Welcome & Introductions

Dana Wollins, DrPH, MGC
Vice President
Clinical Affairs & Practice Guidelines
Infectious Diseases Society of America

- 95th in a series of calls, initiated in 2020 as a forum for information sharing among frontline clinicians caring for patients with COVID-19.

- The views and opinions expressed here are those of the presenters and do not necessarily reflect the official policy or position of the CDC or IDSA. Involvement of CDC and IDSA should not be viewed as endorsement of any entity or individual involved.

- This webinar is being recorded and can be found online at www.idsociety.org/cliniciancalls.
1. Update on Ebola

Mary Choi, MD, MPH  
Lieutenant Commander, U.S. Public Health Service  
U.S. Centers for Disease Control & Prevention

2. Influenza, RSV & COVID-19 — Current State of Play & Considerations for Treatment

Influenza Update
Tim Uyeki, MD, MPH, MPP  
Chief Medical Officer  
Influenza Division  
U.S. Centers for Disease Control and Prevention

Use of COVID-19 Convalescent Plasma
Carlos H. Villa, MD, PhD  
Associate Director for Special Programs  
Center for Biologics Evaluation and Research  
Office of Blood Research and Review  
U.S. Food and Drug Administration

RSV Update
Meredith McMorrow, MD  
Medical Officer  
U.S. Centers for Disease Control and Prevention
3. Masking to Prevent RTI Transmission in Health Care Settings

**Alex J. Kallen, MD, MPH**
Chief of the Prevention and Response Branch
Division of Healthcare Quality Promotion
U.S. Centers for Disease Control & Prevention

**Chanu Rhee, MD, MPH, FIDSA**
Associate Professor, Population Medicine
Harvard Medical School and Harvard Pilgrim Health Care Institute
Associate Hospital Epidemiologist
Brigham and Women's Hospital

**Meghan A. Baker, MD, ScD, FIDSA**
Assistant Professor, Population Medicine
Harvard Medical School and Harvard Pilgrim Health Care Institute
Associate Hospital Epidemiologist
Brigham and Women's Hospital
Question?
Use the “Q&A” Button

Comment?
Use the “Chat” Button
Update on Ebola

Mary Choi, MD, MPH
2022 Uganda Sudan Virus Disease Outbreak

- September 20, 2022 the Ministry of Health declared an outbreak of Sudan virus in Mubende District
- 5th outbreak of Sudan virus in Uganda
- Largest outbreak: Gulu, Uganda with 425 cases
Case Counts as of November 30, 2022

- 142 confirmed cases
- Cases reported in 9 districts:
  - Mubende
  - Bunyangabu
  - Kagadi
  - Masaka
  - Jinja
  - Kassanda
  - Kyegegwa
  - Waskiso
  - Kampala
- 56 deaths; CFR: 39%
Risk of Sudan Virus Disease Spread

- Risk of importation into the US is currently assessed as low
  - Low number of travelers and no direct flights to the United States
  - Exit screening of air passengers is being conducted in Uganda
  - Uganda has experience in responding to Ebola disease including outbreaks of Sudan virus
Ebola Disease

- Serious often fatal disease in humans caused by infection with one of four viruses with the genus *Ebolavirus*:
  - Ebola virus (species *Zaire ebolavirus*) – abbreviated EBOV
  - Sudan virus (species *Sudan ebolavirus*) – abbreviated SUDV
  - Taï forest virus (species *Taï forest ebolavirus*)
  - Bundibugyo virus (species *Bundibugyo ebolavirus*)
- Natural reservoir unknown; presumed to be fruit bats
Person-to-Person-Transmission

- In infected individuals, the virus can be found in all body fluids:
  - Blood
  - Feces/Vomit
  - Urine
  - Tears
  - Saliva
  - Breast milk
  - Amniotic fluid
  - Vaginal secretions
  - Sweat
  - Semen

- Contact (through broken skin or mucous membranes) with the body fluids of a person that is sick or has died of Ebola disease

- Not spread through airborne transmission
Signs and Symptoms

- Signs and symptoms of Ebola disease include:
  - Fever
  - Headache
  - Fatigue
  - Abdominal pain
  - Muscle pain/Joint pain
  - Rash
  - Headache
  - Fatigue
  - Anorexia
  - Diarrhea
  - Vomiting
  - Muscle pain/Joint pain
  - Vomiting
  - Sore throat
  - Conjunctivitis
  - Unexplained bleeding/bruising*

