Review of Select Military Innovations During the COVID-19 Pandemic

Navy LT Piotr Wisniewski, M.D.

Infectious Disease Physician, Naval Health Research Center
Associate Program Director, Internal Medicine Residency Program
Interim Co-chair, Antibiotic Stewardship Program
Naval Medical Center San Diego
Assistant Professor of Medicine, Uniformed Services University of the Health Sciences

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Presenter

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Naval Medical Center San Diego

Assistant Professor of Medicine, Uniformed Services University of the Health Sciences

San Diego, Calif.

Navy LT Piotr Wisniewski, M.D.

- LT Wisniewski was born in Poland where he spent his early childhood until immigrating to San Diego, California in 1997.
- He attended San Diego State University where he earned a Bachelor of Arts degree in biology with a minor in religious studies. He went on to attend the Uniformed Services University of the Health Sciences in Bethesda, Maryland, where he earned his Medical Doctor degree.
- He completed internal medicine residency at the Naval Medical Center San Diego before completing his fellowship in infectious diseases at the same institution.
- He currently serves as an Infectious Disease Physician at the Naval Health Research Center, as Internal Medicine and Infectious Disease Faculty, and as well as Associate Program Director in the Internal Medicine Residency Program at the Navy Medical Center San Diego.
- His research interests include Coccidioidomycosis and Tuberculosis.

Disclosures

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Disclaimer #2: There are MANY DoD contributions to the battle against COVID-19. So MANY, in fact, that I WILL omit important works and efforts from this talk, which is bound by the limits of human attention span and my common decency (and the kind organizers' instructions). This is my great shame and, to those whom I may/will slight, I am eternally sorry and beg your forgiveness.

Learning Objectives

At the conclusion of this activity, participants will be able to:

1. Recognize the history and basic biology of Coronaviruses as it pertains to past, present, and future pandemics.
2. Outline some military-specific challenges during the COVID-19 pandemic.
3. Discuss the importance of infectious disease surveillance and its role in pandemic preparedness.
4. Summarize military contributions to managing the COVID-19 pandemic.

Let's Catch Up

- 1960's: first Coronaviruses isolated and imaged with electron microscopy
- Enveloped ribonucleic acid (RNA) viruses which infect a variety of animals (and are common)
- In humans they cause primarily respiratory infections (and are common!)
  - Human Coronavirus (HCoV) HCoV-NL63, HCoV-OC43, HCoV-229E, HCoV-HKU1

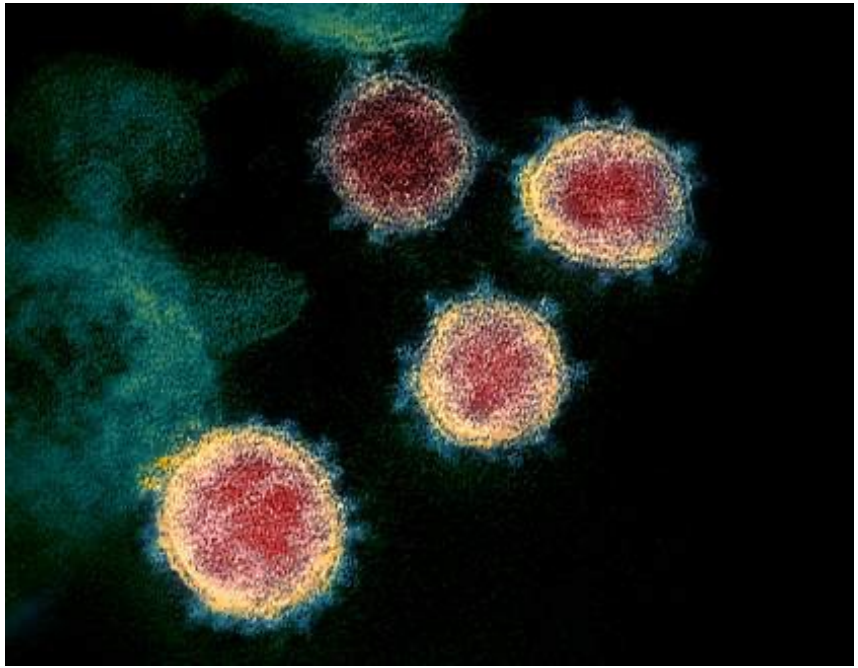


Photo: NIAID-RML

Let's Catch Up

- 2002 – 2004: Severe Acute Respiratory Syndrome (SARS)
  - Worldwide but most cases from China, Hong Kong, Taiwan, Singapore, Canada
  - 8096 cases, 774 deaths
  - Case fatality rate 7 – 17%, >50 in vulnerable (Chen, 2007)
  - Multi-organ involvement, predominantly respiratory

Photo: WHO.int

Photos: Reuters.com

Let's Catch Up

- 2014 – current: Middle East Respiratory Syndrome (MERS)
  - Arabian Peninsula, Korea, scattered others (2 US)
  - 2374 cases, 823 deaths as of March 2019
  - Case fatality rate overall 35%, >50% in Intensive Care Unit (ICU) patients
  - Almost exclusively respiratory, renal failure common

