The 2020 COVID-19 Pandemic: The “8-D’s” of Disaster

- Danger (ignored)
- Dispersal (global)
- Deficient (CDC)
- Disease (heterogeneity)
- Disruption (socioeconomic)
- Dissent (protests)
- Disinformation (distrust)
- Denial (disarray)
Two Missing Critical “D’s”

diagnostics

coherent, comprehensive national testing campaign

real-time situational awareness for coherent decision making and proficient control strategies

data

large scale capture and analysis
Two Missing Critical “D’s”

- fragmented patchwork of uncoordinated testing and control actions (federal, state, local)
- inadequate standardization (tests) and interoperability (data formats)
- Dx supply chain shortcomings
- independence of USG public health/regulatory agencies compromised by political interference
The US Diagnostic Testing Infrastructure for SARS-CoV-2: A ‘F’ Report Card?

- initial CDC RT-PCR test failure (Feb 2020) and six weeks lost for critical early control
- well documented capacity limitations of State public health laboratories to conduct large scale testing
- slow action by CDC (March 2020) to engage private sector testing capacity and scalability
- fragility of supply chains for testing reagents/supplies/PPE - states pitted against each other in bidding wars
SARS-CoV-2 Infections: Disease Spectrum, Prevalence and Extended Timelines

- **Acute infections of graded severity**
  - asymptomatic vs symptomatic
  - lack of biomarkers to predict disease severity
    - immunological
    - genetic
    - SDoH
- **Post-acute inflammatory illness**
  - MIS-C
  - MIS-A
- **Late chronic sequelae in survivors (long-COVID)**
  - prevalence?
  - pathophysiological mechanisms?
  - prognosis?
  - duration?
  - treatment?
The Diagnostic Landscape for SARS-CoV-2 Infections

- Viral detection (RNA, antigens), exposure (serology) and contact tracing
- Viral metagenomics (NGS of global viral clades and mutagenic drift)
- Multiplex diagnostics
  - RT pathogen panels (22 organisms)
  - Host immune and genetic factors affecting disease severity
- Digital platforms
  - Wearables and mobile apps for contact tracing and “immune passports”
The Diagnostic Landscape for SARS-CoV-2 Infections

- obligate foundation of real time epidemiology and effective control measures
- infection prevalence
  - geography, demographics, transmission dynamics
- validation of risk assessment models
  - guide intervention priorities and resource allocation
  - ML/AI algorithms for prognosis of disease severity in hospitalized individuals
- mapping ‘herd immunity’
  - longitudinal cumulative analysis of population exposure (natural infections and vaccination)
  - current uncertain correlates of protective immunity
Pandemic Diagnostics Suddenly Get Long Overdue Attention

- $1.5 billion investment
- test 2% US population/day
  - 6 million tests
- focus on underserved populations
- RADx-rad
  - new and repurposed HTP technologies
  - clinical prognosis makers
## Categories of SAR-CoV-2 Diagnostics*

<table>
<thead>
<tr>
<th>Test Type</th>
<th>High Vol. Reference Labs (CLIA)</th>
<th>Mol DX Labs (CLIA)</th>
<th>CLIA-waived POC</th>
<th>in-home</th>
<th>Global BSV</th>
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<tr>
<td>Viral nucleic acid (NAATs)</td>
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<td>Inflammatory syndromes/late chronic sequelae</td>
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<tr>
<td>Viral metagenomics and mutagenic drift</td>
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</table>

* waste water surveillance, wearables, mobile Apps and other biosensors not listed
The Covid-19 Diagnostic Landscape

2016 Tests (accessed 11/30/20)
Understanding the True Prevalence of SARS-CoV-2 Infections

- asymptomatic and symptomatic true positives
- percent positivity
  - # individuals tested vs # tests
- asymptomatic untested positives
- qualitative vs quantitative PCR and Ct cutpoints
- single time point false negative PCR tests
  - early or late in infection/virus shedding cycle
- test specificity/sensitivity
  - PCR vs antigen vs serology
  - impact of prevalence on false positives and negatives
Dynamics of SARS-CoV-2 Infections
M. Cevik et al. (2020) Lancet Microbe 30172-5

- meta-analysis of 98 studies
- no difference in peak load in asymptomatic vs mild symptomatic individuals but virus cleared faster in former
- significant individual variation in duration of shedding
  - URI and stool av. 17 days
  - LRI av. 14.6 days
  - serum av. 16.6 days
  - longest duration outliers: 83 days URI, 59 days LRI, 35 days in stool
Superspreading Events (SSE)

- outsized contribution to overall transmission
- analysis of 60 SSE SARS-CoV-2 episodes*
  - $R_0$ mean of 19.7 cases
  - extreme outlier of 187 cases in Hong Kong apartment
- logic for prevention of large gatherings of susceptible individuals and isolation/vaccination of select individuals for pandemic control

*F. Wong and J. Collins (2020) PNAS 117, 29416
The RT-PCR Bottleneck in Individual Testing and Infection Tracking

- predominant reliance on large CLIA-certified reference laboratories with high volume throughput
  - capacity outstripped by demand leading to slow TAT
- >48 hr. reporting erodes willingness of asymptomatic individuals to self-isolate
- higher cost versus other test modalities as handicap to sustained widespread use
- catalyst to develop alternative rapid CLIA-waived POC/in-home tests
Point-of-Care (POC) Antigen Testing for SARS-CoV-2

