COVID-19 in Pediatrics: A Health System's Experience

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musc Children's Health
Medical University of South Carolina

Changing What's Possible

Learning Objectives

At the completion of this activity, the pharmacist will be able to:

- 1. Recall the common clinical manifestations and complications from SARS-CoV-2 infection, with a focus on pediatric patients
- 2. Recognize current treatments for COVID-19 and their effectiveness, with a focus on pediatric patients
- 3. Describe a local health system's experience with COVID-19 infection, its complications, and local use of antivirals active against COVID-19 and broad-spectrum antibiotics

Presentation Outline

- Virology and Clinical Manifestations
- COVID pharmacotherapy
- Local experience during COVID-19 epidemic
- COVID-19 Antimicrobial stewardship

Virology and Clinical Manifestations

Virology of SARS-CoV-2

enveloped (+)ssRNA virus

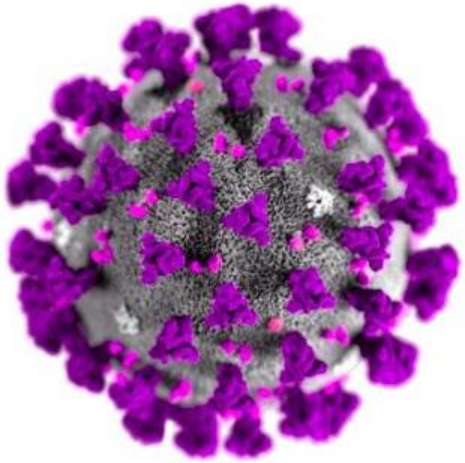
80% genetic similarity

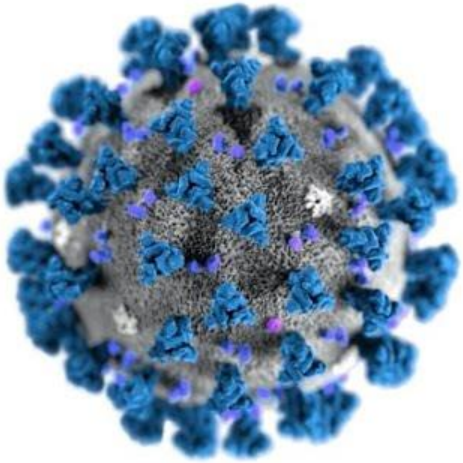
50% genetic similarity

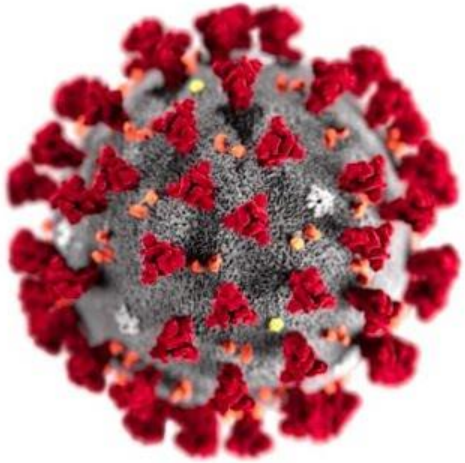
SARS-CoV

MERS-CoV

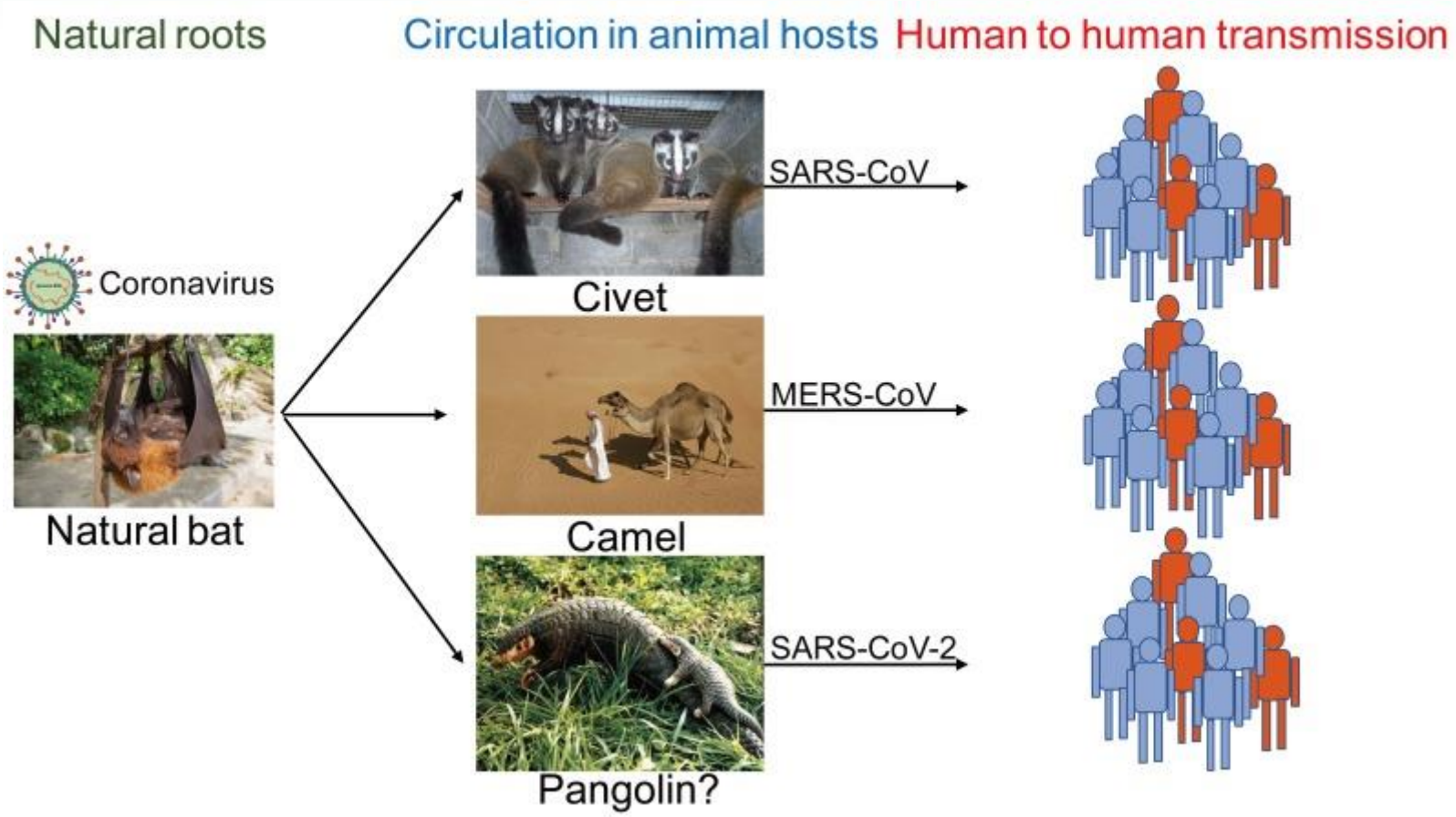
SARS-CoV-2



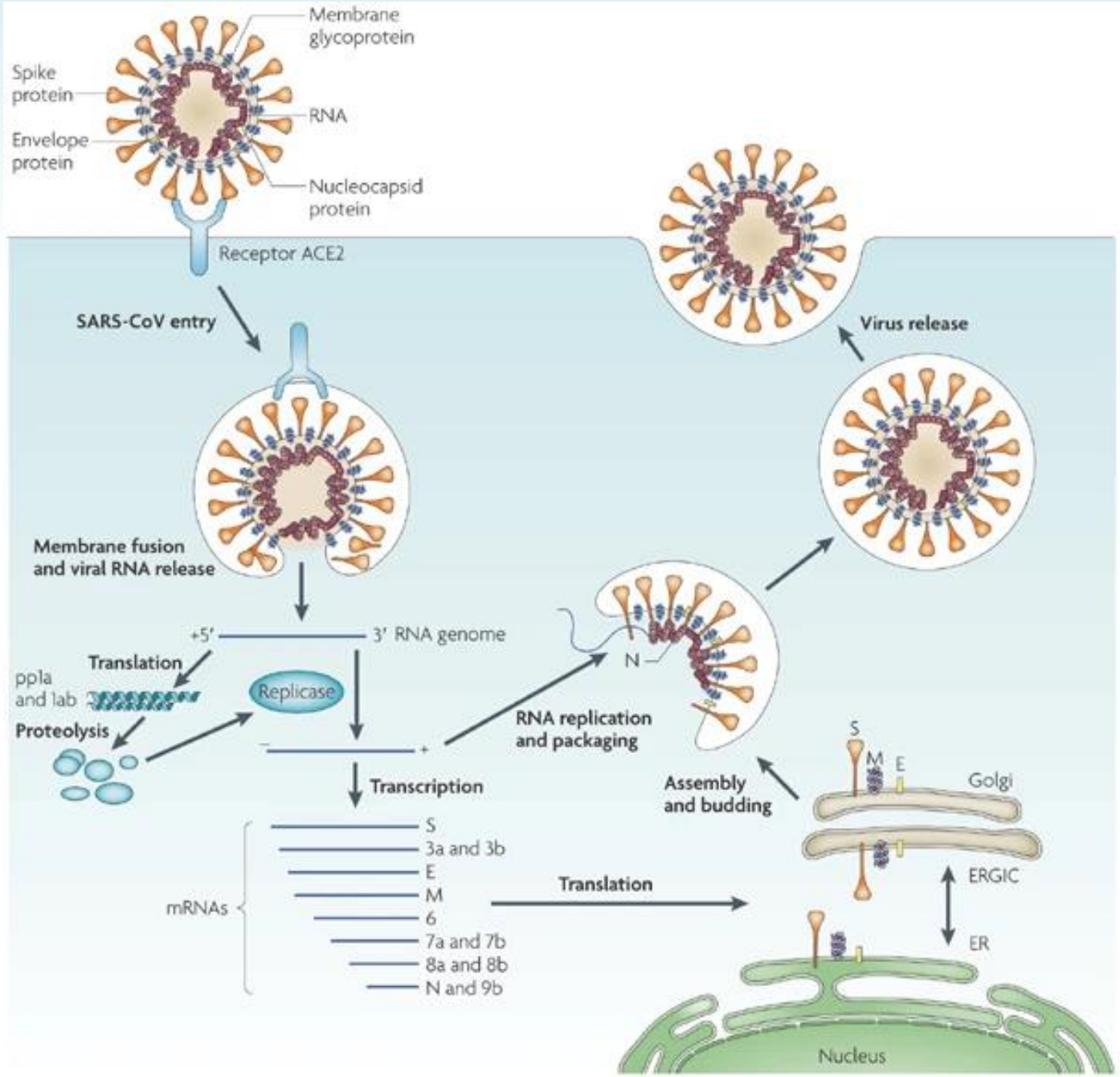




Virology of SARS-CoV-2

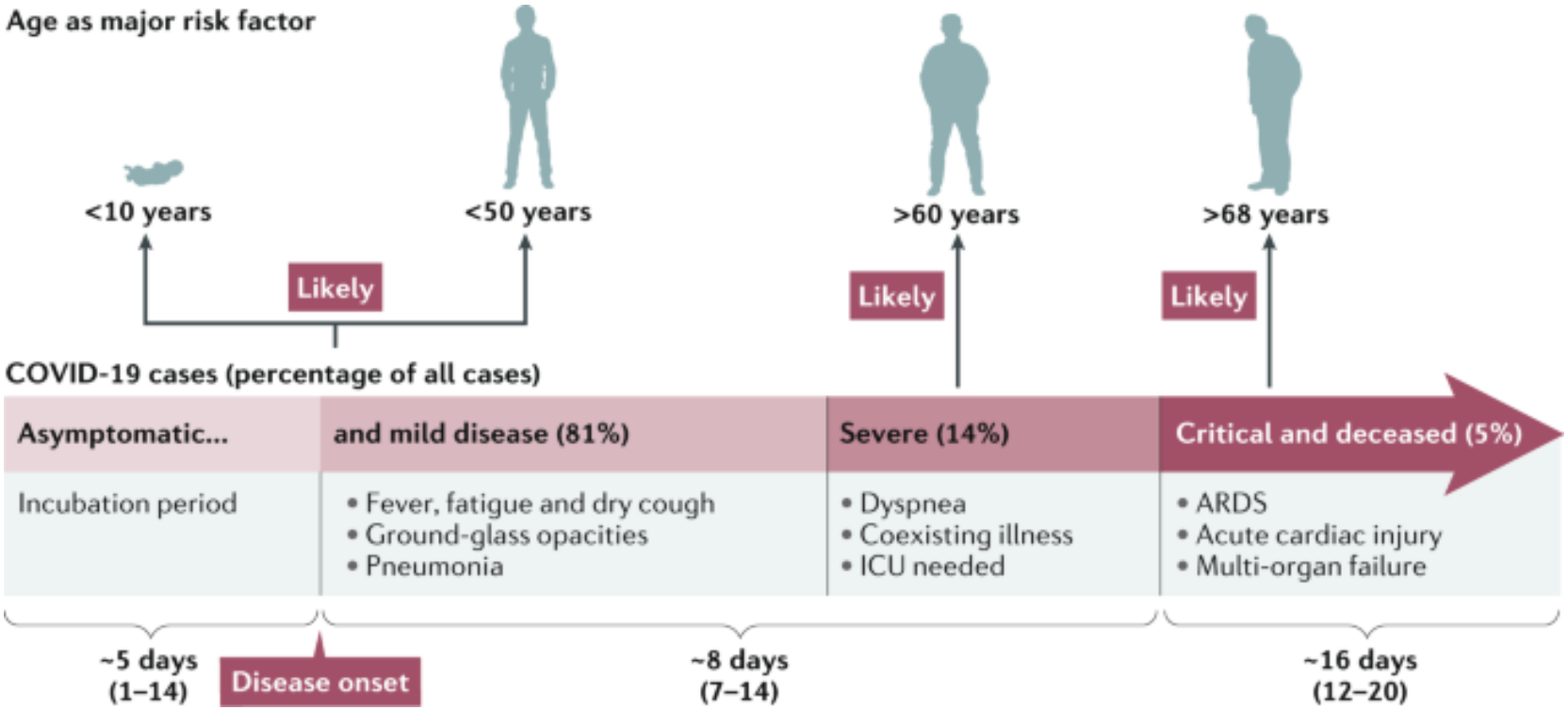


Source: *Viruses* **12**(373):1

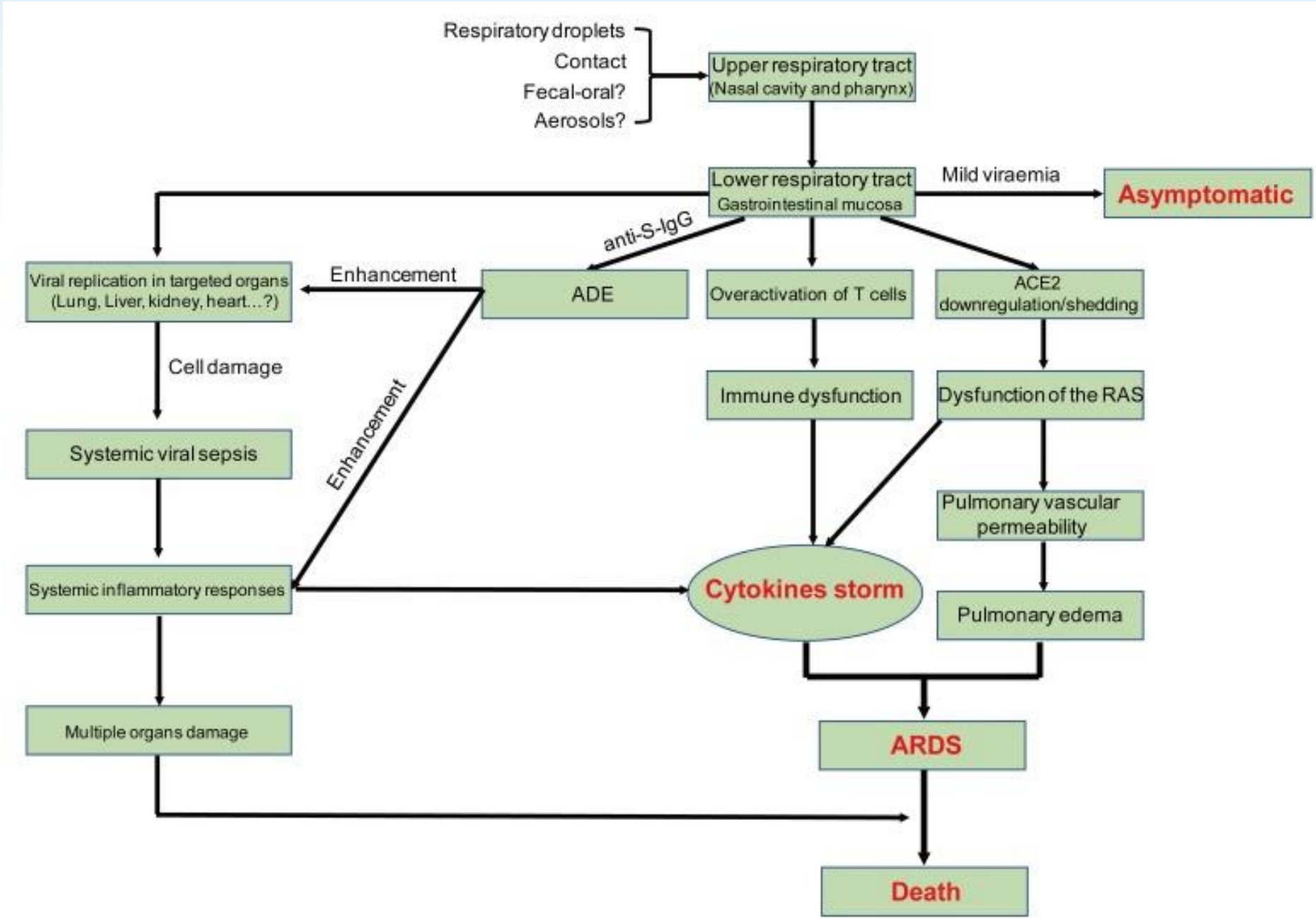


Source: *Nature Rev Microbiol* **7:**226

Virology of SARS-CoV-2



Source: *Nature Rev* **19**:141



Source: *Viruses* **12**(373):1

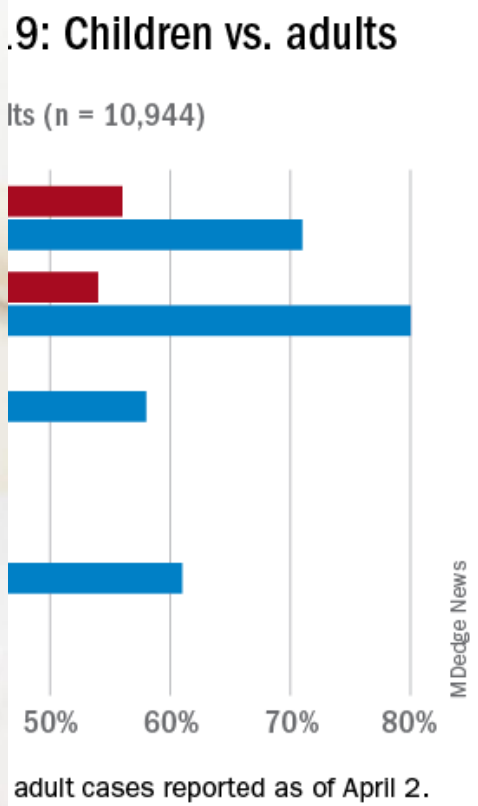
Facts about COVID-19

- While statistically it is true that older people & people with underlying conditions die more often from COVID-19, many "underlying conditions" are very common and people often live normal lives for many decades with many of these chronic conditions.