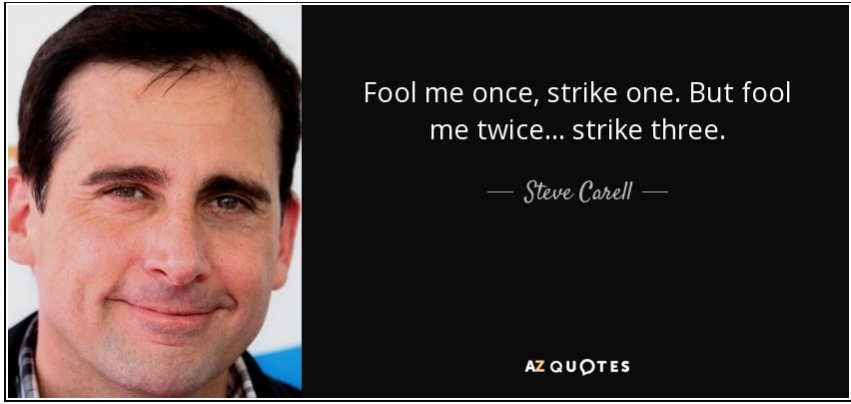
Photo: WHO.int

Photos: Reuters.com

Lessons From the Past

(including pandemic flus)

- Recombination events in RNA viruses lead to explosive epidemics/pandemics
- Surveillance for outbreaks
- Ability to characterize novel pathogens
- Infection control infrastructure
- Vaccine development
- Management of infected patients
- Carrying forward to next pandemic



SARS-CoV-2 and COVID-19

- December 2019: Cluster of pneumonia cases in Wuhan, China (first cases ?November?)
- 20 January 2020: First United States (US) Case
- 30 January 2020: World Health Organization (WHO) declares Global Public Health Emergency
- 06 February 2020: First US death
- March 2020: Shelter in place orders in the US
- December 11, 2020 first vaccine given Emergency Use Authorization (EUA) by the Food and Drug Administration (FDA)
- Late Spring 2021 restrictions loosened but…

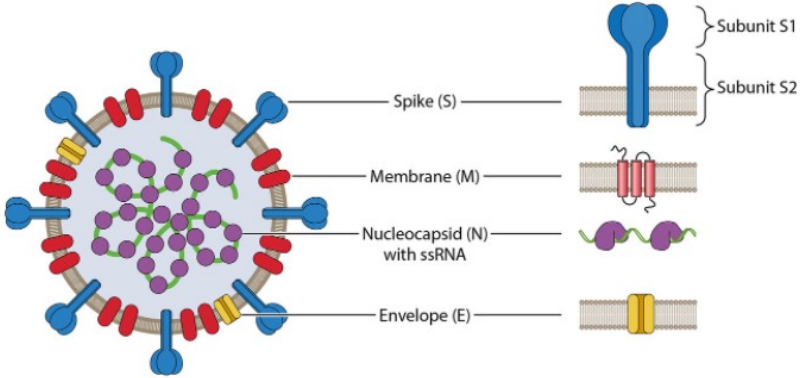
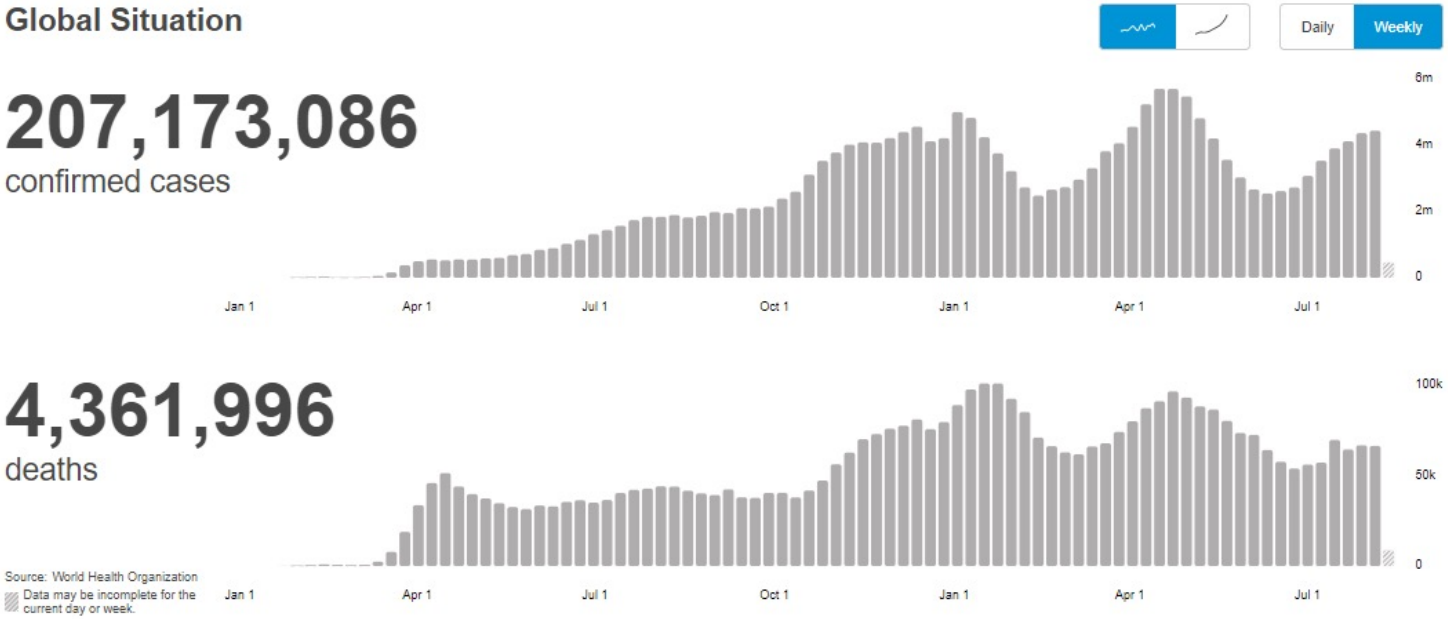


Image: (Synowiec et al, 2021)

