

COVID-19 AND THE FUTURE OF INFECTION PREVENTION

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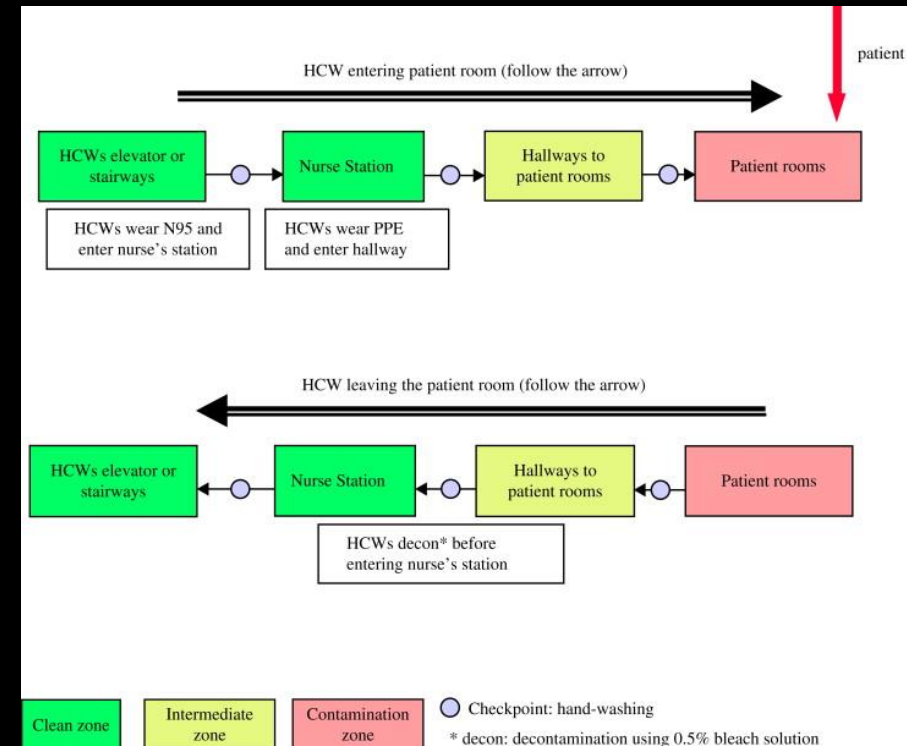
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Pathogens with Pandemic Potential 2002-2016

SARS-CoV, 2002-2003 (SARS Classic)

- Zoonotic coronavirus spreading from China throughout Asia and into Canada
- **Severe Acute Respiratory Syndrome**
- Spread largely identified from individuals who were showing symptoms at the time
- Significant spread to health care personnel / within hospitals
- Quarantine and isolation proved effective in containing the epidemic
- Development of “Traffic Control Bundle” and threat phase system



Avian Influenza (H5N1, H7N9, ...)

- Multiple crossover events from wild birds via poultry to humans in Asia
 - Large scale poultry kill-offs adopted to control transmission
 - Short-chain human-to-human transmission identified but no sustained transmission
 - Served to focus world attention on “bird flu”
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Pandemic H1N1 Influenza, 2009

- Triple reassortant influenza virus involving mixture of human, swine, and avian genes
- Sufficiently different from post-1960 circulating influenza strains that younger patients were essentially immune-naïve
- Critical care resources stressed but ultimately not overwhelmed
- Challenges managing communication and public sentiment/anxiety
- Weaknesses in diagnostics (confirmation chokepoint), rapidly changing guidance
- Need to distinguish pandemics by disease *severity*, not just spread

MERS-CoV (2012 and onward)

- Spillover from camels – detected Sep-2012 at sentinel hospital in traveler
- Retrospective identification of an outbreak in spring 2012
- CDC tracked epidemic through first US case in 2014 and onward
- Characterized as low pandemic potential
- Spread to health care workers identified
- Seen as a successful implementation of lessons learned from SARS

Ebola, 2014-2015, 2019, 2021

- Widespread outbreaks in West Africa and in Congo (complicated by political unrest)
- Multiple importations to USA (2014-2015) with limited onward spread (Texas)
- Worst-case scenario (infected traveler in Karachi/Mumbai) did not occur
- Challenges in diagnostics development and research in complex environment
- Aspects of the biology that may have inhibited explosive growth after importation

