLOROQUINE (HCQ) AND CHLOROQUINE (CQ):

- Why was EUA revoked?
  - CQ and HCQ are unlikely to be effective for the treatment of COVID-19. Earlier reports of decreased viral shedding have not been consistently replicated
  - A large randomized controlled trial showed no evidence of HCQ treatment benefit (mortality, hospital length of stay, or need for mechanical ventilation) in hospitalized patients
  - Due to serious adverse events (including cardiac effects) the risks outweigh the benefit of treatment
- Does this impact the FDA-approved uses of these medications?
  - No, patients should continue taking them as directed
- Should I be concerned if I was given HCQ or CQ for COVID-19?
  - No residual side effects are known for these medications. Express concerns about treatment with your healthcare provider.
- Will clinical trials for these medications in COVID-19 continue?
  - Yes

HTTPS://WWW.FDA.GOV/MEDIA/138946/DOWNLOAD

NIH GUIDELINE RECOMMENDATIONS: HCQ OR CQ

- Do NOT use HCQ or CQ except for in the context of a clinical trial
- Do NOT use high dose CQ
- Do NOT use HCQ with azithromycin except for in the context of a clinical trial

HTTPS://FILES.COVID19TREATMENTGUIDELINES.NIH.GOV/GUIDELINES/COVID19TREATMENTGUIDELINES.PDF

HIV PROTEASE INHIBITORS

- Lopinavir/Ritonavir:
  - Safety and Efficacy not established (with or without other antivirals)
  - This combination is under investigation for COVID-19
  - Clinical Trials have looked at this medication in combination with ribavirin and interferon B-1b
- Darunavir
  - Safety and Efficacy not established
  - The combination of Darunavir with cobicistat or ritonavir is currently under investigation
- Atazanavir, Nelfinavir, Saquinavir, Tipranavir: No data to support use for treatment of COVID-19

HTTPS://WWW.ASHP.ORG/-/MEDIA/8CA43C674C6D4335B6A19852843C4052.ASHX

NIH GUIDELINE RECOMMENDATIONS: HIV PROTEASE INHIBITORS

- Do NOT use HIV Protease Inhibitors except for in the context of a clinical trial

HTTPS://FILES.COVID19TREATMENTGUIDELINES.NIH.GOV/GUIDELINES/COVID19TREATMENTGUIDELINES.PDF

IMMUNE BASED THERAPY UNDER INVESTIGATION

- Blood derived products
  - COVID-19 convalescent plasma
  - SARS-CoV-2 immunoglobulins
  - Mesenchymal stem cells
  - Non-SARS-CoV-2 IVIG
- Immunomodulators
  - Corticosteroids
  - Interleukin Inhibitors
    - Interleukin-1 inhibitors
    - Interleukin-6 inhibitors
  - Interferons
    - Alfa Interferon
    - Beta Interferon
  - Kinase Inhibitors
    - Bruton's tyrosine kinase inhibitors
    - Janus kinase inhibitors

HTTPS://FILES.COVID19TREATMENTGUIDELINES.NIH.GOV/GUIDELINES/COVID19TREATMENTGUIDELINES.PDF

COVID-19 CONVALESCENT PLASMA

- FDA grants EUA 8/23/20
- It is an investigational product
- It is plasma collected from individuals that have recovered from COVID-19 and it contains antibodies to SARS-CoV-2
- “This EUA is based on historical evidence using convalescent plasma in prior outbreaks of respiratory viruses, certain preclinical evidence, results from small clinical trials of convalescent plasma conducted during the current outbreak, and data obtained from the ongoing National Expanded Access Treatment Protocol (EAP) for COVID-19 convalescent plasma sponsored by the Mayo Clinic”
- Convalescent plasma has previously been studied in the following outbreaks:
  - 2003 SARS-CoV-1 infection
  - 2009-2010 H1N1 influenza pandemic
  - 2012 MERS-CoV epidemic

HTTPS://WWW.ASHP.ORG/-/MEDIA/8CA43C674C6D4335B6A19852843C4052.ASHX

EMERGENCY INVESTIGATIONAL NEW DRUG FOR CONVALESCENT PLASMA

- How is this medication eligible:
  - Clinical Trials
  - Expanded Access
  - Single Patient Emergency IND
    - “Laboratory confirmed COVID-19
    - Severe or immediately life-threatening COVID-19, for example,
    - Severe disease is defined as one or more of the following:
      - shortness of breath (dyspnea),
      - respiratory frequency ≥ 30/min,
      - blood oxygen saturation ≤ 93%,
      - partial pressure of arterial oxygen to fraction of inspired oxygen ratio < 300,
      - lung infiltrates > 50% within 24 to 48 hours
    - Life-threatening disease is defined as one or more of the following:
      - respiratory failure,
      - septic shock,
      - multiple organ dysfunction or failure
  - Informed consent provided by the patient or healthcare proxy.