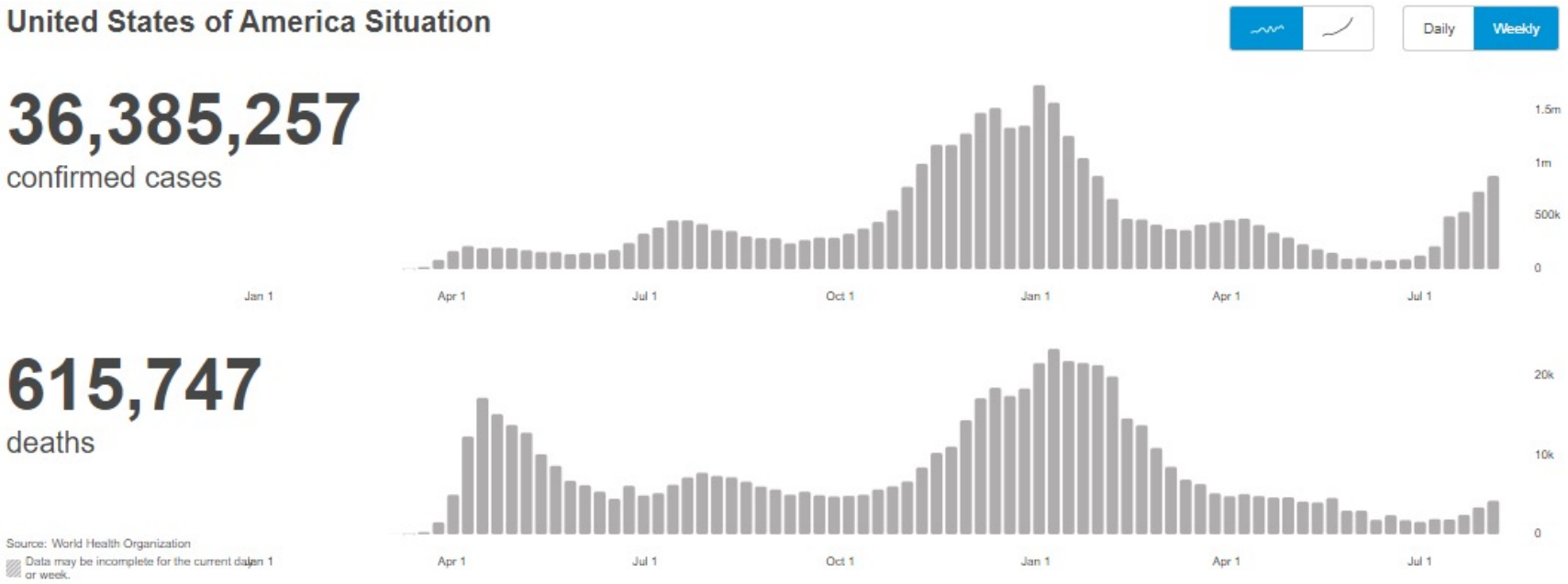
SARS-CoV-2 Delta Variant

- "Variants" are viruses with mutations in relevant structures
- There are several, but the "delta" (B.1.617.2) variant has become dominant
- Data indicate that it is:
  - More transmissible
  - More virulent

Where Are We Now



United States



Military Challenges

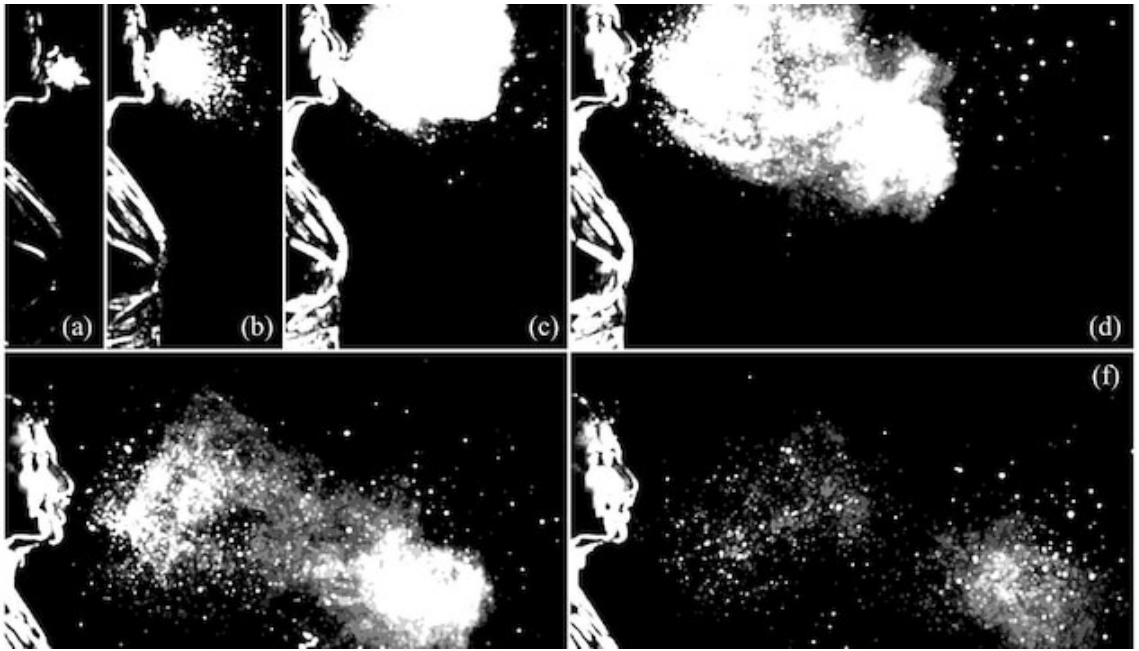


Photo: National Geographic

Military Challenges

- Quintessential “essential” employees
- Cramped quarters
- Intermittently poor access to hygiene supplies
- Supply issues
- Physical distance from intensive care capabilities
- Operational medicine with different set of realities