<https://academic.oup.com/milmed/article-pdf/182/1-2/e1507/21740501/milmed-d-16-00074.pdf>

[https://journals.asm.org/doi/pdf/10.1128/JCM.00053-](https://journals.asm.org/doi/pdf/10.1128/JCM.00053-17)

Zika, 2015-2016

- Mosquito-borne virus originally identified in Africa in 1970's
- Mild illness to asymptomatic in adults, but affects fetus if acquired in pregnancy
- Outbreaks well-studied in island settings
- Importation to South America and thence to southern USA
- Slow process for diagnosis (short PCR window, acute/convalescent serology)
- Ultimately, a combination of vector control and community immunity

Systemic Weaknesses Driven by Lack of Evidence about a Novel Pathogen

Contact vs. Respiratory Transmission

- Initial belief that transmission “must” be via fomites and contaminated surfaces
- Emphasis on avoiding face touching and on cleaning surfaces
- Persists as “hygiene theater”



Droplet vs. Airborne Transmission

ORIGINAL PARADIGM

- Driven by the idea that, for most respiratory viruses, only “large droplets” are significantly infectious
- Conflation of two characteristics of tuberculosis infectivity
 - Very small particles required to penetrate into small airways*
 - Particles of varying sizes can remain airborne and travel significant distances*
- Implication: 6-foot distance or surgical masks should be absolutely protective

REVISED PARADIGM

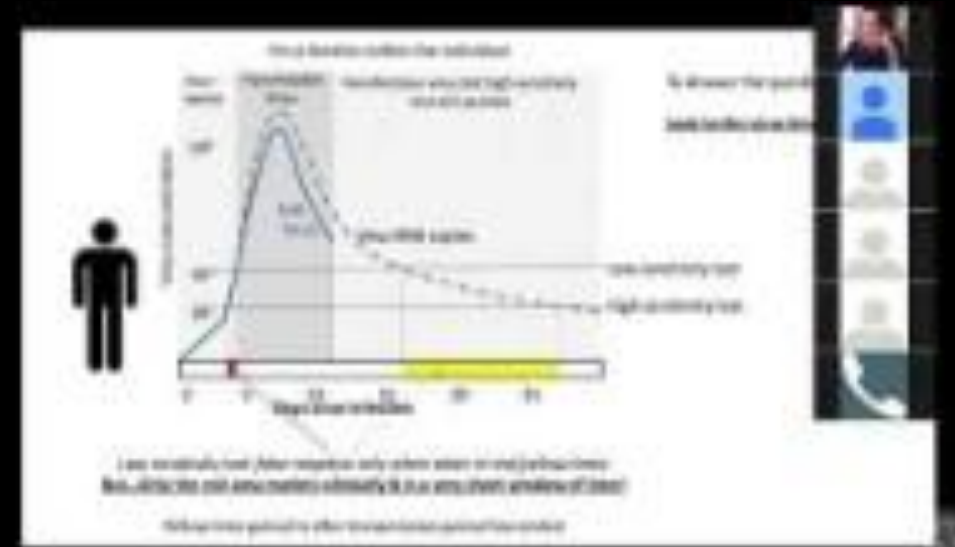
- Highly infectious pathogens (measles, chickenpox) show airborne transmission and are able to infect upper respiratory epithelium
- Studies demonstrate patterns of spread that are explainable only by long-lived, longer-distance infectious aerosols
- Distance is *still* important, just not absolute
- Implication 1: Better masks are, well, better
- Implication 2: Air exchange is also important