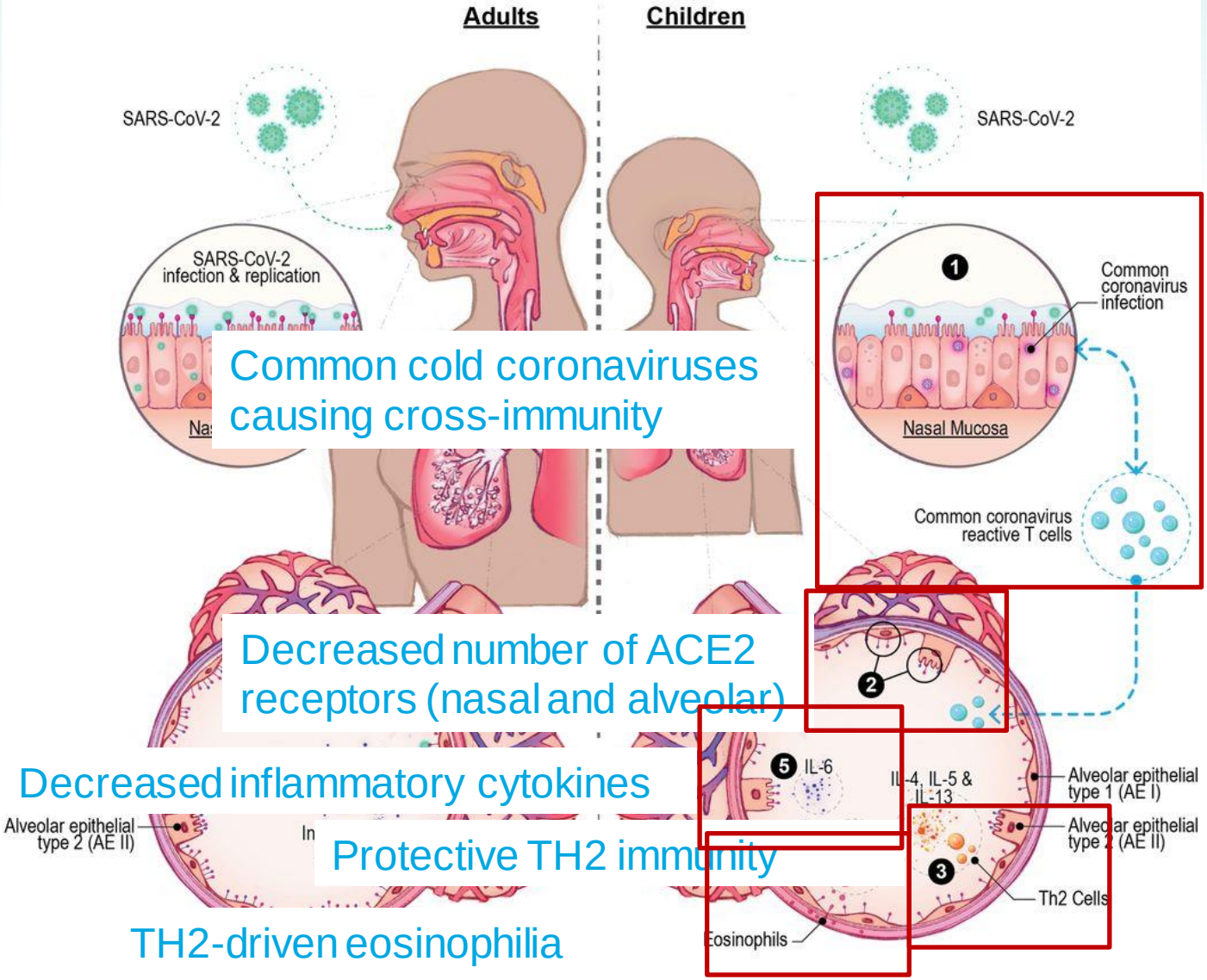
  - CDC list of underlying conditions (independent of age) that increase or might increase your risk of severe disease is extensive & includes many common conditions:
    - Obesity (42.4% of Americans)
    - Diabetes (10.5% of Americans)
    - Hypertension (45% of Americans)
    - Smoking (14% of Americans)

Source: CDC

COVID-19 symptoms: Not small adults



Five Clues Why Children Have Reduced Susceptibility to COVID-19



Common cold coronaviruses causing cross-immunity

Decreased number of ACE2 receptors (nasal and alveolar)

Decreased inflammatory cytokines

Protective TH2 immunity

TH2-driven eosinophilia

Source: *PNAS* **117**(40):24620

Facts about COVID-19 in Children

- Children of all ages can get COVID-19 and numbers of children who have been infected continue to rise.
- COVID-19 in children tends to be very mild; severe disease can happen but is rare.
- **Children can transmit SARS-CoV-2 even if asymptomatic.**
- Evidence does suggest that younger children (particularly ≤5 years old) are not as likely to get infected or transmit the virus.

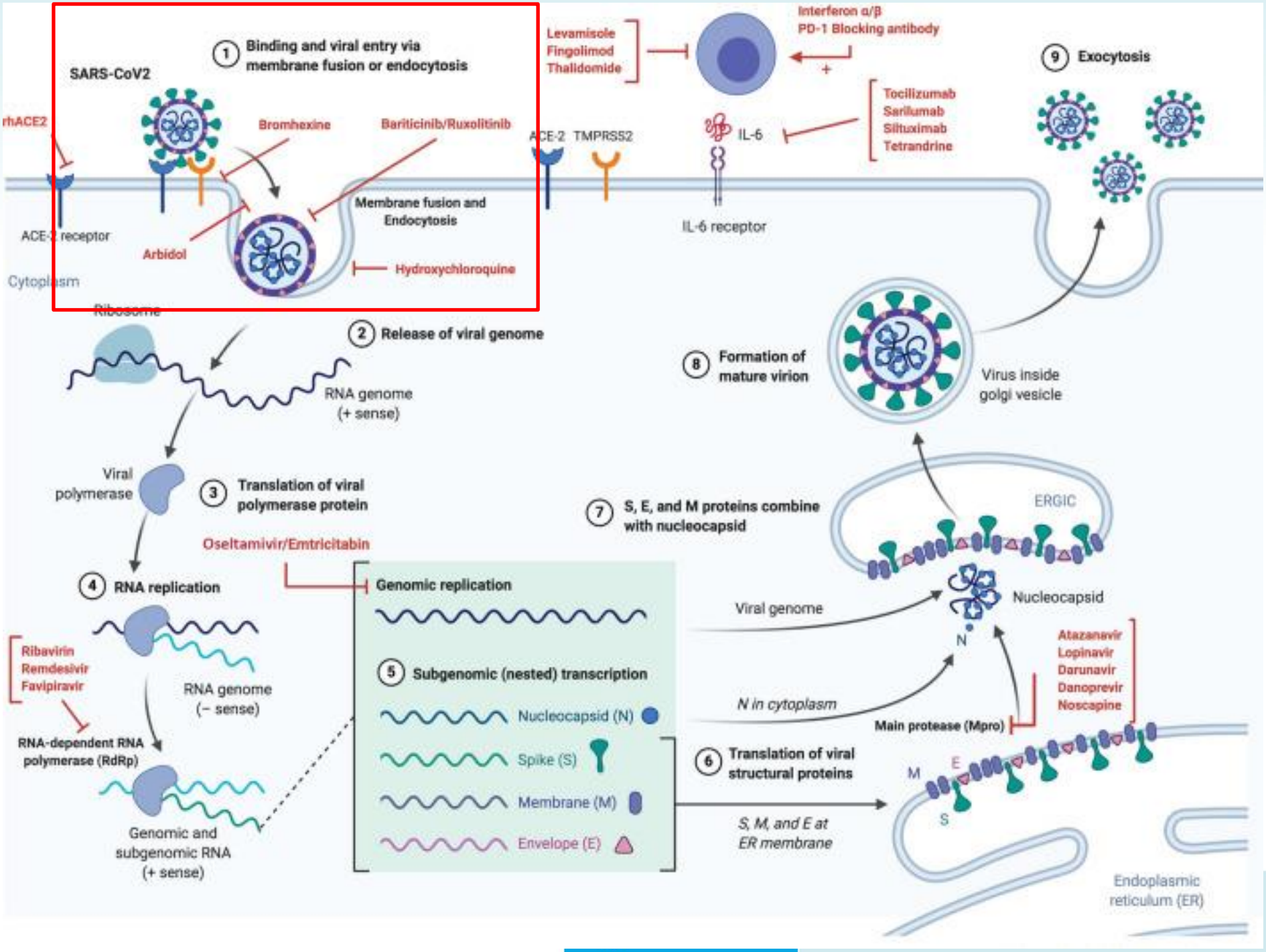
Source: CDC, AAP

Long-Term Effects of COVID-19

- Most people recover completely from COVID-19 within a few weeks.
- But some people continue to have symptoms for weeks to months, even those with mild symptoms and those without underlying medical conditions (including young adults and children).
- A recent systematic review of published studies found >50 described long-term effects of COVID-19.
  - Most common were fatigue, headache, attention disorder, hair loss, and dyspnea (trouble breathing)
- There is still much to learn about how COVID-19 may increase the risk of long-term health problems, including in children and those with mild symptoms.