Surveillance

Global Emerging Infections Surveillance (GEIS)

- Network of surveillance sites around the world
  - Antimicrobial resistance and sexually transmitted infections
  - Enteric infections
  - Febrile and vector-borne infections
  - Respiratory infections

Naval Health Research Center

- Operational Infectious Disease directorate provided first SARS-CoV-2 testing capability to the DoD
  - First testing 25 February 2021
- Sole provider of DoD SARS-CoV-2 testing on the West Coast in the initial months of the pandemic
- To date:
  - 55,000 specimen tested
  - 1269 specimen sequenced
  - Sequence all positives with cycle threshold (CT) < 30 (priority to vaccine breakthroughs or reinfections)

Pooled Specimen Testing

- Combining multiple specimens and performing a single test
- Saves supplies, increases testing capability
- Useful for asymptomatic infection screening in operational setting (active surveillance)
- But does it work?

Pooled Specimen Testing

- Problem: pooling = dilution
- Depends on how many positives are “low titer”
- Two studies done to answer feasibility
  - 5x 8x study (Applied Biosystems (ABI) 7500, BioFire, Cepheid)
  - The Rim of the Pacific Exercise (RIMPAC) prospective pooling study (Cepheid)
  - Funding by The Joint Program Executive Office for Chemical, Biological, Radiological and Nuclear Defense

Slide courtesy of Jason Opdyke, Ph.D.

5x 8x Pooled Study

- Archived specimens previously determined positive or negative by the Centers for Disease Control and Prevention (CDC) assay on the ABI 7500 were tested
- Specimens were assembled in 5 and 8 sample pools
- Tested all samples using the ABI 7500 (CDC assay), BioFire FilmArray and Cepheid GeneXpert
- Specimens were selected based on original CDC test results
  - Ct < 25 = high viral load
  - Ct >35 = very low viral load

Slide courtesy of Jason Opdyke, Ph.D.

5x 8x Pooled Study

CT range (original CDC test)	Number of Samples
< 25	5
25-30	5
30-35	5
>35	5

Slide courtesy of Jason Opdyke, Ph.D.

5x 8x Pooled Study

Summarized Data			
	CDC	BioFire	Cepheid
Individual Samples	20/20	20/20	20/20
5:1 pools	17/20	20/20	19/20
8:1 pools	16/20	19/20	18/20

5 Sample Pool Breakout			
CT Criteria	CDC	BioFire	Cepheid
<25	5/5	5/5	5/5
25-30	5/5	5/5	5/5
30-35	4/5 (2 inconclusive)	5/5	5/5
>35	3/5 (2 inconclusive)	5/5 (1 equivocal)	4/5

8 Sample Pool Breakout			
CT Criteria	CDC	BioFire	Cepheid
<25	5/5	5/5	5/5
25-30	5/5	5/5	5/5
30-35	5/5 (3 inconclusive)	4/5	4/5
>35	1/5	5/5 (1 equivocal)	4/5

Slide courtesy of Jason Opdyke, Ph.D.

RIMPAC Prospective Pooling Study

- Use: pre-deployment screening of Navy personnel
  - 14 day restriction of movement (ROM) + test on day 14
- 1,433 asymptomatic individuals tested
- All specimens were assembled in 5x sample pools
  - All pools were tested with Cepheid and ABI 7500

Slide courtesy of Jason Opdyke, Ph.D

RIMPAC Prospective Pooling Study

Cepheid Data Summary (pools)	
5 sample Pools	284
4 sample pools	1
3 sample pools	3
TOTAL POOLS	**288**
TOTAL (+) POOLS	**18**
TOTAL (-) POOLS	**270**

Slide courtesy of Jason Opdyke, Ph.D.

Cepheid Data Summary (Individuals)	
Positive pools resolved	18/18#
Negative pools resolved	7/270*
Total # of positive pools based on individual results	**25**

One positive pool had two individual positives
* One negative pool had two individual positives

Preliminary Ct Analysis (All Pools)	
Individual Ct <37	14/14
Individual Ct ≥39	4/11

RIMPAC Prospective Pooling Study

- Pooling is a feasible strategy but requires careful validation in the intended population
- Performance of pooled testing is a function of how many positives in the test population reside near the LoD of the test
- Careful consideration of the Concept of Use and associated risks with pooled testing is required prior to implementation
  - Risk tolerance changes for each Concept of Use
    - Example: basic training vs submarine deployment

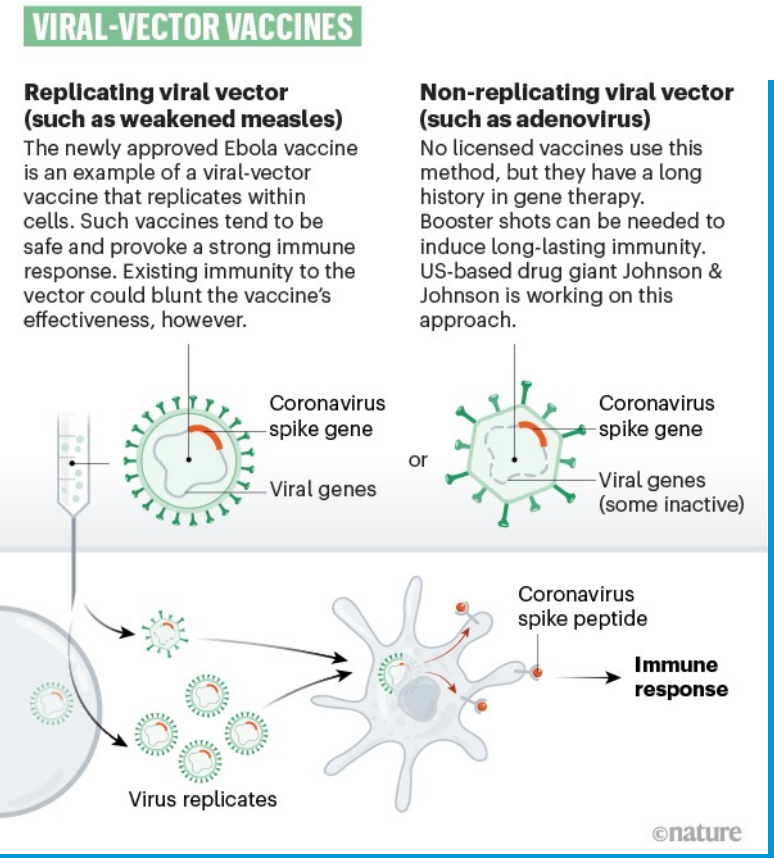
Slide courtesy of Jason Opdyke, Ph.D.