Transmission Without Symptoms

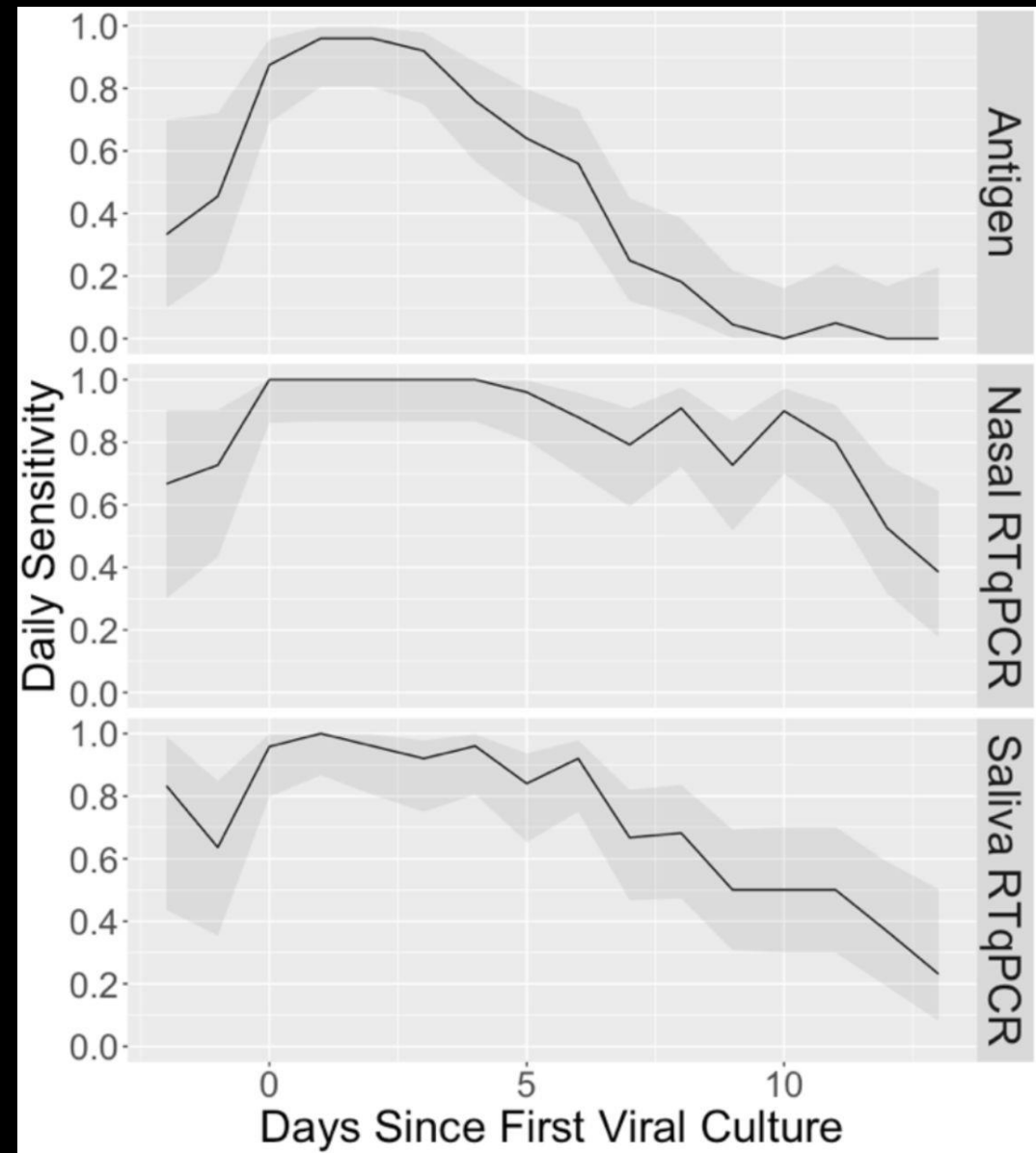
- Initial data from large Chinese case series: only 1% asymptomatic
- May have resulted from inadequate testing of asymptomatic (SARS Classic example)
- German case: debate about presymptomatic vs. asymptomatic transmission led to entrenchment of opinion among health organizations
- **Implication:** isolation at start of symptoms should be sufficient to control spread
- **Emerging paradigm:** 30-40% completely asymptomatic; >50% of transmission from PAMS (**P**resymptomatic, **A**symptomatic, or **M**ildly **S**ymptomatic)
- **Implication:** contact tracing & quarantine of the exposed are critical to control spread

Utility of Diagnostics

- PCR seen as “gold standard” for diagnosis of COVID-19 in individuals – and for clearance to discontinue isolation precautions
- PCR can persist positive for weeks, often months, and can be intermittently positive late after resolution; however, the infectious period is much shorter
- Antigen testing sacrifices “lead time” before the infectious period, but eliminates “lag time” after
- PCR as a “**golden calf**” standard