Lopez-Leon, et al; Mayo Clinic

COVID pharmacotherapy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SARS-CoV2
rhACE2
Bromhexine
Bariticinib/Ruxolitinib
ACE-2 receptor
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Membrane fusion and Endocytosis
Hydroxychloroquine
Cytoplasm
Levamisole
Fingolimod
Thalidomide
Interferon α/β
PD-1 Blocking antibody
ACE-2
TMPRSS2
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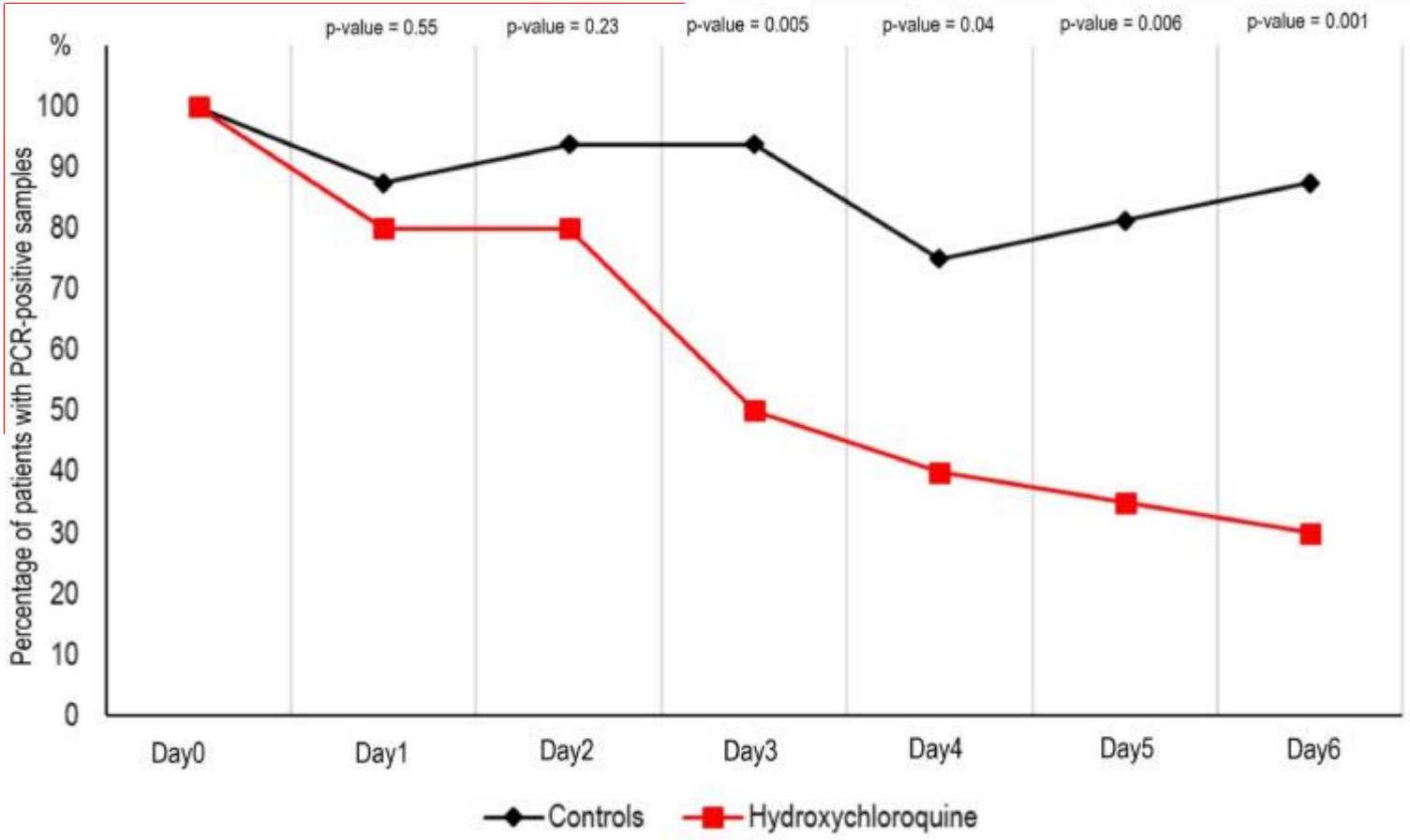
Tocilizumab
Sarilumab
Siltuximab
Tetrandrine
IL-6 receptor
9 Exocytosis
Ribosome
2 Release of viral genome
RNA genome (+ sense)
8 Formation of mature virion
Virus inside golgi vesicle
Viral polymerase
3 Translation of viral polymerase protein
7 S, E, and M proteins combine with nucleocapsid
ERGIC
Oseltamivir/Emtricitabin
4 RNA replication
Genomic replication
Viral genome
Nucleocapsid
N
Ribavirin
Remdesivir
Favipiravir
RNA genome (− sense)
5 Subgenomic (nested) transcription
N in cytoplasm
Atazanavir
Lopinavir
Darunavir
Danoprevir
Noscapine
Main protease (Mpro)
RNA-dependent RNA polymerase (RdRp)
Nucleocapsid (N)
Spike (S)
Membrane (M)
Envelope (E)
6 Translation of viral structural proteins
M
E
S
S, M, and E at ER membrane
Genomic and subgenomic RNA (+ sense)
Endoplasmic reticulum (ER)

Hydroxychloroquine probably doesn't work



S-CoV-1 *in vitro*

vitro killing of

S-CoV-1 *in vitro*

20 Treatment
19 Control
Not randomized

Int J Antimicrob Agents. 2020 Jul; **56**(1): 105949.

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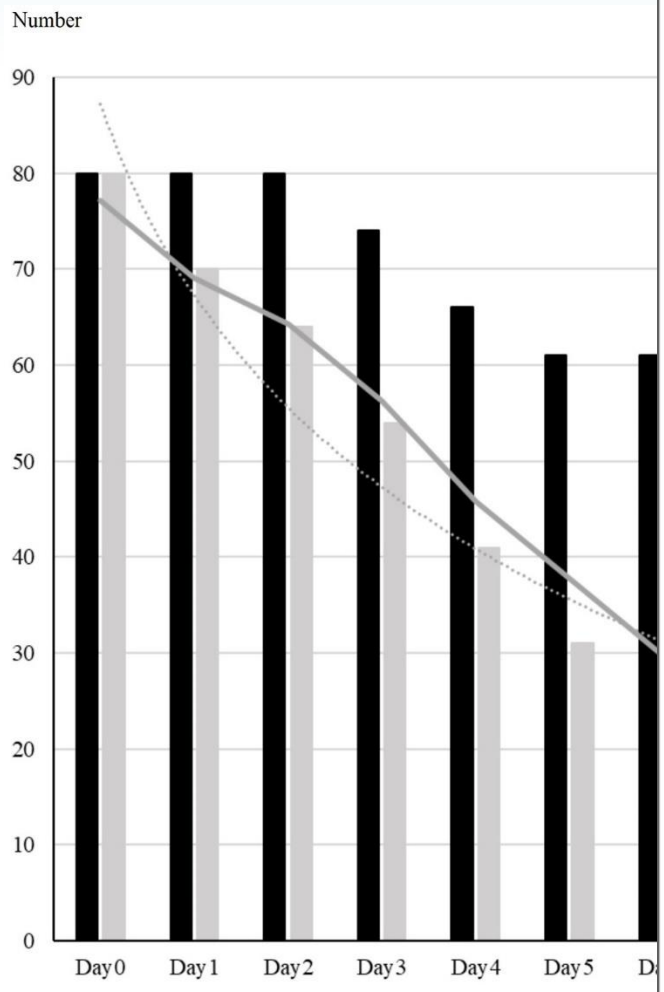
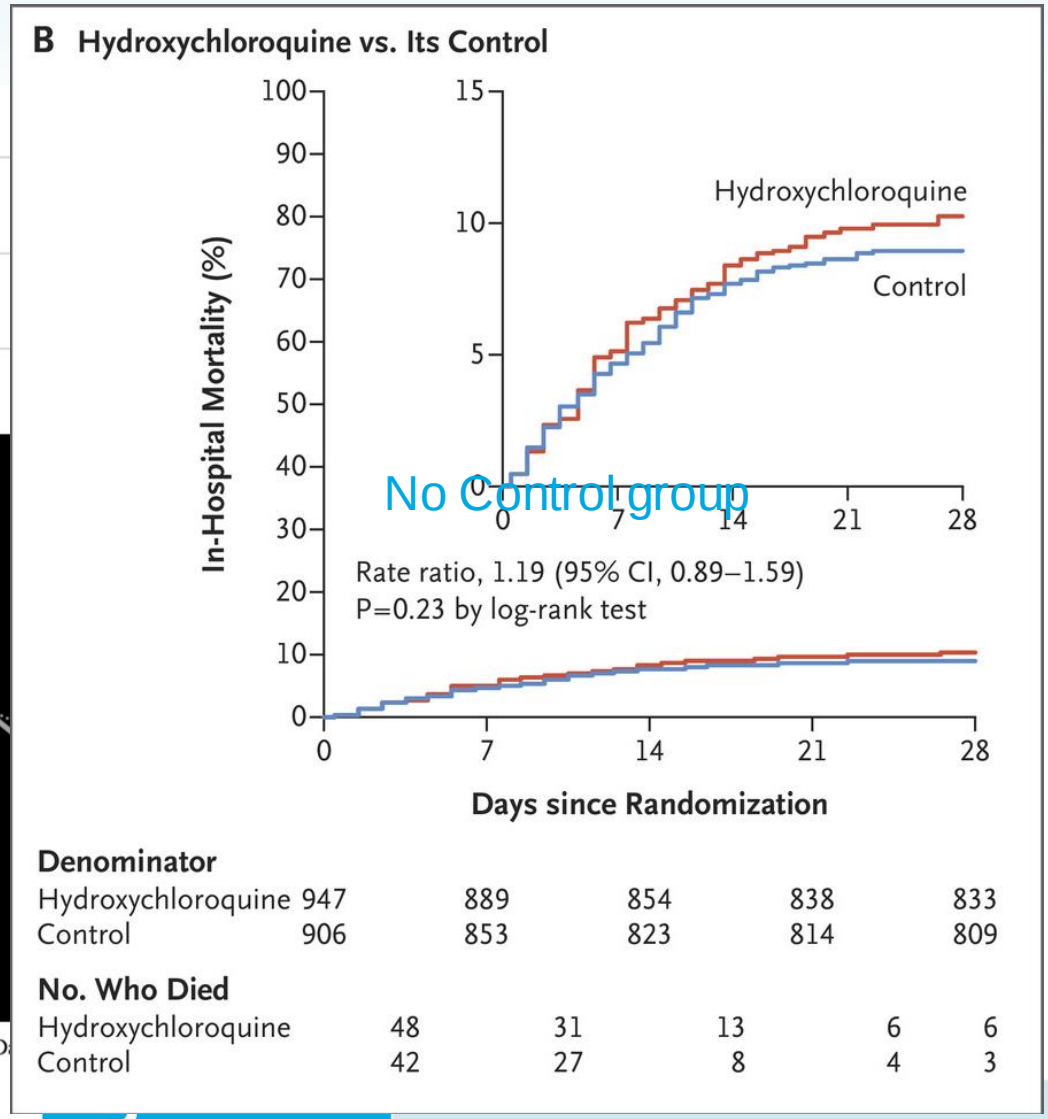
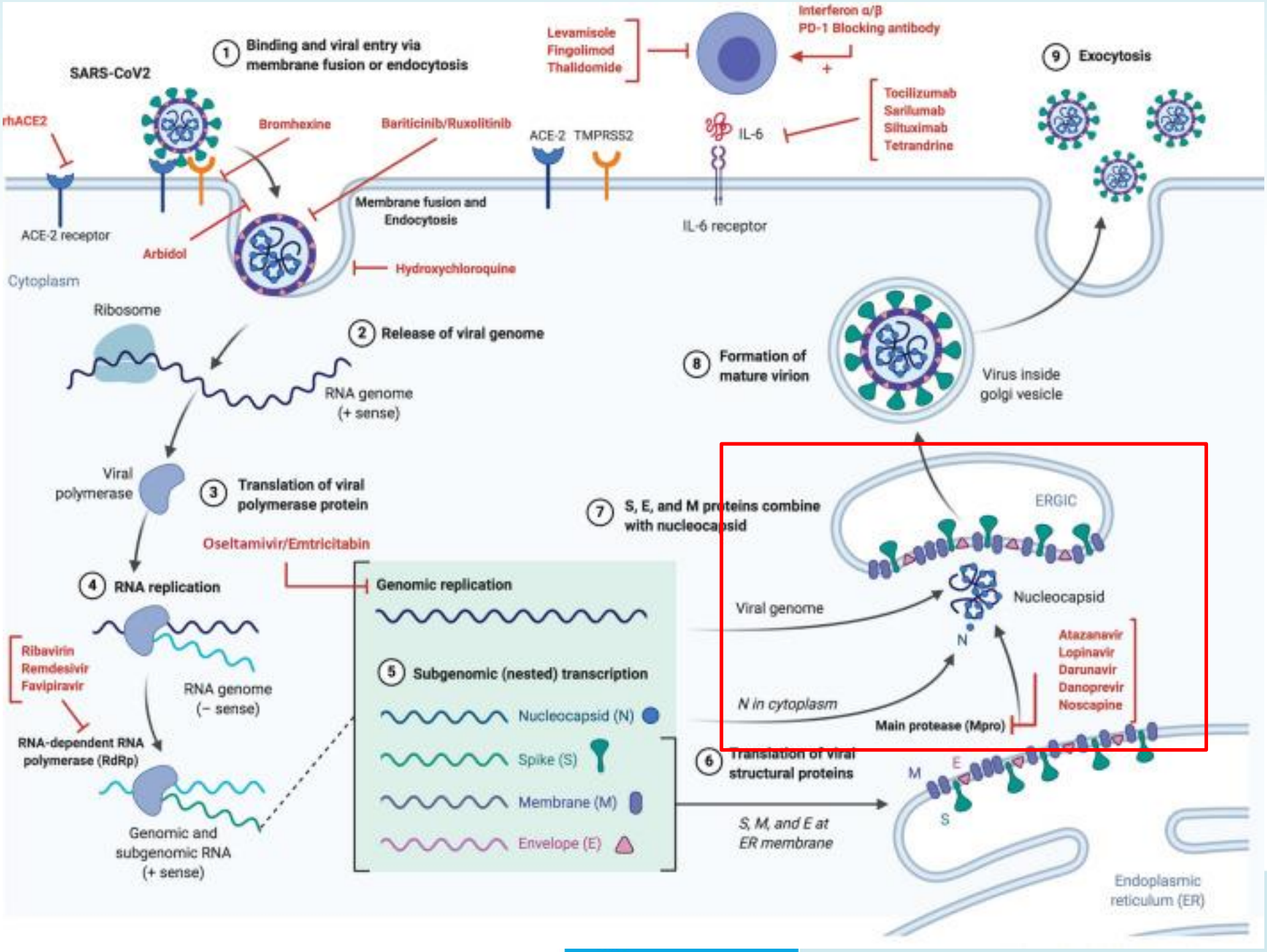