HTTPS://WWW.FDA.GOV/VACCINES-BLOOD-BIOLOGICS/INVESTIGATIONAL-NEW-DRUG-IND-OR-DEVICE-EXEMPTION-IDE-PROCESS-CBER/RECOMMENDATIONS-INVESTIGATIONAL-COVID-19-CONVALESCENT-PLASMA

COVID-19 CONVALESCENT PLASMA

- “Patients must receive a FACT sheet, and providers must comply with specific reporting requirements
- Appropriate criteria for selection of patients to receive investigational COVID-19 convalescent plasma, optimal time during the course of the disease to receive such therapy, and appropriate dosage (e.g., volume, number of doses) not determined.
- Current data suggest that the clinical benefit is greatest when high-titer convalescent plasma is given early in the course of the disease
- Providers should obtain plasma from FDA blood registered facility
- Donors must meet specified requirements
- The NIH COVID-19 Treatment Guidelines Panel states that there are insufficient data to recommend for or against the use of convalescent plasma in patients with COVID-19”

HTTPS://WWW.ASHP.ORG/-/MEDIA/8CA43C674C6D4335B6A19852843C4052.ASHX

NIH GUIDELINE RECOMMENDATIONS: BLOOD DERIVED PRODUCTS

- Insufficient data for NIH guideline recommendations for or against use of:
  - SARS-CoV-2 immunoglobulins
- NIH panel does NOT recommend the use of:
  - Mesenchymal Stem Cells except in a clinical trial
  - Non-SARS-CoV-2 IVIG except in a clinical trial

HTTPS://FILES.COVID19TREATMENTGUIDELINES.NIH.GOV/GUIDELINES/COVID19TREATMENTGUIDELINES.PDF

NIH GUIDELINE RECOMMENDATIONS: CORTICOSTEROIDS

- Preliminary results of the RECOVERY trial showed that mortality rates were lower in dexamethasone treated patients that required supplemental oxygen compared to patients treated with standard of care
- Based on preliminary results of the RECOVERY trial the NIH recommends dexamethasone 6 mg per day for up to 10 days for patients that are mechanically ventilated and in those that require supplemental oxygen.
- If the patient does not require supplemental oxygen, then dexamethasone use is NOT recommended
- Prednisone, methylprednisolone, or hydrocortisone can be used if dexamethasone is not available

HTTPS://FILES.COVID19TREATMENTGUIDELINES.NIH.GOV/GUIDELINES/COVID19TREATMENTGUIDELINES.PDF

NIH GUIDELINE RECOMMENDATIONS: OTHER IMMUNOMODULATORS

- Interleukin-1 inhibitors
  - Example: Anakinra
  - Insufficient data for recommendations
- Interleukin-6 inhibitors
  - Examples: Sarilumab, Siltuximab, Tocilizumab
  - Insufficient data for recommendations

HTTPS://FILES.COVID19TREATMENTGUIDELINES.NIH.GOV/GUIDELINES/COVID19TREATMENTGUIDELINES.PDF

NIH GUIDELINE RECOMMENDATIONS: OTHER IMMUNOMODULATORS

- Interferons
  - NIH recommends AGAINST use of alfa and beta interferons for severe and critical COVID-19 except in a clinical trial
  - Insufficient data for interferon-beta for early COVID-19 treatment
- Kinase inhibitors
  - Examples:
    - Bruton's Tyrosine Kinase inhibitors (acalabrutinib, ibrutinib, zanubrutinib)
    - Janus Kinase Inhibitors (baricitinib, ruxolitinib, tofacitinib)
  - NIH recommends AGAINST use except in a clinical trial

HTTPS://FILES.COVID19TREATMENTGUIDELINES.NIH.GOV/GUIDELINES/COVID19TREATMENTGUIDELINES.PDF

NIH GUIDELINE RECOMMENDATIONS: EMPIRIC BROAD SPECTRUM ANTIMICROBIALS

- NIH does NOT recommend the use of empiric broad-spectrum antimicrobial in the absence of another indications for patients with severe or critical illness
- If antimicrobial therapy is started, then reassess use daily