Prevention and Treatment

Vaccines

(wanted to find a funny meme but got too depressed at the search results)

SARS-CoV-2 Vaccine Landscape: Viral Vector Vaccines



Source: (Nature, 2020)
Slide courtesy of CAPT (ret) Ryan Maves

- DoD is participating in the phase 3 trial of the AstraZeneca viral vector vaccine.
  - ChAdOx1 -> non-replicating chimpanzee adenovirus that produces the SARS-CoV-2 spike protein.
  - Hopefully safe to administer to immunocompromised hosts
  - Lack of host antibodies at baseline (unlike human adenovirus vectors)
- Five MTFs, plus 60+ civilian sites:
  - Navy Medical Center San Diego (NMCSD)
  - Walter Reed National Military Medical Center (WRNMMC)
  - Fort Belvoir Community Hospital (FBCH)
  - Brooke Army Medical Center (BAMC)
  - WFASC

ChAdOx1 = chimpanzee (Ch) adenovirus-vectored vaccine (Ad), University of Oxford (Ox)

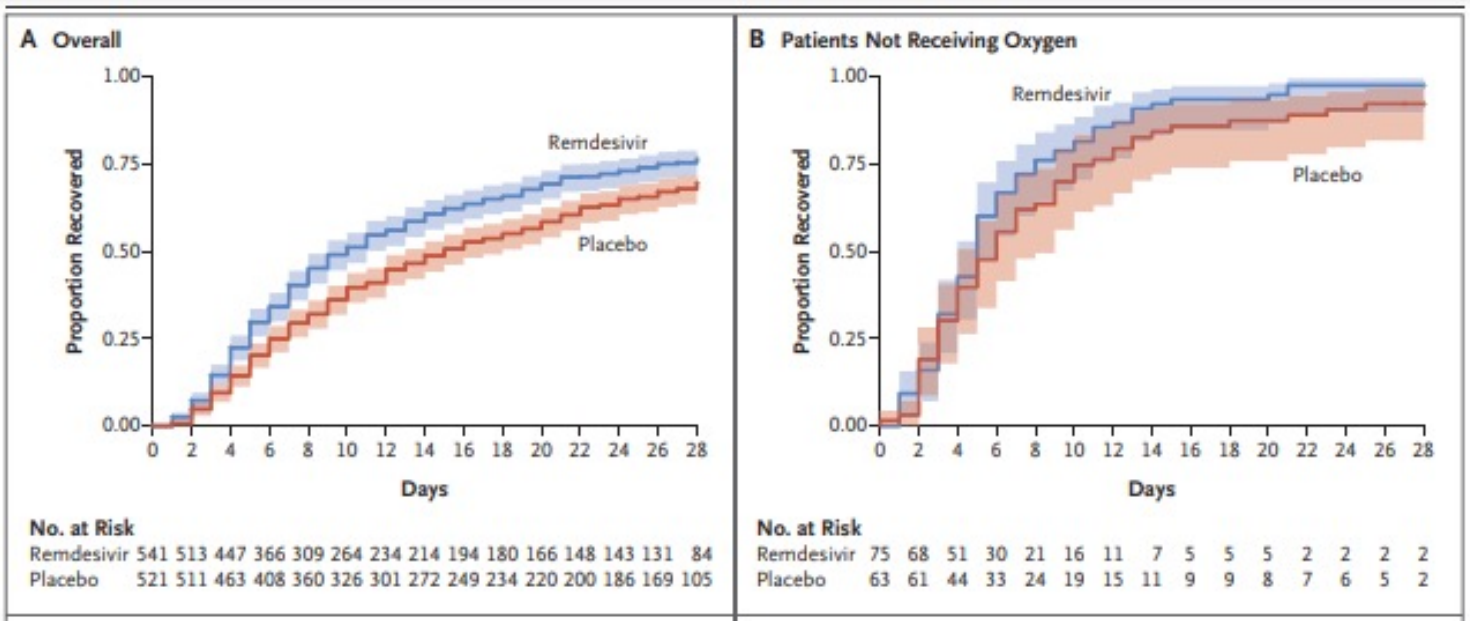
Therapeutics

- Remdesivir - Adaptive COVID-19 Treatment Trial (ACTT)
- Corticosteroids – RECOVERY
- Baricitinib - ACTT
- Tocilizumab - RECOVERY