No Control group

N Engl J Med 2021; 384:497-511.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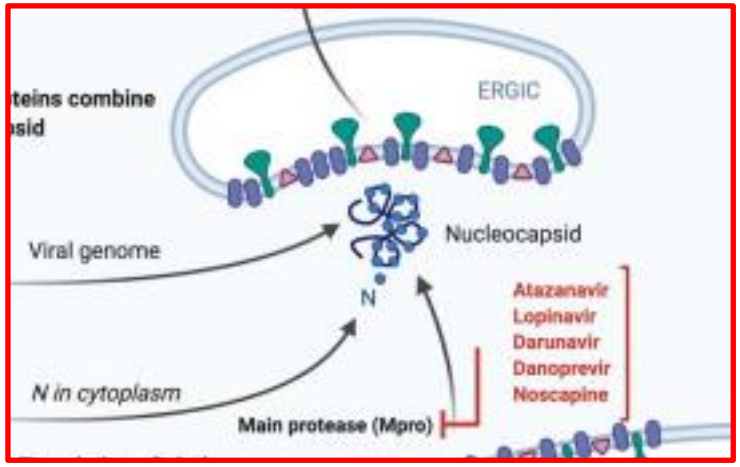
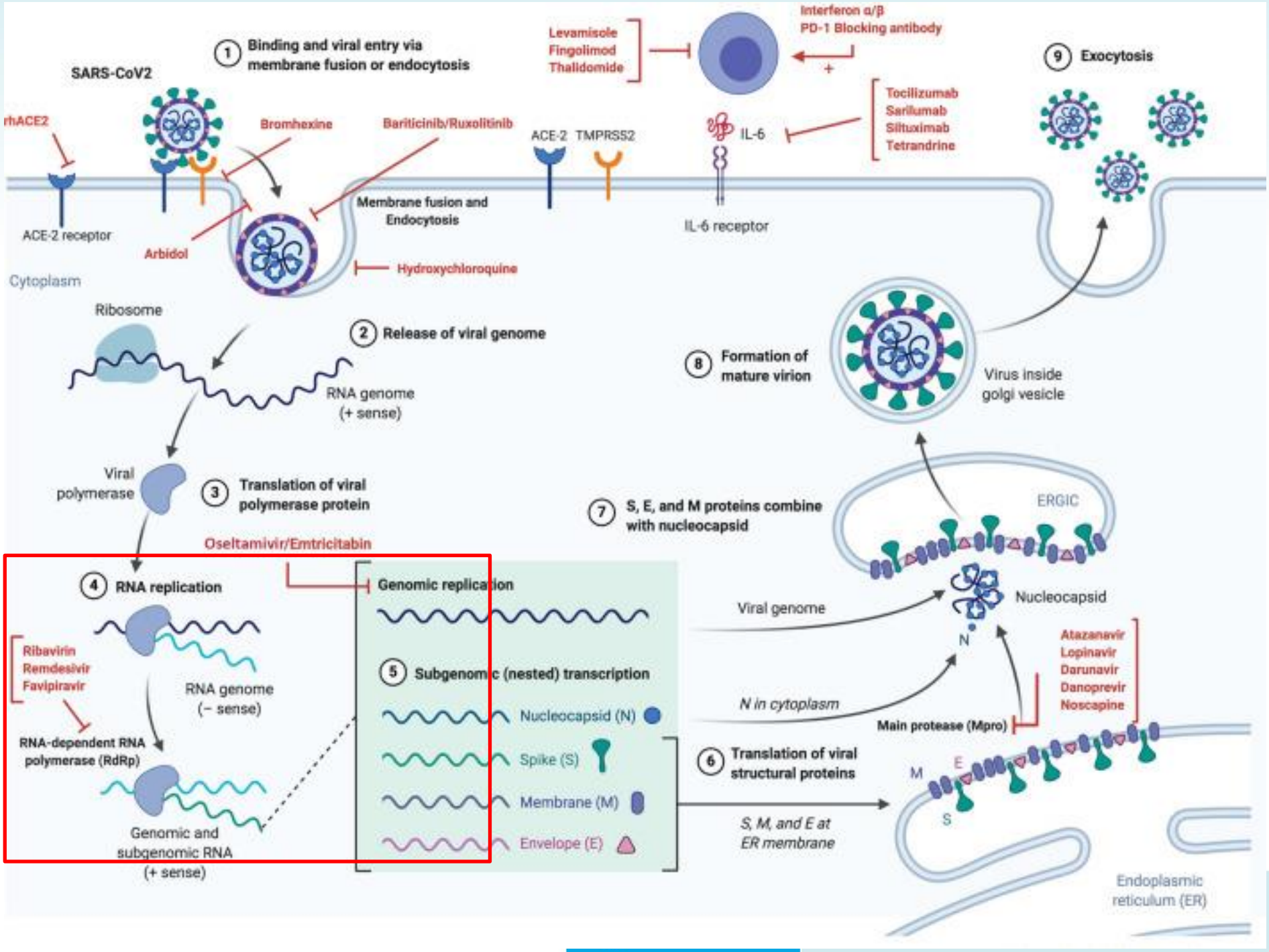
M
E
S
Endoplasmic reticulum (ER)

Other antivirals that did not work



- Atazanavir
- Darunavir
- Lopinavir
- All showed very little *in vivo* activity
- Ribavirin, replication inhibitor, also with little *in vivo* activity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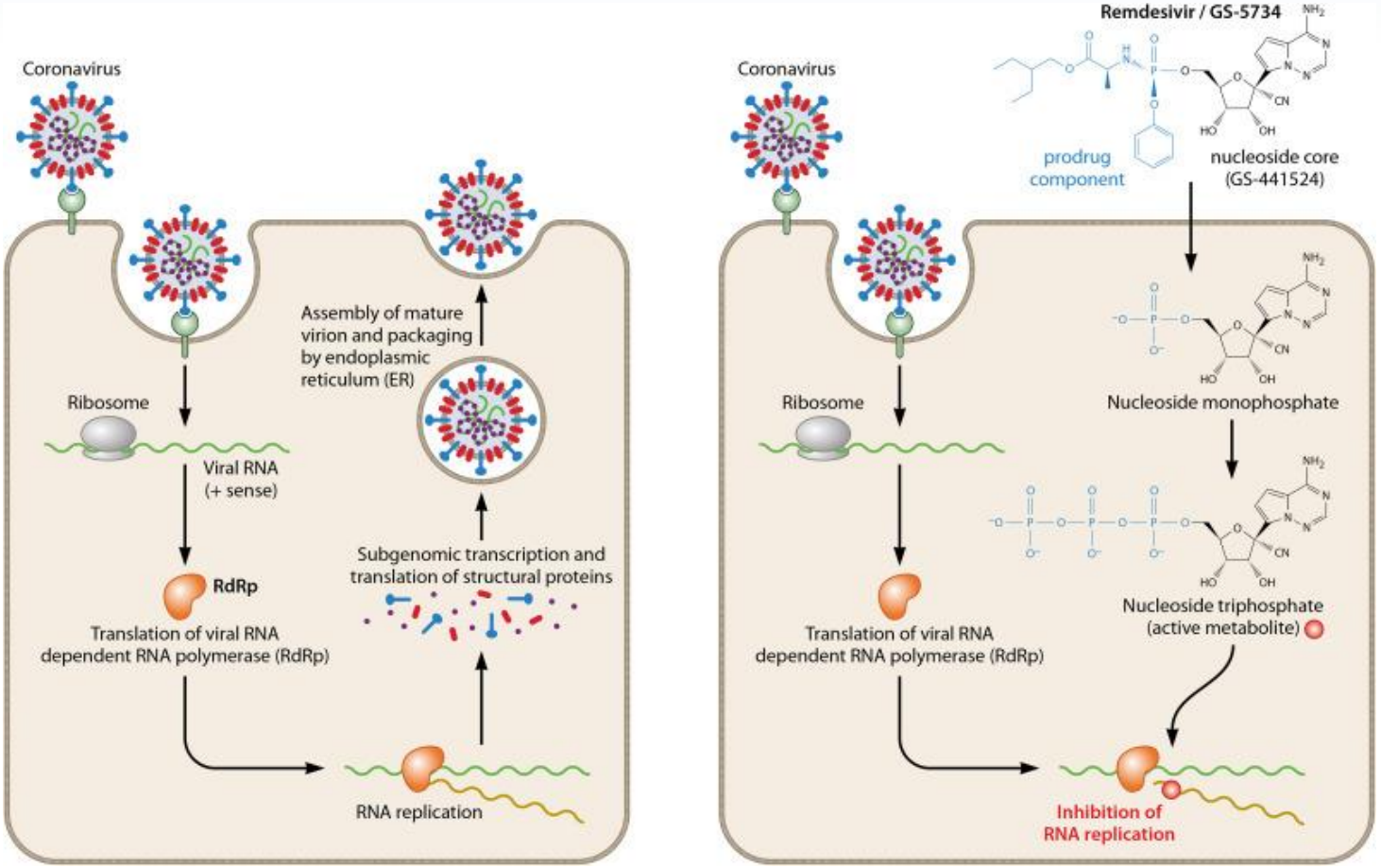
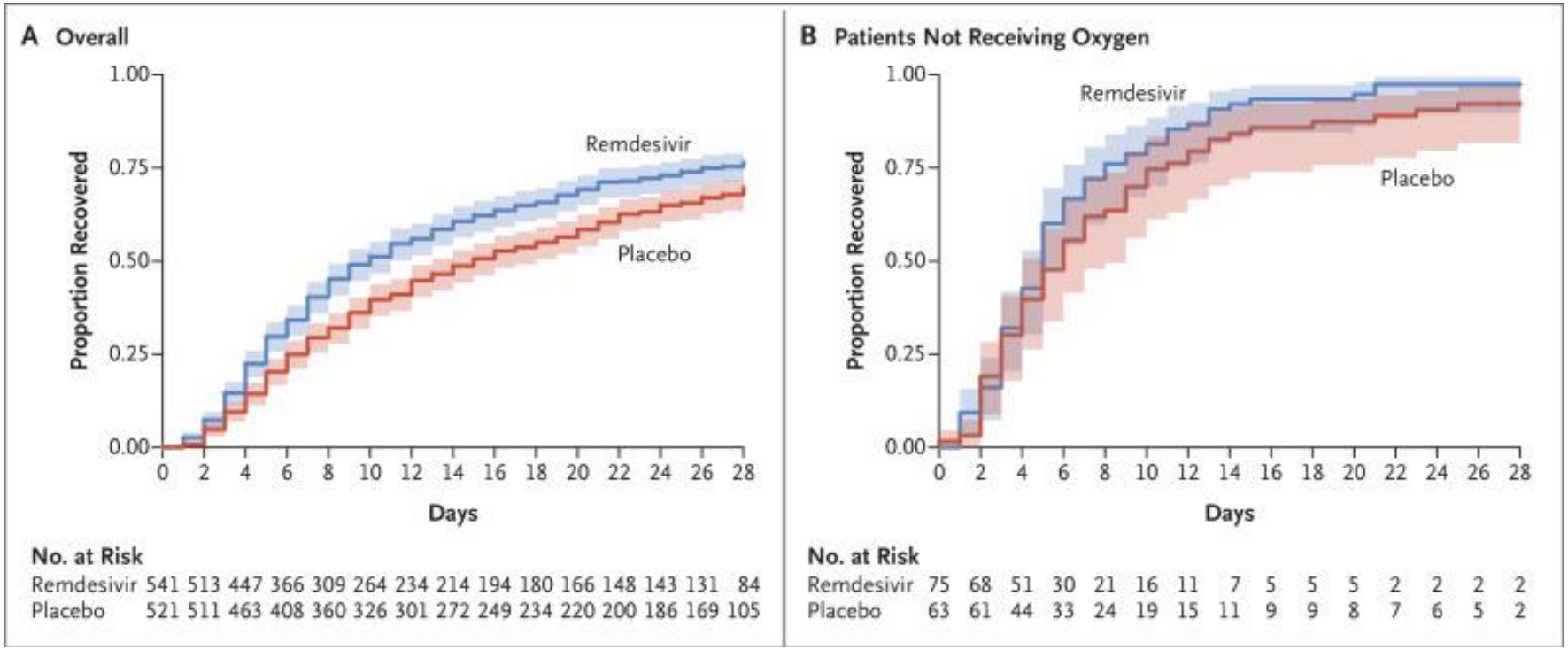
Remdesivir



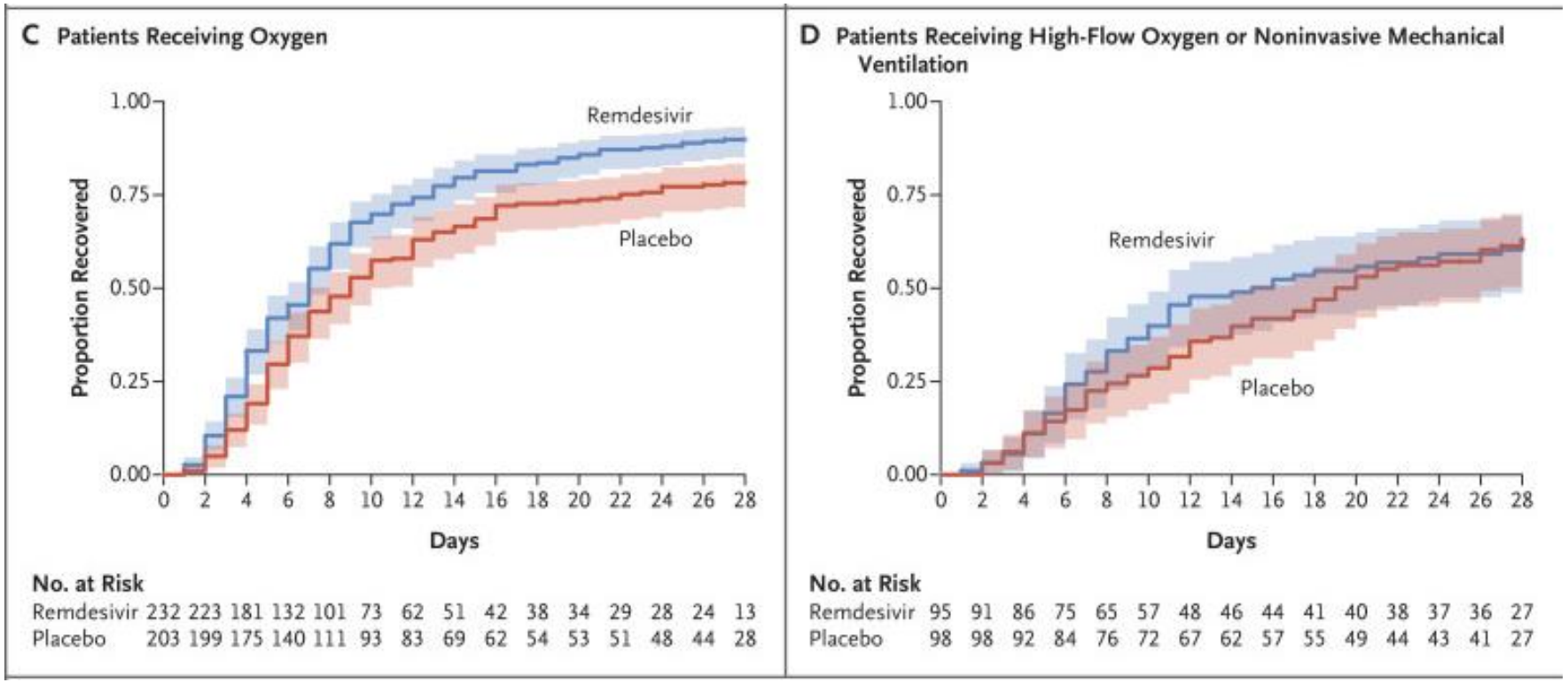
Clin Microbiol Rev. 2021 Jan; 34(1): e00162-20.