HTTPS://FILES.COVID19TREATMENTGUIDELINES.NIH.GOV/GUIDELINES/COVID19TREATMENTGUIDELINES.PDF

NIH GUIDELINE RECOMMENDATIONS: ADJUNCTIVE THERAPY

- Antithrombotic Therapy (extensive guideline information regarding monitoring, prevention and treatment)
  - If the patient is already receiving anticoagulant therapy, then it should be continued
  - Follow usual hospital standards of care for VTE prophylaxis
  - Follow usual hospital standards of care for thromboembolic event treatment
  - Follow usual hospital standards of care for anticoagulant therapy for patients receiving ECMO, continuous renal replacement therapy, or who have thrombosis of catheters or extracorporeal filters
- Vitamins and Minerals (insufficient data to recommend Vitamin C, Vitamin D or Zinc)
  - Do NOT use zinc above the recommended dietary allowance for prevention of COVID except for in a clinical trial

HTTPS://FILES.COVID19TREATMENTGUIDELINES.NIH.GOV/GUIDELINES/COVID19TREATMENTGUIDELINES.PDF

NIH GUIDELINE RECOMMENDATIONS: CONCOMITANT THERAPY

- ACE-inhibitors and ARBs
  - Continue treatment for other indications in patients with COVID-19
  - Do NOT use ACE-inhibitors or ARBs for the treatment of COVID-19 except for in a clinical trial
- Corticosteroids
  - Continue treatment for other indications in patients with COVID-19. Supplemental or stress doses may be required in certain cases.
  - Continue inhaled corticosteroids for asthma/COPD
- Statins
  - Continue treatment for other indications in patients with COVID-19
  - Do NOT use statins for the treatment of COVID-19 except for in a clinical trial
- Nonsteroidal Anti-inflammatory Drugs (NSAIDs)
  - Continue treatment for other indications in patients with COVID-19
  - There is no difference in the use of antipyretic strategies (Acetaminophen vs NSAIDs) between patients with or without COVID

HTTPS://FILES.COVID19TREATMENTGUIDELINES.NIH.GOV/GUIDELINES/COVID19TREATMENTGUIDELINES.PDF

REFERENCES

- https://www.cdc.gov/coronavirus/2019-ncov/faq.html
- https://www.who.int/emergencies/diseases/novel-coronavirus-2019/technical-guidance/naming-the-coronavirus-disease-(covid-2019)-and-the-virus-that-causes-it
- https://www.cdc.gov/coronavirus/2019-ncov/prevent-getting-sick/prevention.html
- https://www.cdc.gov/coronavirus/2019-ncov/communication/print-resources.html?Sort=Date%3A%3Adesc&Search=symptoms
- https://www.ajmc.com/view/a-timeline-of-covid19-developments-in-2020
- https://www.hhs.gov/about/news/2020/06/16/fact-sheet-explaining-operation-warp-speed.html
- https://www.hhs.gov/about/news/2020/05/15/trump-administration-announces-framework-and-leadership-for-operation-warp-speed.html
- https://www.fda.gov/news-events/press-announcements/coronavirus-covid-19-update-daily-roundup-july-30-2020
- https://www.cdc.gov/coronavirus/2019-ncov/cases-updates/cases-in-us.html
- https://www.cdc.gov/coronavirus/2019-ncov/covid-data/images/US-Mortality-graph-animated.gif
- https://www.ashp.org/-/media/8CA43C674C6D4335B6A19852843C4052.ashx

REFERENCES

- https://files.covid19treatmentguidelines.nih.gov/guidelines/covid19treatmentguidelines.pdf
- https://online.lexi.com/lco/action/home
- https://www.medicaid.alabamaservices.org/ALPortal/NDC%20Look%20Up/tabId/39/Default.aspx
- https://www.fda.gov/media/137564/download
- https://www.fda.gov/media/137565/download
- https://www.niaid.nih.gov/news-events/nih-clinical-trial-shows-remdesivir-accelerates-recovery-advanced-covid-19
- https://www.gilead.com/-/media/files/pdfs/remdesivir/eua-fact-sheet-for-hcps.pdf
- https://www.fda.gov/media/138945/download
- https://www.fda.gov/media/138946/download