ACTT-1 Trial and Remdesivir

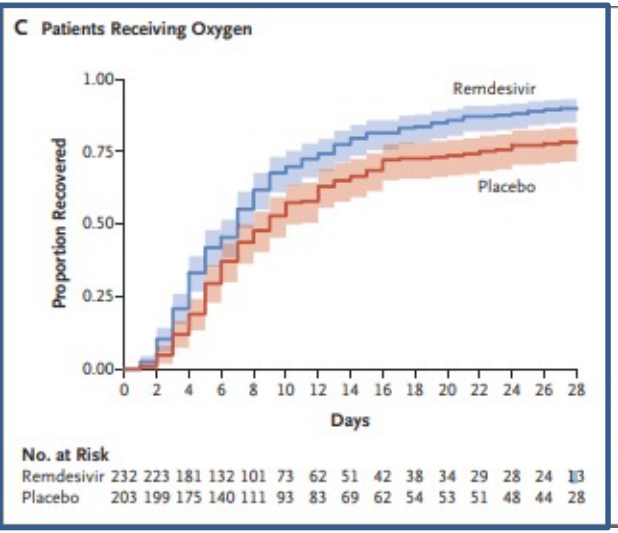
- Double-blind, randomized, placebo controlled trial, multi-site
- Remdesivir (10 days) versus placebo
- Primary outcome = time to recovery
- 8 point ordinal scale used
- 1066 patients

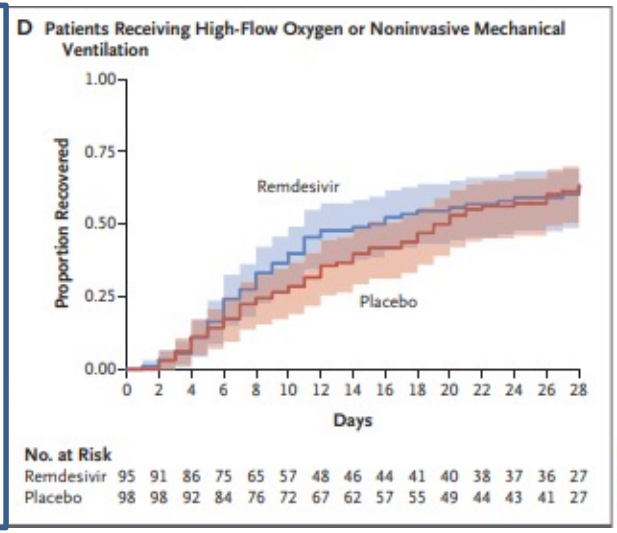
ACTT-1 Trial and Remdesivir

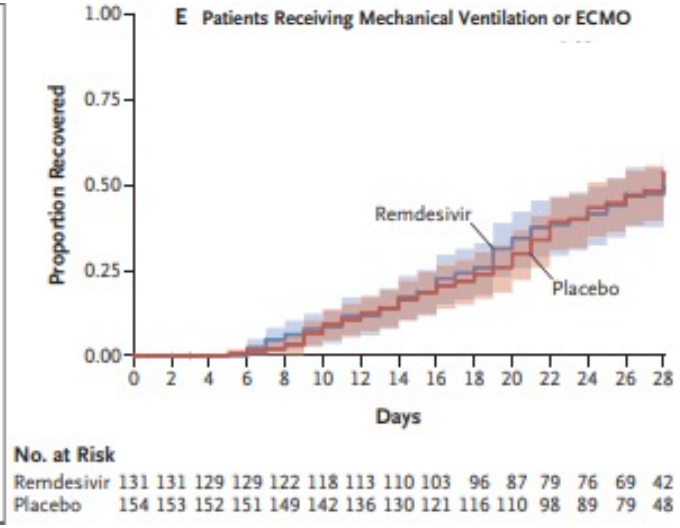


(Beigel, J. et al., 2020)

ACTT-1 Trial and Remdesivir







(Beigel, J. et al, 2020)