Remdesivir



N Engl J Med. 2020 Oct 8 : NEJMoa2007764.

Remdesivir



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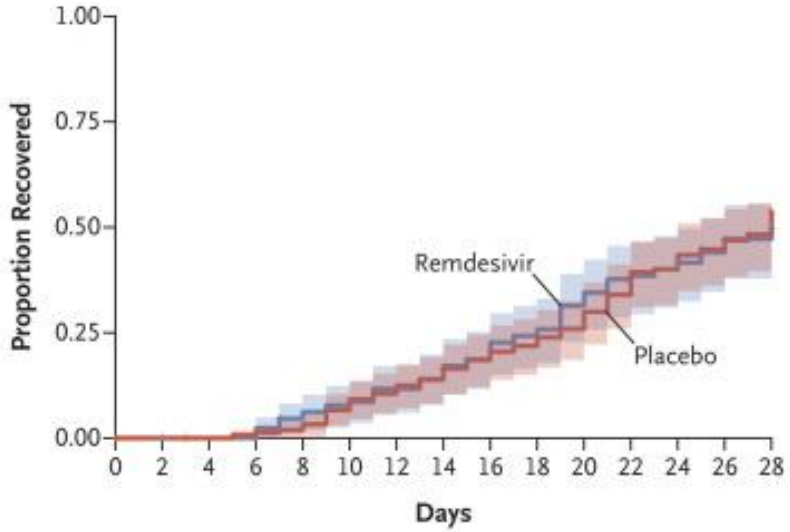
Remdesivir

E Patients Receiving Mechanical Ventilation or ECMO



No. at Risk

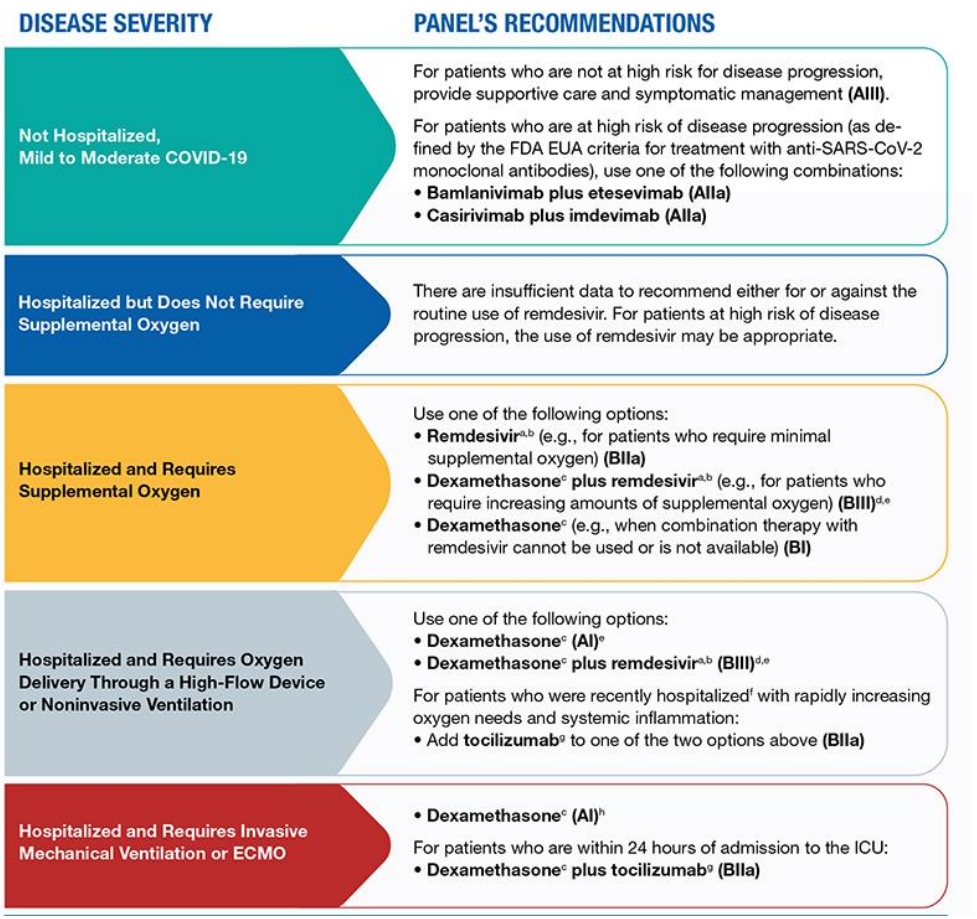
Remdesivir	131	131	129	129	122	118	113	110	103	96	87	79	76	69	42
Placebo	154	153	152	151	149	142	136	130	121	116	110	98	89	79	48

N Engl J Med. 2020 Oct 8 : NEJMoa2007764.

Remdesivir

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

Doses and durations are listed in the footnotes.



Source: CDC

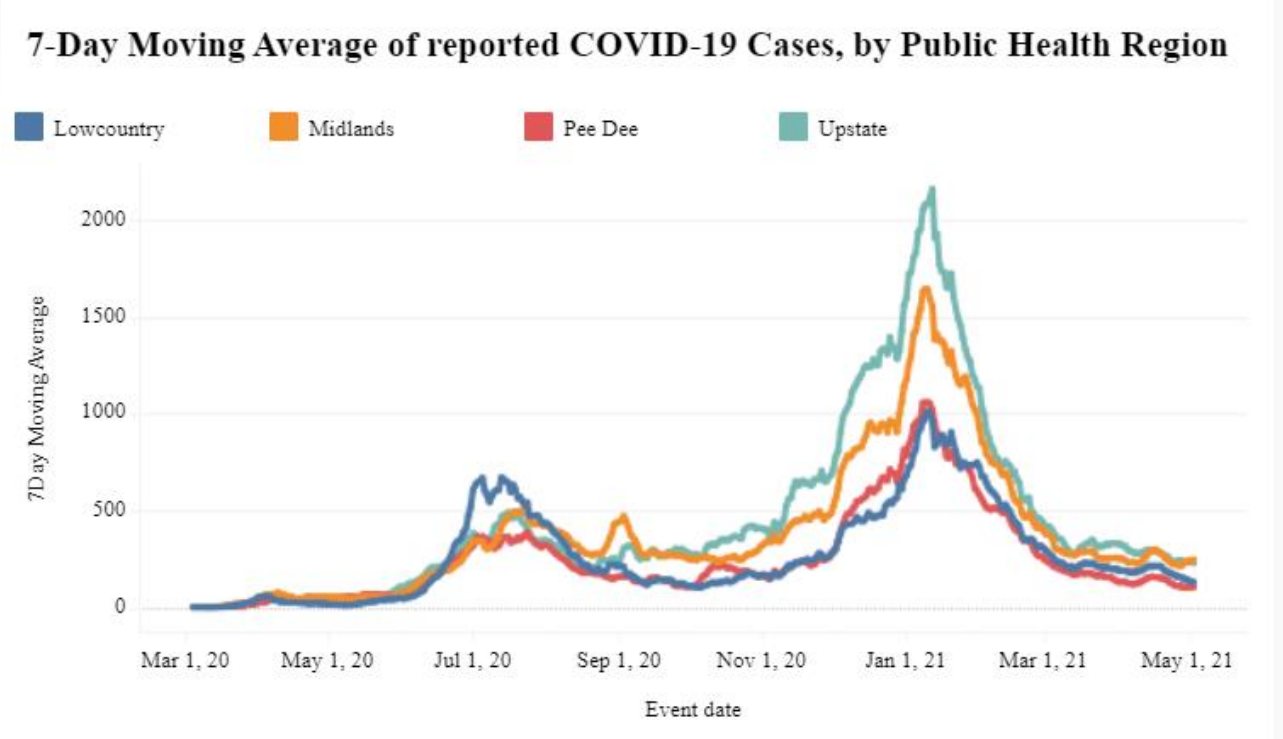
Local experience during COVID-19 epidemic

COVID-19 in SC

COVID-19 in South Carolina As of 11:59 PM on 5/3/2021			
Tests	Cases	Hospitalizations	Deaths
7,496,105	581,835	22,760	9,536

- South Carolina has been hit hard by COVID-19, especially when you consider case rate and death rate per 100k population.
- Much of South Carolina is rural and not necessarily equipped to handle this type of public health/medical crisis.
- Many hospitals in SC are struggling to keep up with the many demands that COVID-19 has created.