Timing Matters

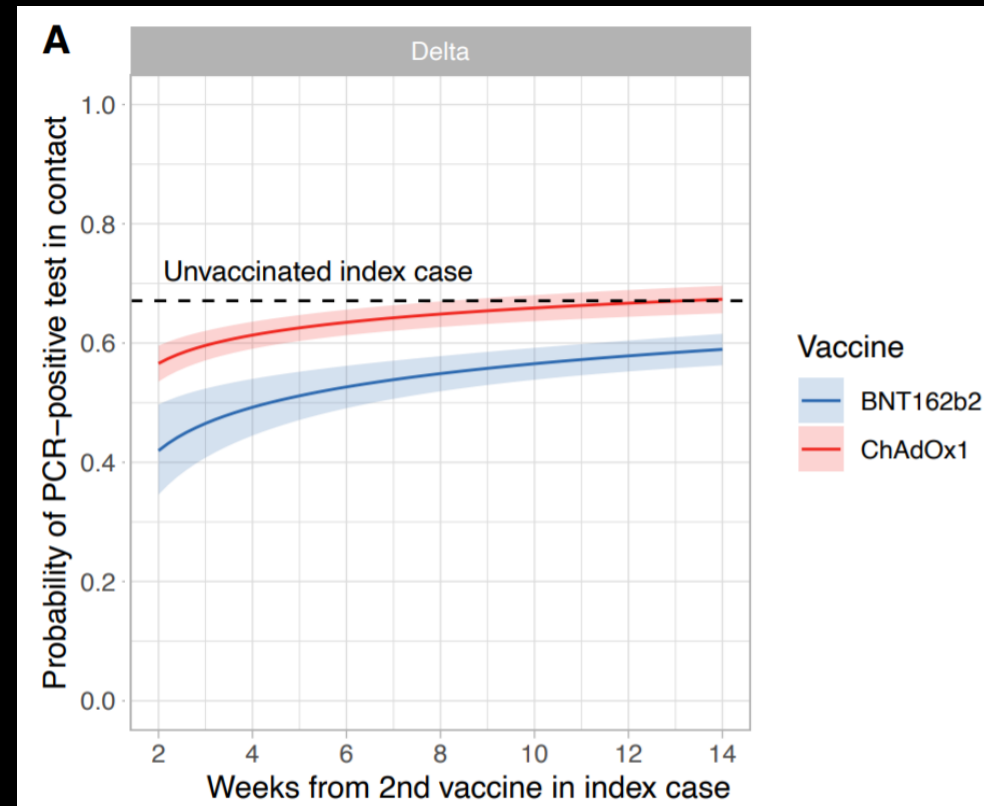


Treatment Options

- **Hydroxychloroquine +/- azithromycin** widely adopted based on a small, uncontrolled open-label case series
- **Remdesivir** adopted based on data showing earlier hospital discharge without mortality benefit – later associated with longer hospitalization
- **Convalescent plasma** adopted based on an observational trial comparing high-titer to low-titer plasma
- **Ivermectin** adopted based on *in vitro* data at nonphysiologic doses and fabricated clinical trial results
- Large-scale adaptive clinical trials demonstrate benefit of **steroids** or **monoclonals**