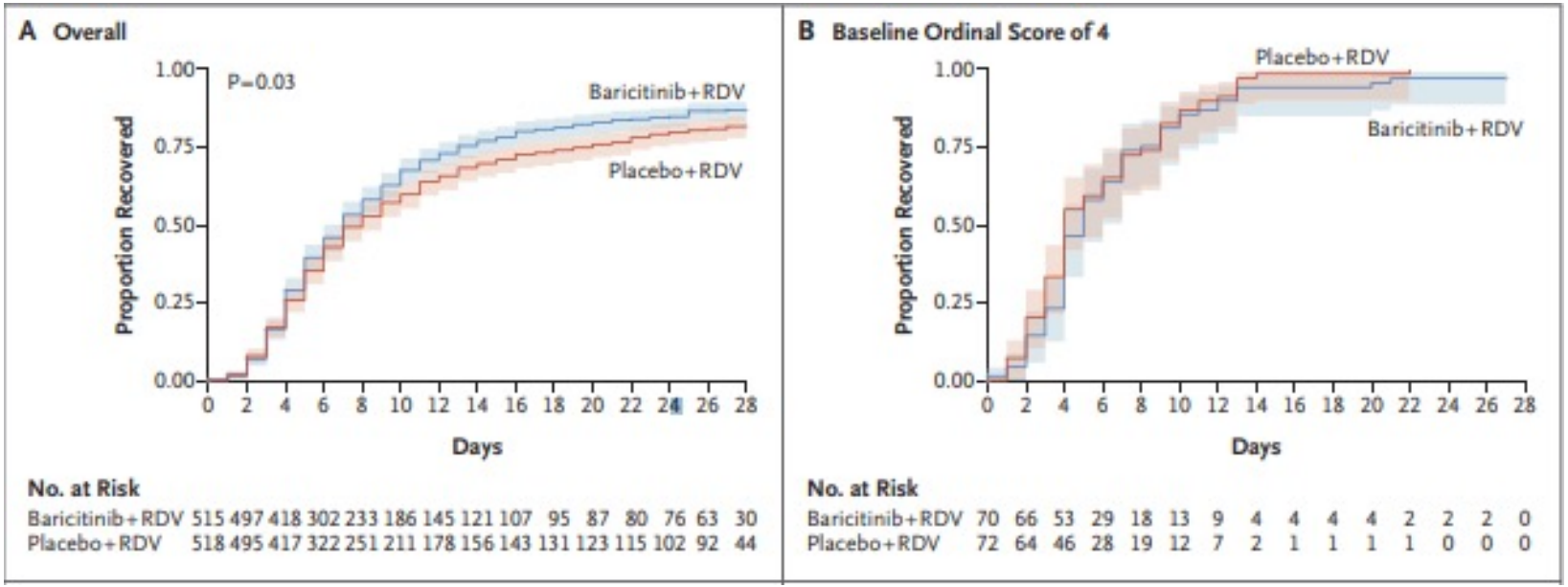
ACTT-1 Trial and Remdesivir

- Overall conclusions:
  - Shortened median recovery time by 5 days
  - Greatest benefit in patients receiving supplemental oxygen
  - Serious events more common in placebo
  - Less deaths in Remdesivir group

ACTT-2 Trial and Baricitinib

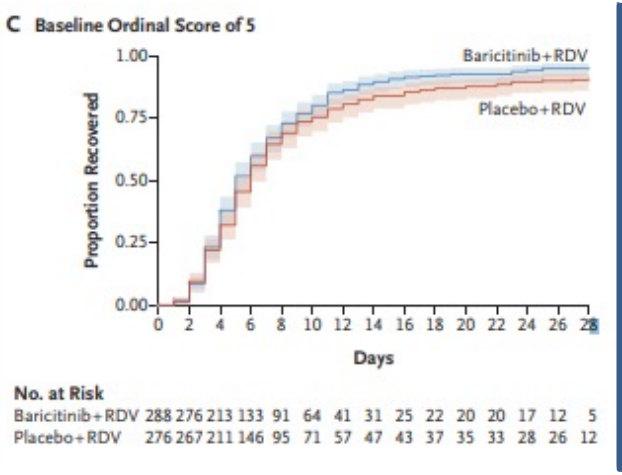
- Double-blind, randomized, placebo controlled trial, multi-site
- Remdesivir + baricitinib versus remedsivir + placebo
- Primary outcome = time to recovery
- 1033 patients

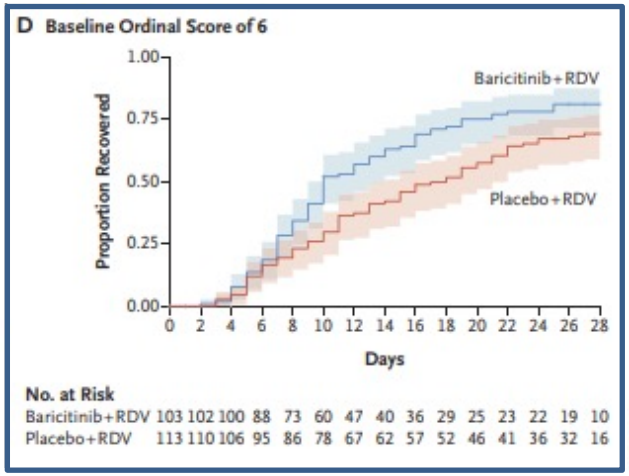
ACTT-2 Trial and Baricitinib

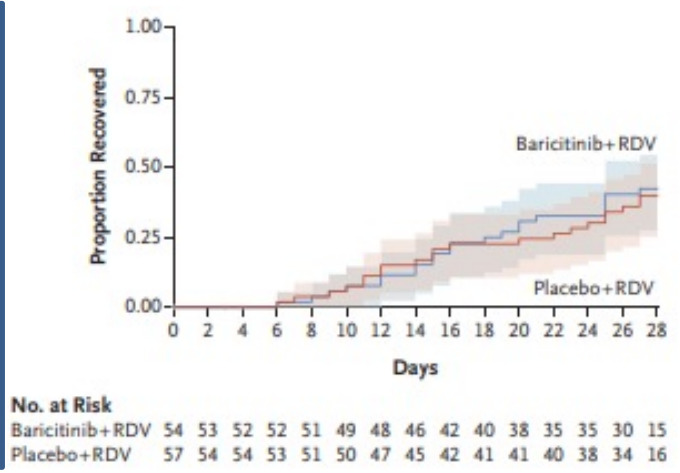


(Kalil et al, 2021)