COVID-19 in South Carolina & by Region

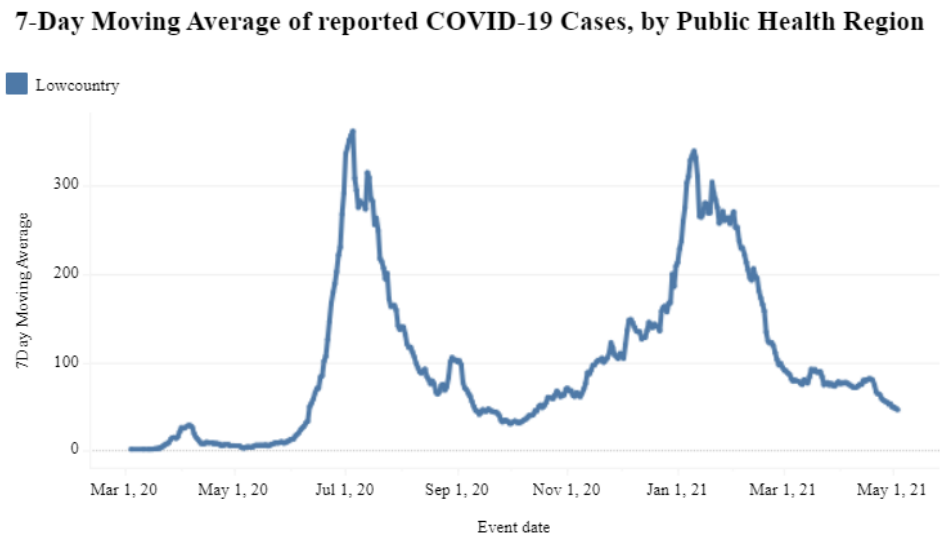


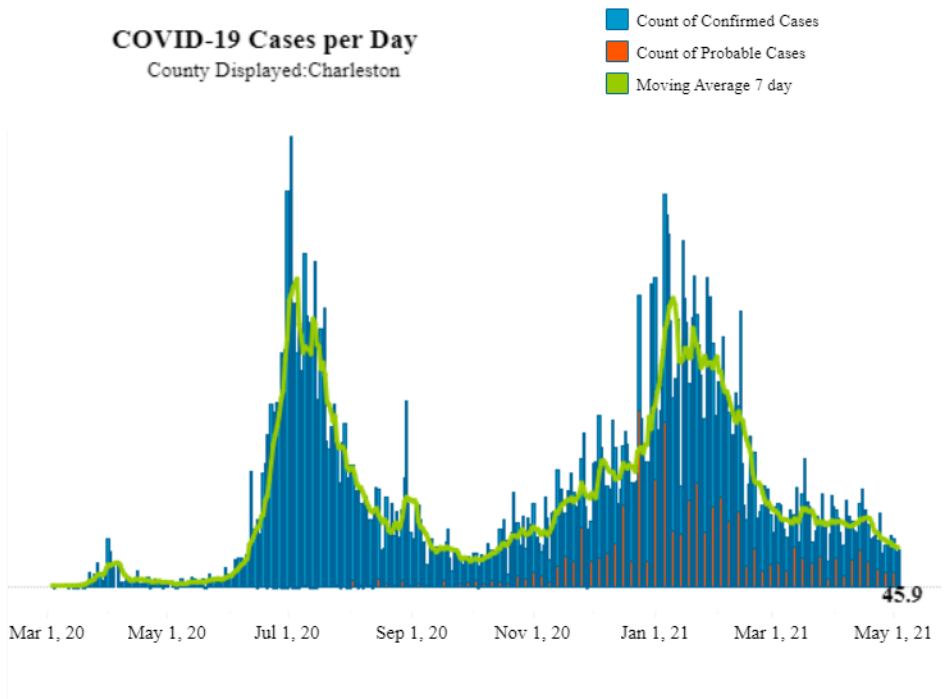
Low; 0-50	Moderate; 51-200	High; >200

Recovery Estimate South Carolina

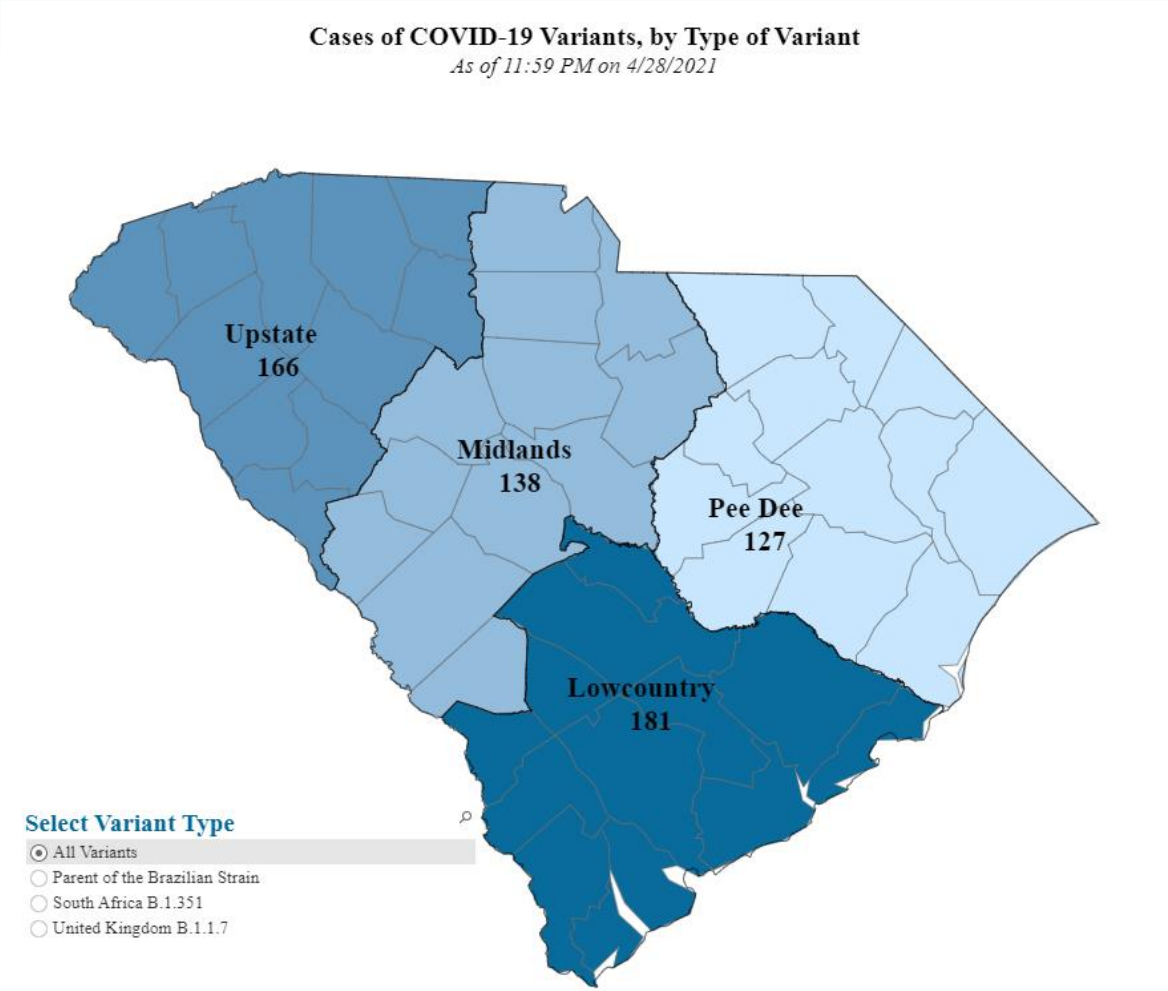
97.4%

COVID-19 in South Carolina & by Region



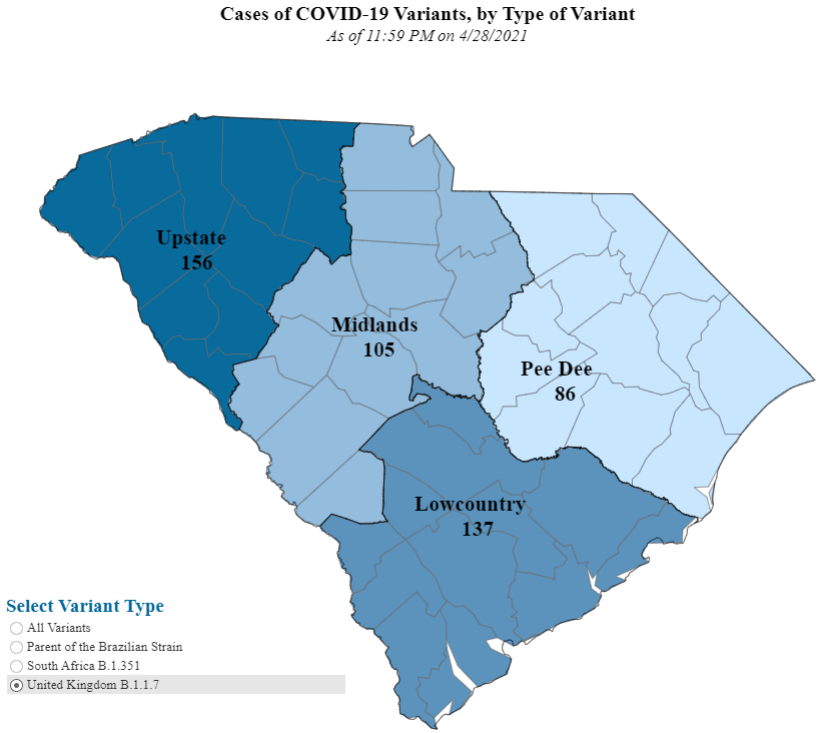


COVID-19 variants in SC



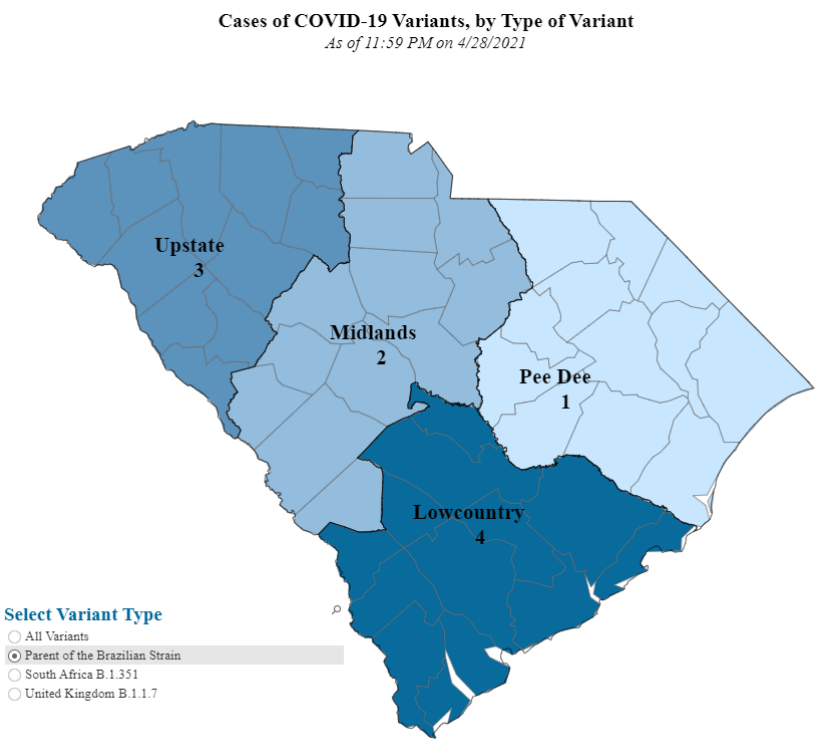
COVID-19 variants in SC

- ~50% increased transmission
- Potential increased severity based on hospitalizations and case fatality rates
- No impact on susceptibility to EUA monoclonal antibody treatments
- Minimal impact on neutralization by convalescent and post-vaccination sera



Source: CDC, SCDHEC

COVID-19 variants in SC



- Significant decrease in susceptibility to the combination of bamlanivimab and etesevimab monoclonal antibody treatment, but other EUA monoclonal antibody treatments are available
- Reduced neutralization by convalescent and post-vaccination sera

Source: CDC, SCDHEC

COVID-19 variants in SC

- ~50% increased transmission[1]
- Significant decrease in susceptibility to the combination of bamlanivimab and etesevimab monoclonal antibody treatment, but other EUA monoclonal antibody treatments are available
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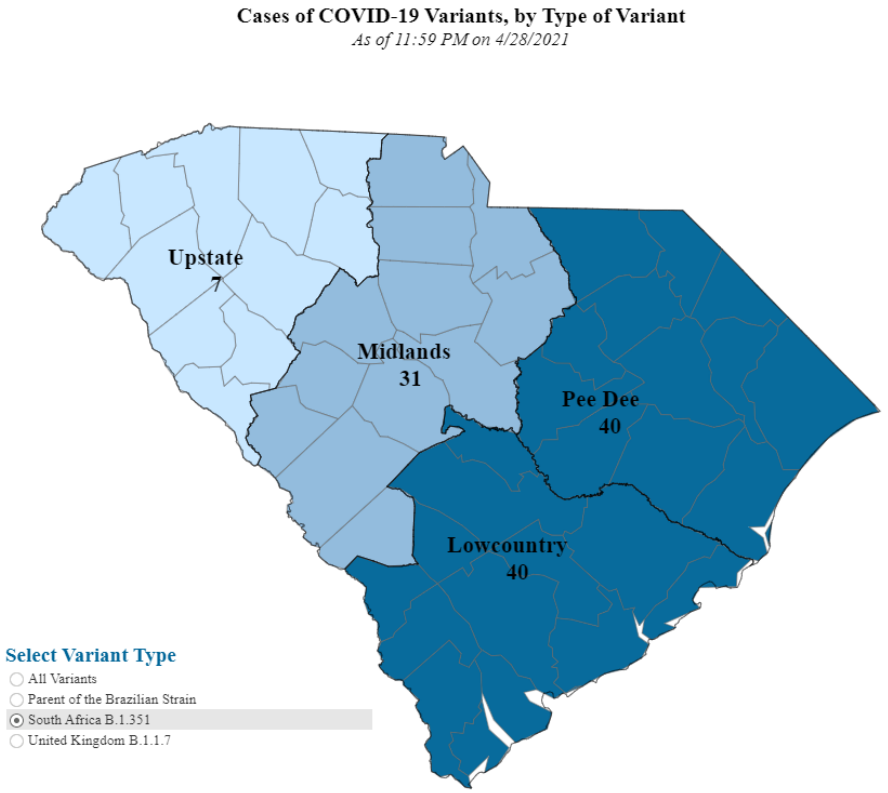
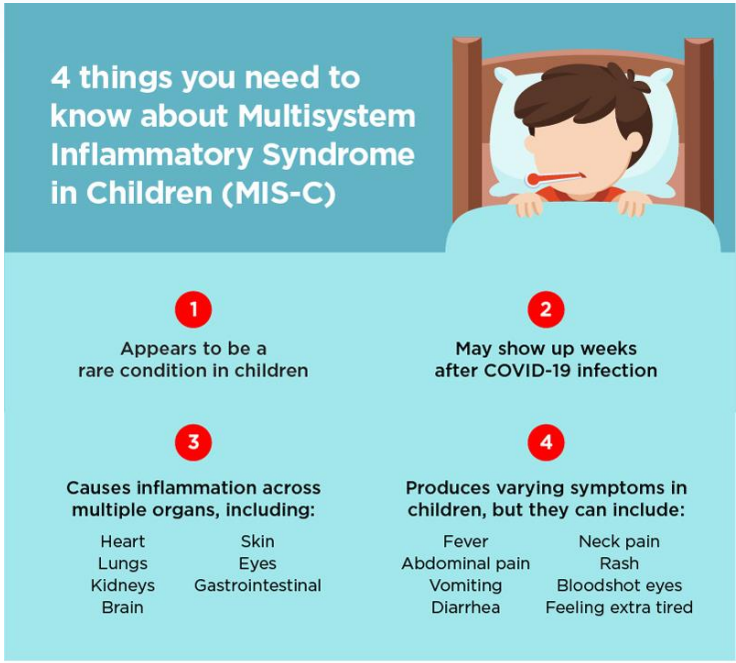


Source: CDC, SCDHEC

Multi-System Inflammatory Syndrome in Children (MIS-C)

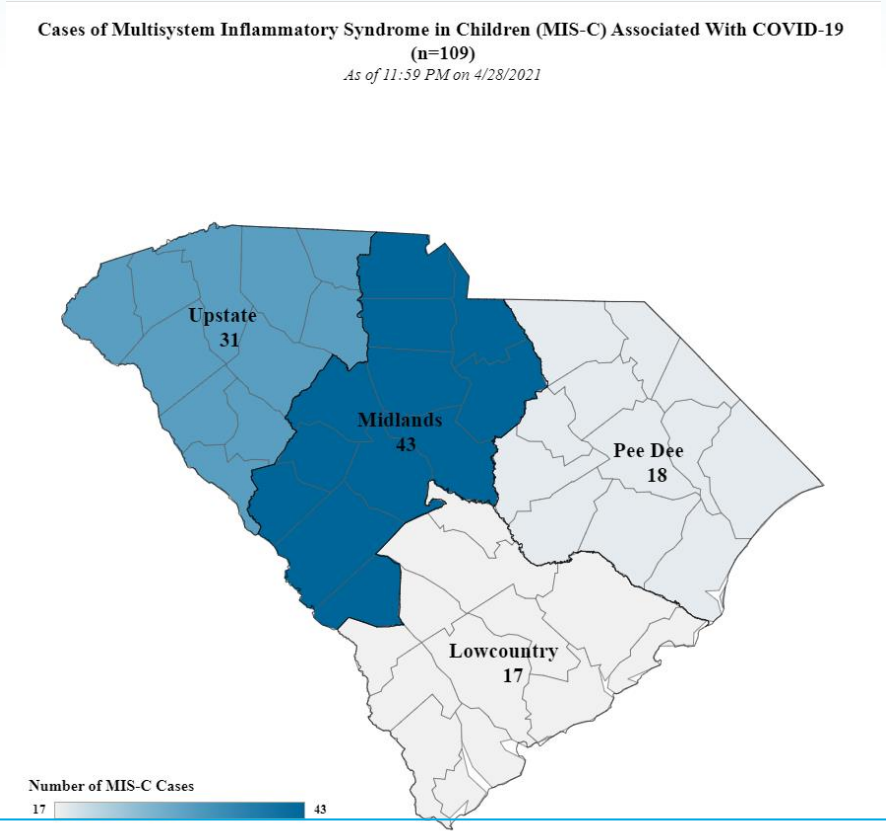
- A rare but very serious and often life-threatening post-infectious inflammatory syndrome in children (0-21 yrs) that occurs 2-4 weeks after having COVID-19.
- Most families do not know their children had COVID-19 or even were exposed to the virus.
- Most children with MIS-C were completely healthy before.
- Most common symptoms = fever, vomiting/diarrhea, fatigue (can include rash and/or red eyes)



- 2060 cases and 30 deaths so far in U.S.