• speed: overcome TAT lag from PCR testing overloads
• comprehensive screening of large population
  - employers, schools and colleges, military
• contact tracing
Critical Dependence on Private Sector for Expanded Testing Using POC Viral Antigen Platforms

- up to 50 million BinaxNow tests/month
- USG contract to purchase/distribute 150 million tests
- 80 million tests/month by 12/20
- 12 million tests/month by 1Q/21
- additional state contracts with smaller companies/universities to expand antigen testing capacity
Pending Innovations in High Accuracy POC Tests With Rapid TAT

- CUE
- automated PCR cartridge
- 20-30 minute TAT readout
- mobile phone reporting
- $481 million HHS contract for 100,000 tests/day (3/21)
- value for POC confirmation to eliminate false positives from antigen tests
The Wild West of SARS-CoV-2 Diagnostics

- wide variation in performance, QC/QA of EUA tests
- sensitivity span of greater than 3 log 10
- Removal Lists of Tests that Should No Longer Be Used and/or Distributed for COVID-19 Testing
  - diagnostic tests
  - serological tests
- cease-and desist letters to 171 facilities testing without CLIA certification and/or compliance
Value of FDA Emergency Use Authorization (EUA) for SARS-CoV-2 LDTs

- Public Readiness and Emergency Preparedness (PREP) Act
  - immunity from liability claims
- Family First Coronavirus Act (FFCRA)
  - broad reimbursement including out-of-network labs
- FDA (8/15/20) action to no longer review LDTs for EUA
  - new tests blocked from these benefits
- HHS (11/17/20) directed FDA to reinstate EUA review and complete “in a timely manner”
uncontrolled access overloads testing capacity and slows TAT
meaningful negative status requires two negative tests 5-7 days apart
non-quantitative PCR testing
  - useful for isolation recommendations
  - no data on viral load and potential individual infectiousness and superspreader event risks
National Reporting of Aggregated SARS-Cov-2 Testing

- patchwork of different testing platforms, instruments and data formats
- requirements to report to county, state, CDC, CMS and HHS (FEMA sometimes)
- report both positive and negative assays
- HHS/CDC guidelines inconsistent for ‘required’ vs ‘requested’ data elements and CMS non-compliance penalties
- requirement to report to state public health lab of an individual’s residence
Contact Tracing

- estimated 14 million tests/day needed
- current capacity 4.5 million tests/day
- Biden proposal for 100,000 contact tracers current = 2000 people
- uncertain public acceptance and cooperation?
  - potential adverse effects of isolation/quarantine actions on income of many already economically compromised individuals
Mobile Phone Apps, Contact Tracing and “Immune Passports”
Immunity Passports:
A Scientifically and Ethically Questionable Concept?

- ill-defined determinants of true immune protection
  - antibodies (neutralizing (N) vs non-N; titers), T cell responses?
  - duration of immune protection (natural vs vaccine)?
- risk from tests with inadequate specificity (false positives) and low sensitivity tests (false negatives with low antibody titer)
- discrimination risks for employment and travel?
Individual Heterogeneity in Antibody Responses to SARS-CoV-2

Days since Onset of Symptoms vs. Ratio of Anti-SARS-CoV-2 IgG Antibody Titer

Host Inflammatory and Immune Biomarkers and Prediction of Clinical Deterioration in Hospitalized COVID-19 Patients

- multiparameter clinical risk algorithms
- cytokine storms
- autoantibodies to IFN-I
- decoupling of CD4/CD8 T-Cell responses
- genetics
  - hypo-and hyper-inflammatory response genes
  - ACE2 receptor polymorphism
  - HLA genotypes
  - chromosome 3 Vindija 3.3.19 Neanderthal alleles?
Correlograms of Adaptive Immunophenotypes in COVID-19 Patients

C. Rydyznski et al. (2020) Cell 183, 996
Comprehensive Biosurveillance of Potential New Zoonotic SARS-CoV-2 Reservoirs and Novel Mutational Drift

- cull of 17 million mink (Denmark) due to emergence of new SARS-CoV-2 variant (“cluster 5”) - suspected human to mink transmission (spill-back)
- six countries (5EU, USA) reported mink infections to WHO
Global SARS-CoV-2 Phylogenetic Trees and Rapid Evolution in an Immunocompromised Patient *

B. Choi et al (2020) NEJM 383, 2291
Global Biosurveillance of Protein Mutations in SARS-CoV-2 Clades: Implications for Vaccine Efficacy
Evolution or Deliberate Design of SARS-CoV-2 Variants: Challenges for Future Vaccine Design and an Expanded Bioterrorism Threat

SARS-CoV-2 Outbreak: USS Theodore Roosevelt April 2020

Increased Dual-use Risk from Open Literature Publications?

Rapid reconstruction of SARS-CoV-2 using a synthetic genomics platform

Pandemic Control:
The Need for a Systems-Based End-to-End Preparedness

- diagnostics: too long ignored and under-invested as a critical component of biosurveillance, bioincident management and national security
- pandemics are complex, multi-dimensional dynamic (adaptive) systems
- unidimensional control responses are futile
- robust preparedness requires integrated system-based adaptive strategies to match this multi-dimensionality complexity
  - public and private sector collaboration
  - domestic and international coordination
- proactive sustained investment to limit impact of future pandemics
Happy Holidays

Stay Safe and Hoping for a Less Challenging 2021

Slides available at: https://casi.asu.edu/presentations/