ACTT-2 Trial and Baricitinib





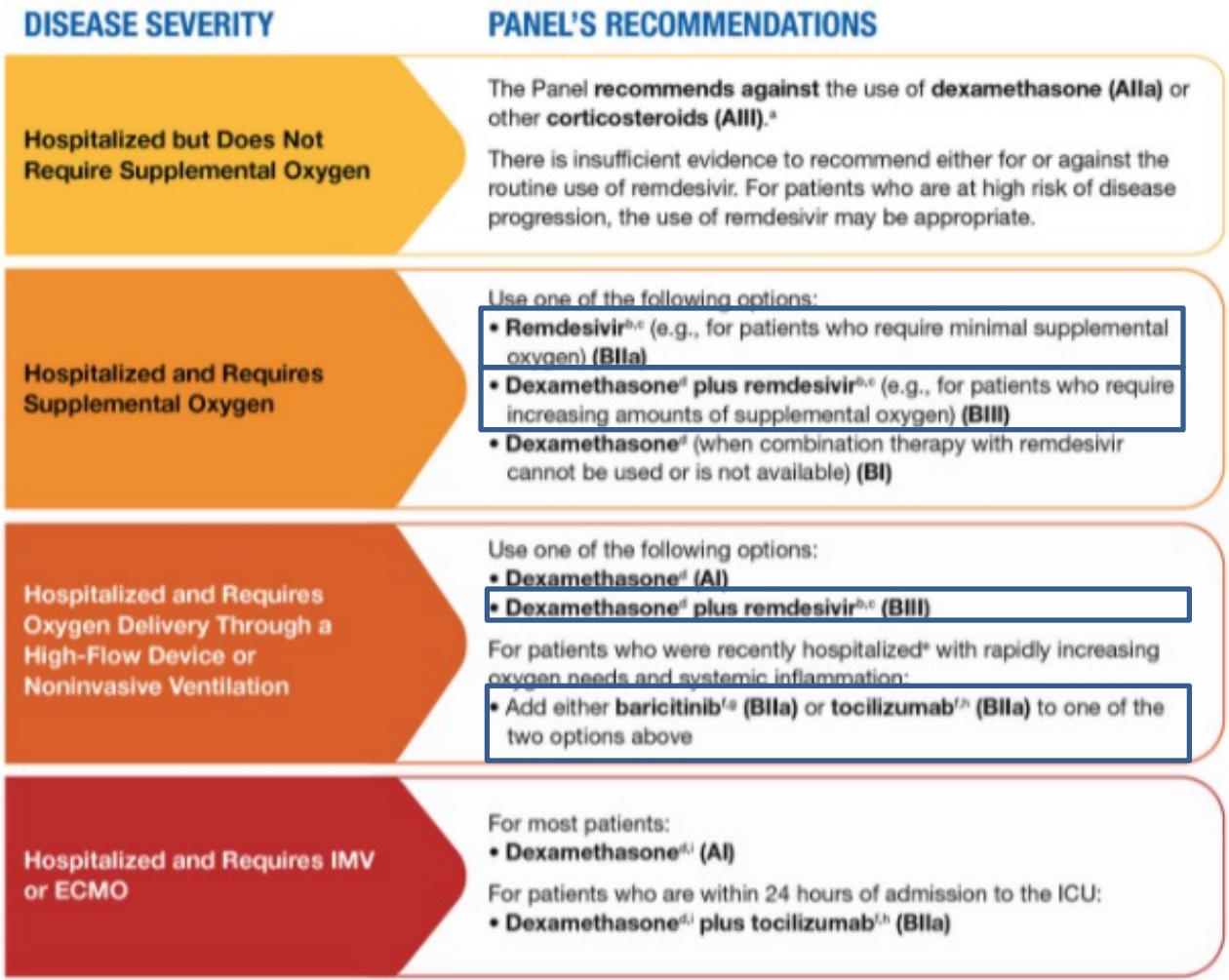


*6 = on high flow or Noninvasive positive-pressure ventilation (NIPPV)
Median time to recovery 10 v 18

(Kalil et al, 2021)

ACTT-2 Trial and Baricitinib

- Overall conclusions:
  - Shortened median recovery by 1 day
  - Highest benefit in those on brink of mechanical ventilation
  - Adverse events less common in Bari group
  - Less deaths in Bari group


DISEASE SEVERITY
PANEL'S RECOMMENDATIONS
Hospitalized but Does Not Require Supplemental Oxygen
The Panel recommends against the use of dexamethasone (AIIa) or other corticosteroids (AIII).[a]
There is insufficient evidence to recommend either for or against the routine use of remdesivir. For patients who are at high risk of disease progression, the use of remdesivir may be appropriate.
Hospitalized and Requires Supplemental Oxygen
Use one of the following options:
• Remdesivir[b,c] (e.g., for patients who require minimal supplemental oxygen) (BIIa)
• Dexamethasone[d] plus remdesivir[b,c] (e.g., for patients who require increasing amounts of supplemental oxygen) (BIII)
• Dexamethasone[d] (when combination therapy with remdesivir cannot be used or is not available) (BI)
Hospitalized and Requires Oxygen Delivery Through a High-Flow Device or Noninvasive Ventilation
Use one of the following options:
• Dexamethasone[d] (AI)
• Dexamethasone[d] plus remdesivir[b,c] (BIII)
For patients who were recently hospitalized[e] with rapidly increasing oxygen needs and systemic inflammation:
• Add either baricitinib[f,g] (BIIa) or tocilizumab[f,h] (BIIa) to one of the two options above
Hospitalized and Requires IMV or ECMO
For most patients:
• Dexamethasone[d,i] (AI)
For patients who are within 24 hours of admission to the ICU:
• Dexamethasone[d,i] plus tocilizumab[f,h] (BIIa)

Select Other Military Projects

- Monoclonal antibodies
- Convalescent plasma
- Prospective COVID-19 cohorts
- Telecritical care
- DoD and local infection control studies and protocols

Acknowledgements

- Chris Myers, Ph.D.
- Ryan Maves, M.D.
- Jason Opdyke, Ph.D.
- George Haltski, baby

Key Takeaways

- It is important to know the history and basic biology of Coronaviruses as it pertains to past pandemics to better prepare for the current and future pandemics.

- There are Military-specific challenges and successes during the COVID-19 pandemic that should be recognized

- Infectious disease surveillance plays a vital role in pandemic preparedness.

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Questions

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1. Go to URL: https://www.dhaj7-cepo.com/content/aug-2021-ccss-exploration-innovations-health-care
2. Search for your course using the **Catalog**, **Calendar**, or **Find a course** search tool.
3. Click on the REGISTER/TAKE COURSE tab.
   a. If you have previously used the CEPO CMS, click login.
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4. Follow the onscreen prompts to complete the post-activity assessments:
   a. Read the Accreditation Statement
   b. Complete the Evaluation
   c. Take the Posttest
5. After completing the posttest at 80% or above, your certificate will be available for print or download.
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