Source: SC DHEC & CDC

Multi-System Inflammatory Syndrome in Children (MIS-C)

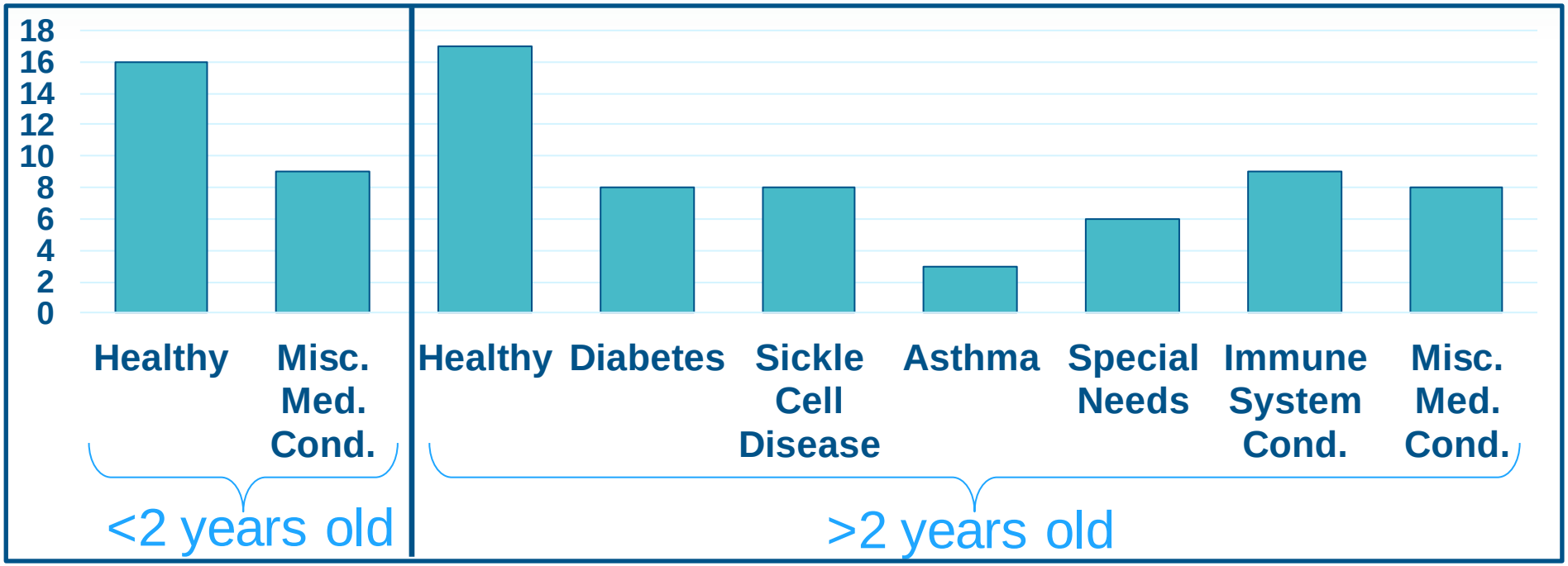


- MIS-C cases rise in an area as the prevalence of COVID-19 increases.
- MUSC Children's has cared for 18 children with MIS-C.
- All but one were previously healthy with no underlying medical condition.
- Some required a respirator to help them breathe and two required ECMO (machine that acts as heart and lungs).
- **All have recovered so far but long-term effects are unknown.**

- Can occur in child of any age and race/ethnicity
- >70% occur among African American and Hispanic children

Source: CDC

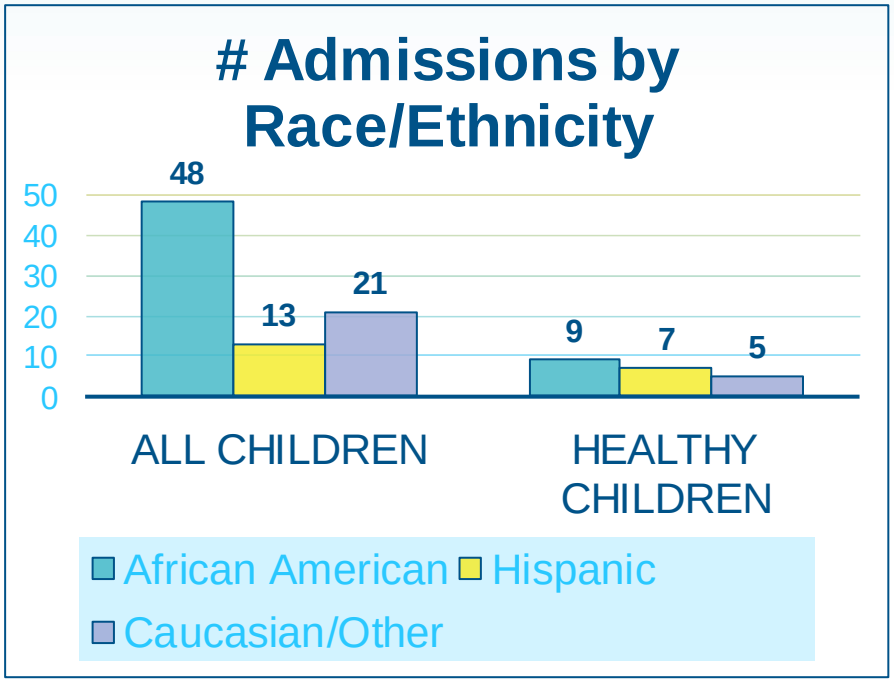
82 Children Admitted to MUSC with Acute COVID-19 in the Last Year (0-21 years old)*

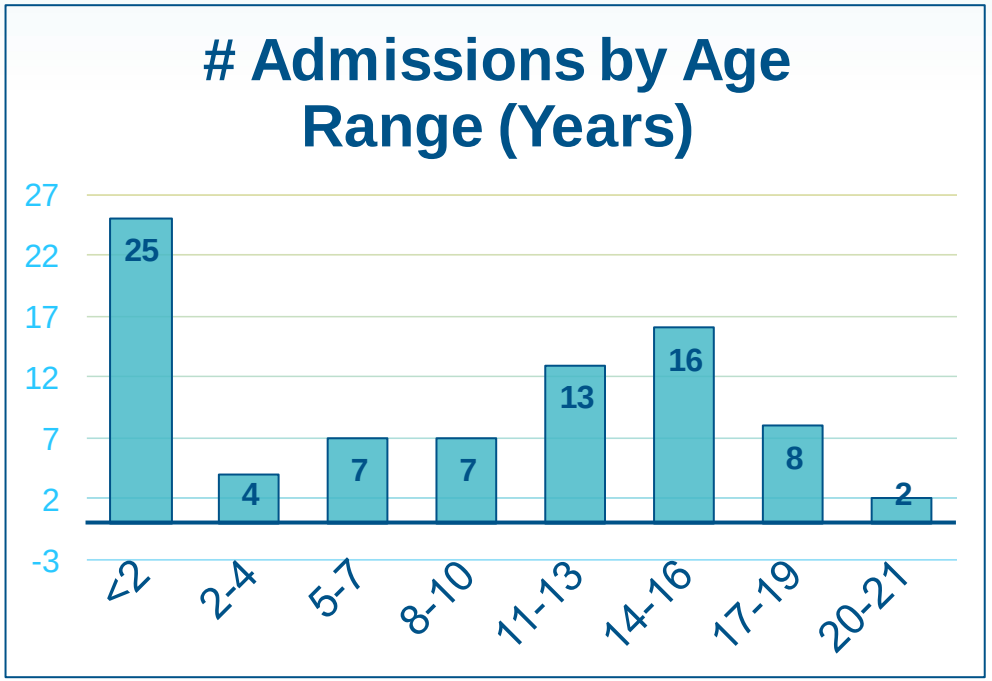


- Some admitted b/c COVID-19 worsened their underlying condition
- A few developed serious disease from COVID-19; all survived
- 3 healthy children presented w/ new Type 1 diabetes related to COVID

*Excludes those with a positive COVID test found incidentally on admission

African-American Children and <2 Years Old Have Been Hit Hardest by COVID-19 at MUSC





- COVID-19 poses a greater risk to many of the same children who obtain essential services at school (e.g., OT/PT/speech therapy, medical and mental health treatment, nutrition, etc.) and/or are most at risk for educational disparities w/ virtual learning.
- We have the responsibility to provide a safe in-person school environment for these at risk and disadvantaged children.

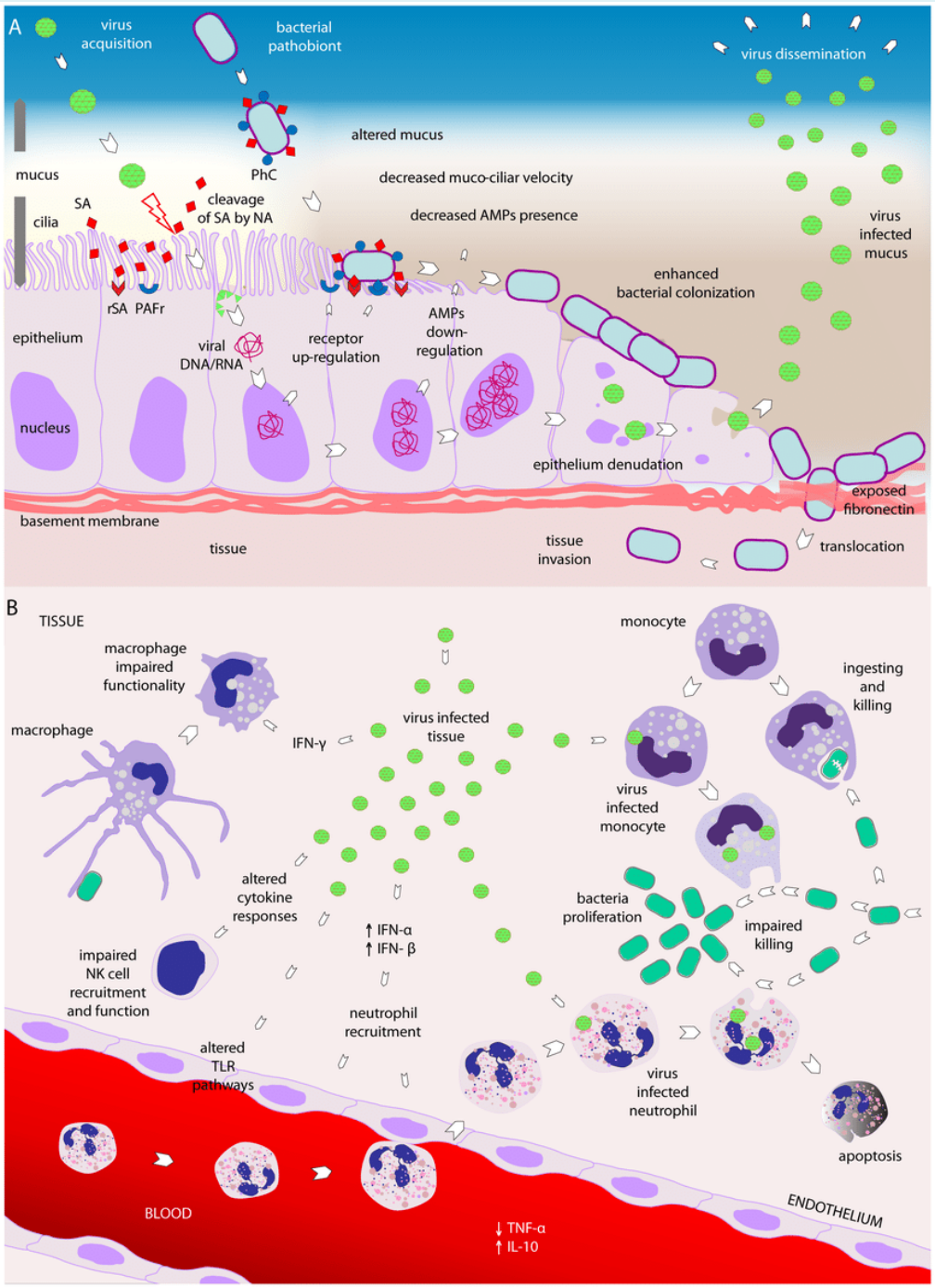
*Excludes those with a positive COVID test found incidentally on admission

Antiviral Stewardship

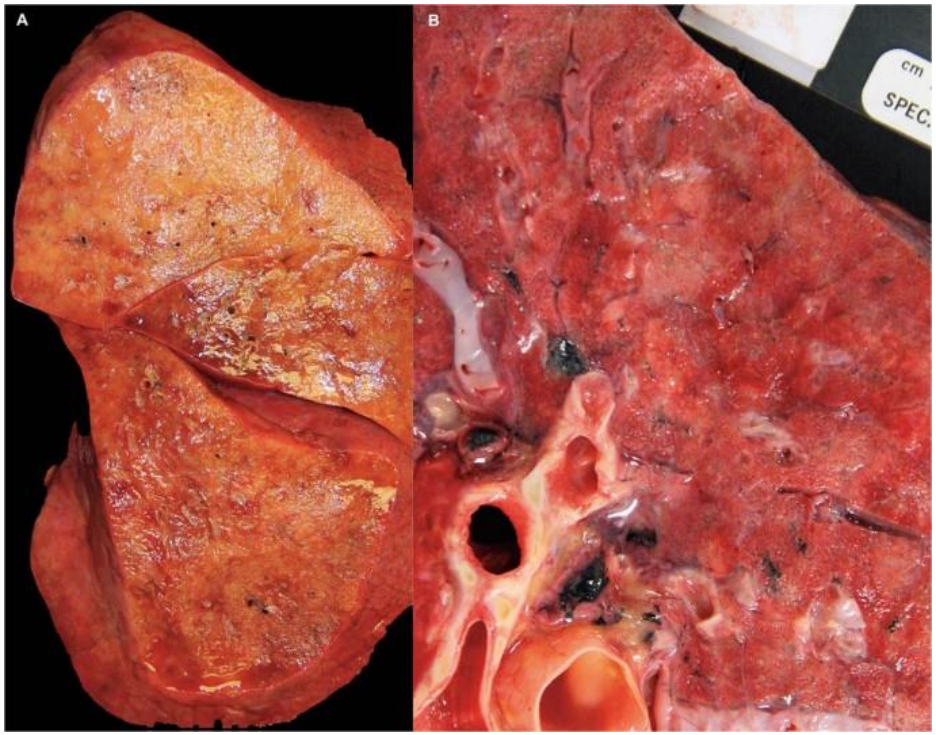
Bacterial Superinfection of viral pneumonia