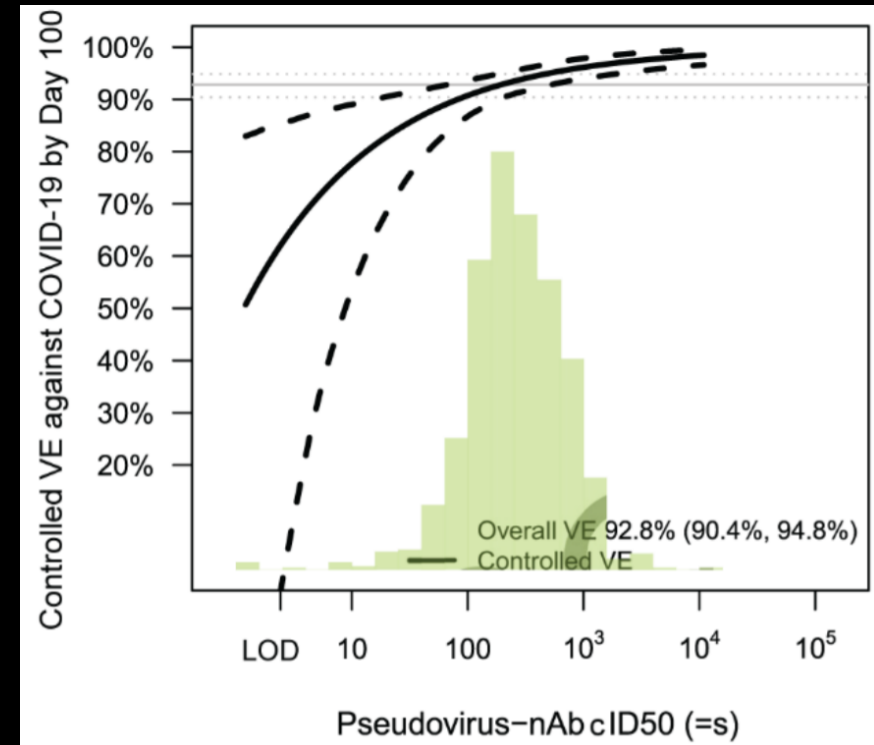
Understanding the Effect(s) of Vaccines

- Registrational trials had an endpoint of **symptomatic disease**
- Vaccines were then widely deployed as a public health tool for **effect on transmission**
- Guidance re unmasking for vaccinated
- Reversed in light of growing evidence of transmission from breakthroughs (particularly Delta variant)



Intersection of Vaccines and Diagnostics

- Registrational trials of vaccines were powered to show efficacy against symptomatic, PCR-positive disease
- Measures of infectiousness were not collected
- Underpowered to evaluate correlates of immunity, postmarketing not done
- Arguments for additional/booster doses rely on unproven correlates
- FDA still discourages use of serology



Questions to Inform Preparedness for the Next Pandemic

What do we now wish we had done differently?

What do we wish we had been ready for?

Would we be ready today for another pandemic?

The Future of COVID-19 in Acute Care Settings

Another Seasonal Cold Virus?

- Coronavirus OC43 may have started as a pandemic virus (spillover from cows) over 100 years ago
- Reinfections, and infections in the very young, seem to have a lower fatality ratio
- Likely scenario: everyone is infected early with mild disease
- Then reinfections (mild colds) occur periodically throughout the lifespan
- Protection against severe disease is maintained
- Requires waning of immunity to mild disease faster than severe disease

Vaccinated vs. Unvaccinated

- Vaccinated people can transmit
- Unvaccinated people remain at higher risk for severe disease
- Some element of waning protection
- For the vaccinated: boosting by reinfection or vaccination
- For the unvaccinated: “ricochet” phenomenon
- “Protective isolation?” Community risk?



Viral Variation and Evolution

- Increased spread

Alpha, Delta

Faster viral replication (“outrun” the immune response)