- 1918 Influenza Pandemic
- 10 to 15% fatal cases severe ARDS
- 85 to 90% fatal cases acute bronchopneumonia
  - *Streptococcus pneumoniae*
  - *S. pyogenes*
  - *Haemophilus influenzae*
  - *Staphylococcus aureus*

Morens and Fauci. *JID* 2007.195(7):1018



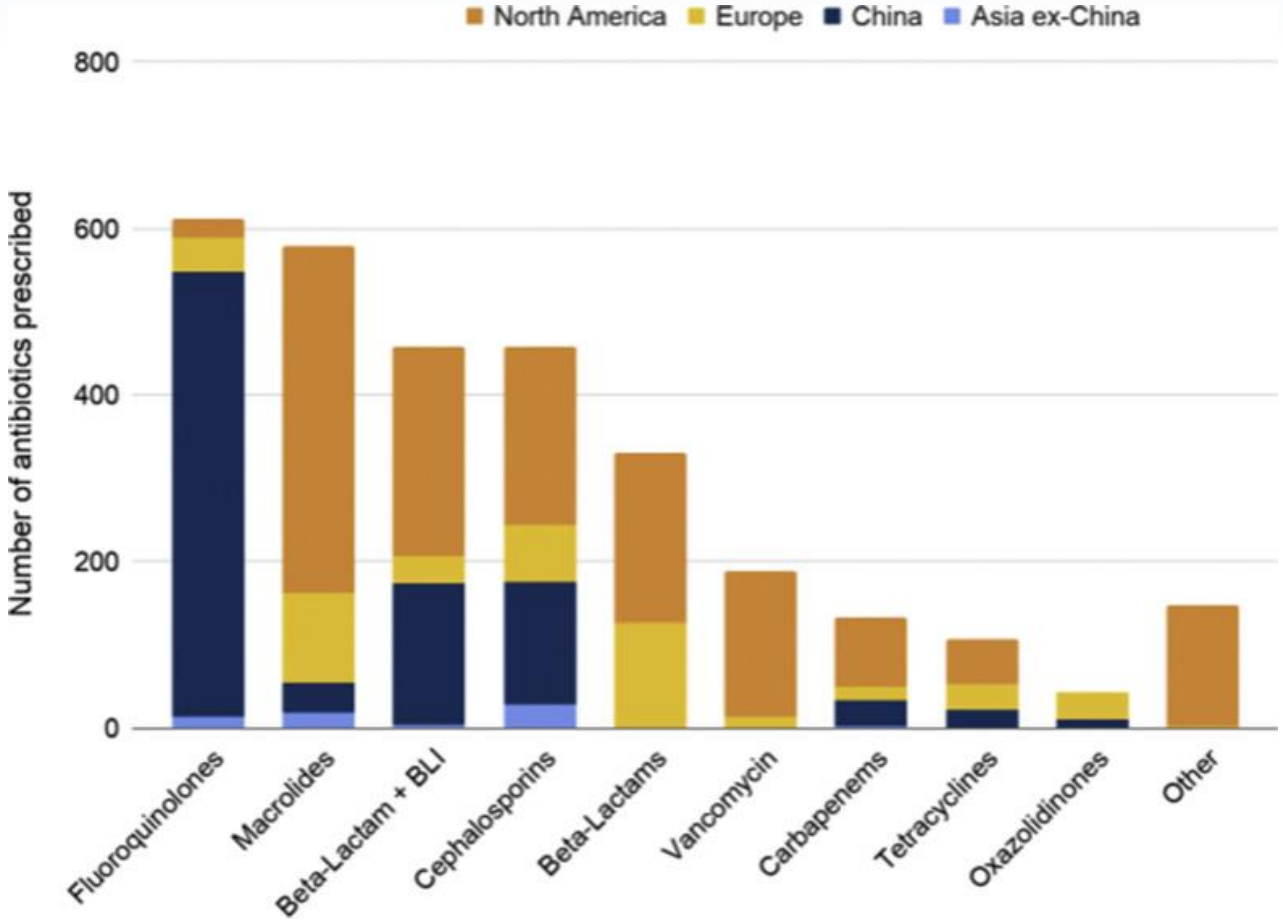
Bacterial superinfection – COVID-19



- 2019 Sars-CoV-2 pandemic
- 8% fatal cases acute bronchopneumonia
  - *Acinetobacter baumannii*
  - *Staphylococcus aureus*
  - *Pseudomonas aeruginosa*
  - *Klebsiella pneumoniae*

Clancey *et al*., 2021. *Op For Infect Dis*. 8(3):1

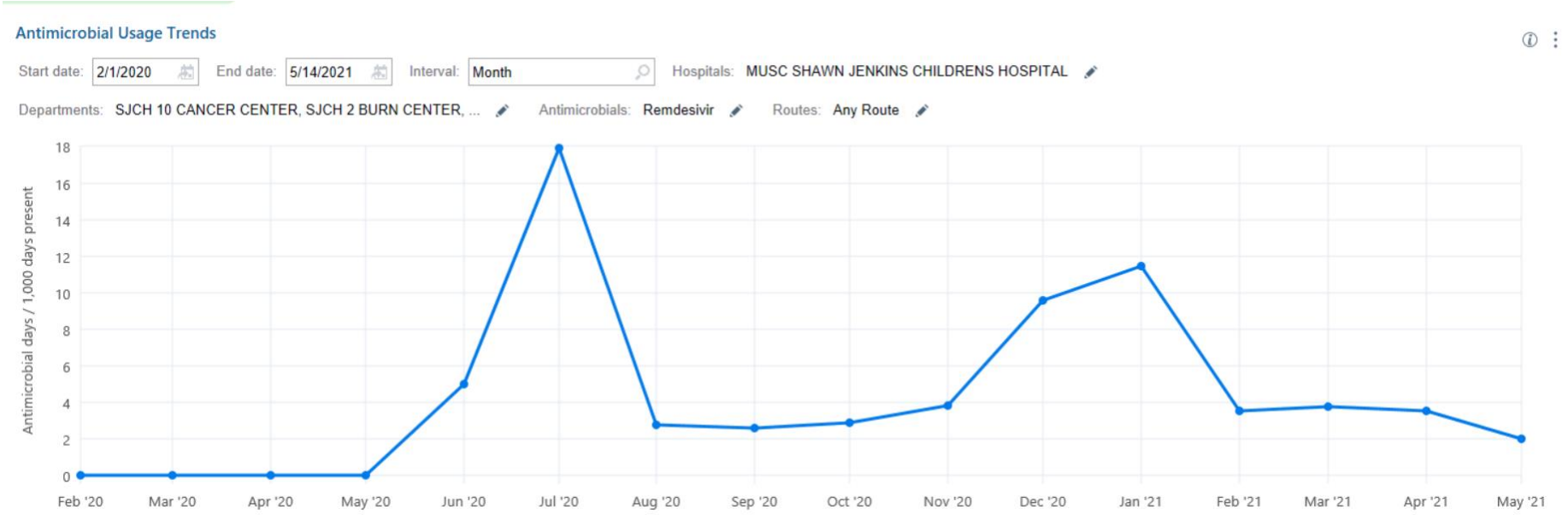
Antibiotic Usage in COVID-19 infection



75% of cases received antibiotics

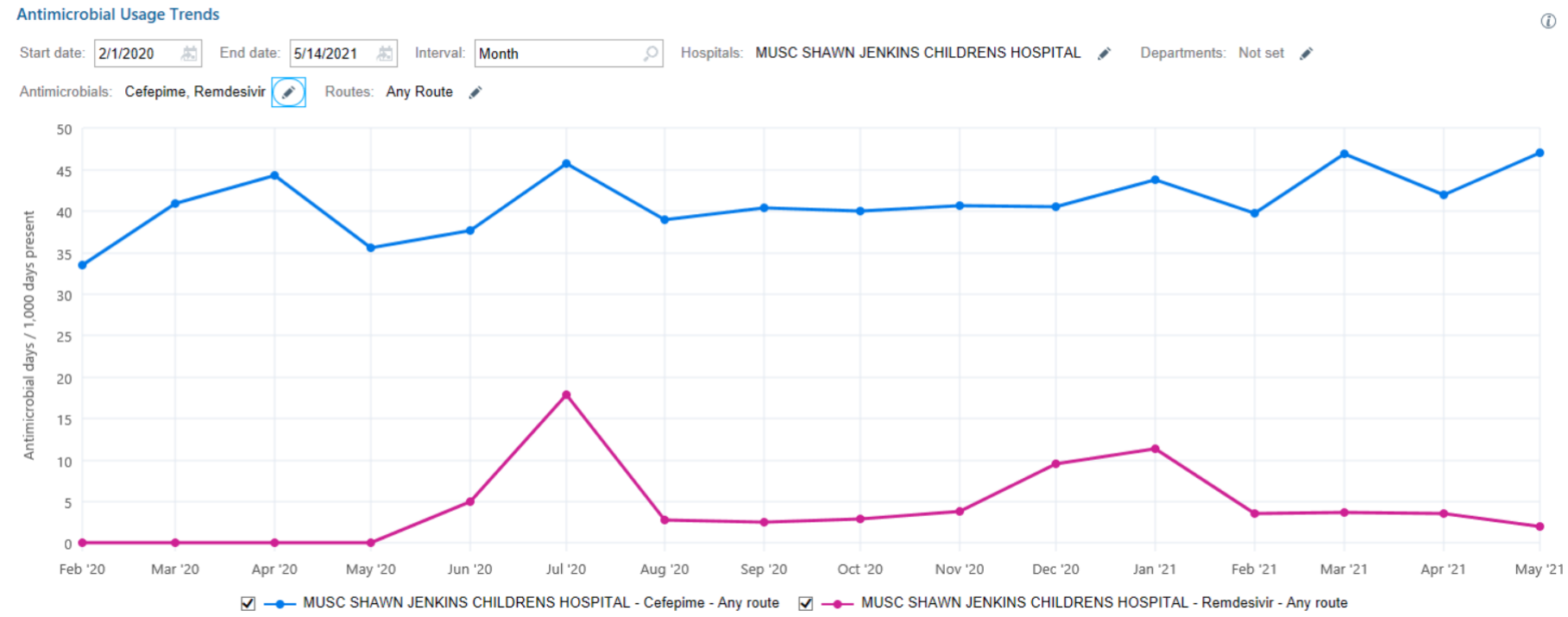
Clin Microbiol Infect. 2021 Apr; 27(4): 520–531.

Antibiotic Usage in COVID-19 infection

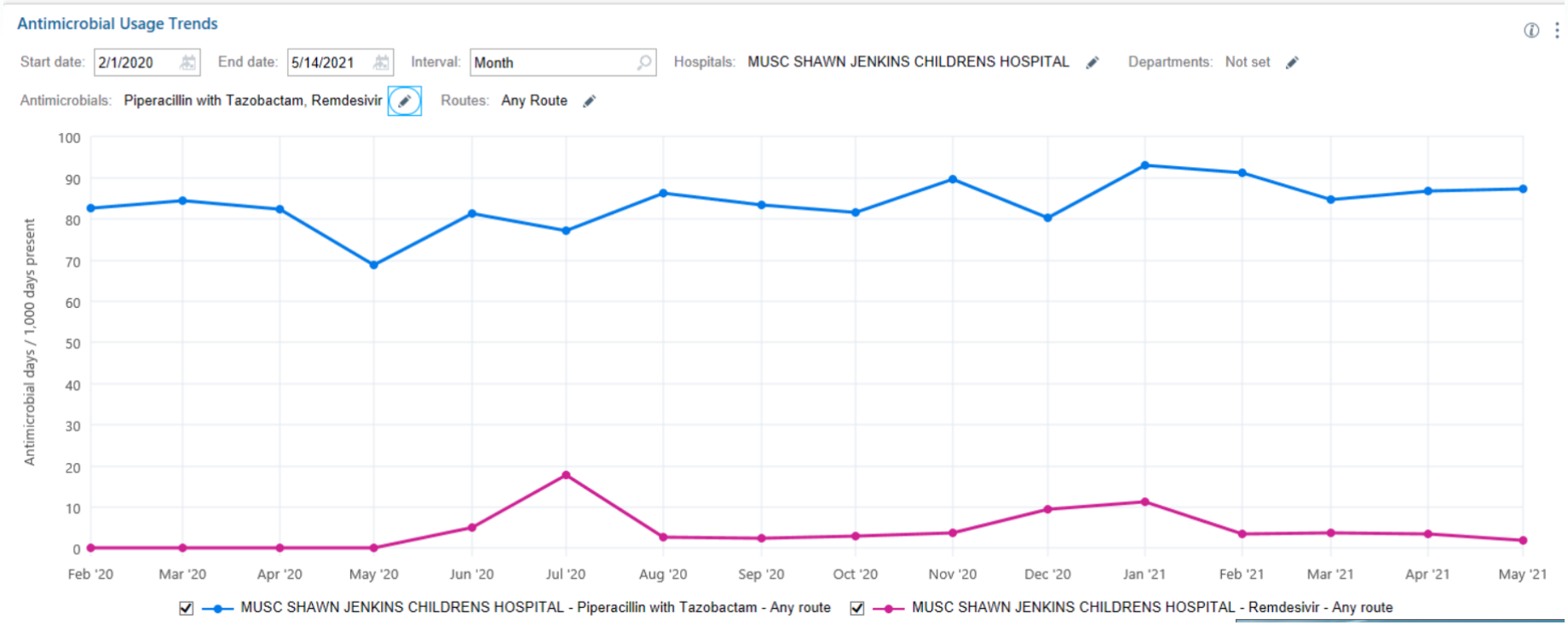


Antibiotic Usage in COVID-19 infection

Antibiotic Usage in COVID-19 infection



Antibiotic Usage in COVID-19 infection



…also no effect on Linezolid, Vancomycin, or Meropenem use

Learning Objectives

At the completion of this activity, the pharmacist will be able to:

- 1. COVID-19 symptoms and complications are different in pediatric patients
- 2. Remdesivir is the antiviral of choice in certain clinical scenarios
- 3. Bacterial superinfection occurs less often during COVID-19, we should continue to be good stewards of broad-spectrum antibiotics.

QUESTIONS?