More frequent testing can help

- Immune escape

Beta, Gamma

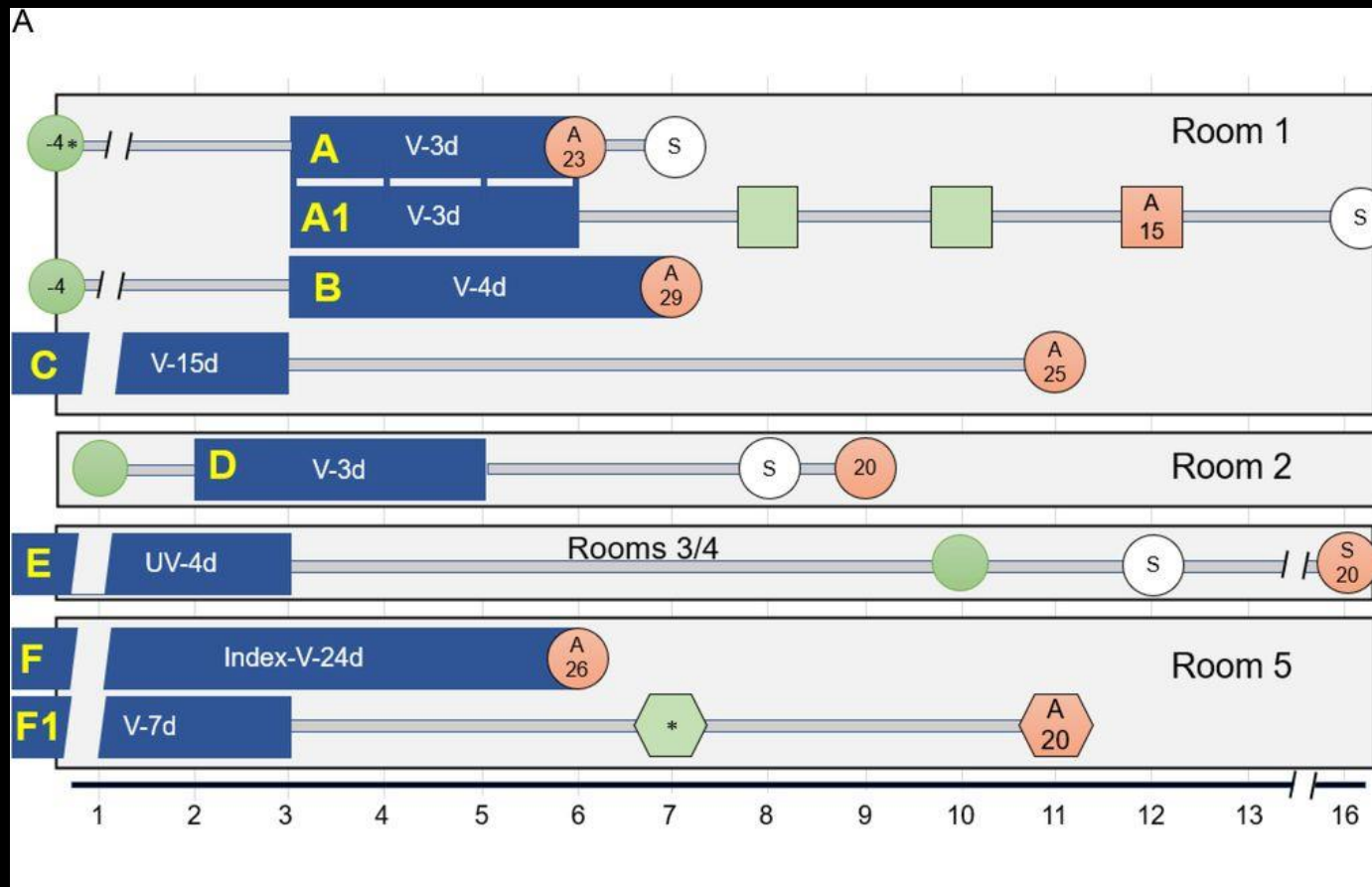
Spike epitope mutation (“evade” the immune response)

Vaccines against variant epitopes may help

Testing, Isolation, Quarantine in Acute Care

- Testing at time of admission: antigen tells you about the moment, PCR sees into the future
 - Retesting after a few days inpatient? If community rates are high enough
 - Vaccination for staff may damp the chance of importing but may not extinguish it
 - Testing the unvaccinated: Sutton's Law
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Putting It Together: Cluster Workup



Scenarios for the Next Pandemic

Respiratory

- Coronaviruses
 - Pandemic influenza
 - Measles
 - Other respiratory viruses
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Viral Hemorrhagic (Contact)

- Ebola
 - Lassa fever
 - Marburg fever
 - Others with less well established human-to-human spread
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Arthropod-Borne

- Dengue
 - Chikungunya + virulence
 - Malaria + virulence
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Other Possibilities

- Norovirus + virulence / neurotoxicity? (Fomites and food supply become important)
 - Poxvirus spillover?
 - *Cryptococcus gattii*?
 - *Candida auris*?
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Keeping Our Eye on the Ball of Antimicrobial Resistance

- Emergence of community-acquired USA300 MRSA
 - Emergence of KPC-producing *Enterobacteriaceae*
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Suggestions for Improving Preparedness for Next Time

Common Language: Threat Level Matrix

PROPOSAL

- Phase 0: baseline readiness
 - Phase 1: outbreak abroad with potential for importation (screening/surveillance)
 - Phase 2: limited local transmission
 - Phase 3: widespread local transmission
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SINGAPORE: DORSCON

- Green: little person-to-person spread
- Yellow: mild and contained *or* severe, spreading, but remote
- Orange: contained local spread
- Red: widespread local transmission

Toward a Pandemic Research Program

- Decrease lead time to developing evidence about a novel pathogen
 - Low-hanging fruit: clinical trials of therapies; trials of nonpharmaceutical strategies
 - Even before therapy: understanding natural history and how it relates to diagnostic performance; may require biorepository specimens and widespread “fishing”
 - Small corps of full-timers writing and maintaining protocols
 - Larger reserve corps – all research staff in a large network at 1% time for refresher trainings on the protocols, “call up” the reserves in an emergency
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A Chance for Questions