- Fever is not universally present
- Bleeding/bruising is not universally present

* Includes bleeding from the gums, mouth, nose, bloody vomit, bloody stools, bleeding from injection sites, vaginal bleeding outside of a menstrual cycle
Differences Between Ebola Virus and Sudan Virus
Ebola Virus vs. Sudan Virus — Epidemiology

▪ Ebola virus
  • 33 outbreaks from 1976 – November 30, 2022
  • >31,000 infected; >12,000 deaths
  • Affected countries*: Democratic Republic of Congo, Guinea, Republic of Congo, Gabon

▪ Sudan Virus
  • 8 outbreaks from 1976 – November 30, 2022
  • 942 cases, 490 deaths**
  • Affected countries*: South Sudan, Uganda

*excludes imported cases
** as of November 30, 2022
Ebola Virus vs. Sudan Virus — Animal Studies

- Animal studies demonstrated differences in the degree of virulence in animals experimentally infected with SUDV and EBOV
  - Less pathological lesions in rhesus monkey infected with SUDV compared to lesions in rhesus monkeys infected with EBOV*
  - Less viremia and immune disturbances in African green monkeys and cynomolgus macaques infected with SUDV compared to EBOV
  - Degree of viremia and liver enzymes in SUDV infected animals did not reach the levels seen in EBOV infected animals**

*Ellis. Ebola virus: a comparison at ultrastructural levels of the behavior of the sudan and zaire strains in monkeys
**Fisher-Hoch et al. Pathogenic potential of filoviruses rôle of geographic origin of primate host and virus strain
Ebola Virus vs. Sudan Virus — Clinical Course

- Limited clinical information available from prior Sudan virus outbreaks
- Review of available data suggests clinical course in SUDV-infected individuals is similar to EBOV-infected individuals
- Case fatality rate consistently lower in SUDV infection (40-50%) compared to EBOV infection (70-90%)

<table>
<thead>
<tr>
<th>Year</th>
<th>Country</th>
<th>Number of Cases</th>
<th>Case Fatality Rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>1976</td>
<td>South Sudan</td>
<td>284</td>
<td>53%</td>
</tr>
<tr>
<td>1979</td>
<td>South Sudan</td>
<td>34</td>
<td>65%</td>
</tr>
<tr>
<td>2000</td>
<td>Uganda</td>
<td>425</td>
<td>53%</td>
</tr>
<tr>
<td>2004</td>
<td>Uganda</td>
<td>17</td>
<td>41%</td>
</tr>
<tr>
<td>2011</td>
<td>Uganda</td>
<td>1</td>
<td>100%</td>
</tr>
<tr>
<td>2012</td>
<td>Uganda</td>
<td>11</td>
<td>35%</td>
</tr>
<tr>
<td>2012</td>
<td>Uganda</td>
<td>6</td>
<td>50%</td>
</tr>
<tr>
<td>2022*</td>
<td>Uganda</td>
<td>154</td>
<td>48%</td>
</tr>
</tbody>
</table>

* As of November 30, 2022
Ebola Virus vs. Sudan Virus — Virus Persistence

- No published data is available on viral persistence in survivors of SUDV infection
- EBOV persistence documented in immune privileged sites and in breast milk
  - EBOV RNA detected in semen 3.3 years after recovery
  - EBOV RNA detected in the aqueous humor 14 weeks after recovery
  - EBOV RNA detected in breast milk 16 months post-recovery

*excludes imported cases
** as of November 30, 2022
Ebola Virus vs. Sudan Virus — Viral Relapse

- No reports of viral relapse in survivors of SUDV infection
- Four confirmed cases of viral relapse in survivors of EBOV infection
  - U.K 2015: 39 y.o. female nurse; survived; no onward EVD transmission*
  - DRC 2019: 25 y.o. motorcycle taxi driver; died; generated 91 EVD cases**
  - 2 additional cases from the 2018 DRC outbreak***

*Received brincidofovir and convalescent plasma during initial EVD infection
**Received mAb114 during initial EVD infection
***Limited clinical information available
Ebola Virus vs. Sudan Virus — Treatment/Vaccine

- **Ebola virus**
  - Two FDA-licensed therapeutics: Inmazeb and Ebanga
  - One FDA-licensed vaccine: Ervebo

- **Sudan virus**
  - No FDA-licensed therapeutic or FDA-licensed vaccine
  - Experimental two antibody cocktail therapy available (MBP134) has demonstrated efficacy in preventing mortality due to infection with SUDV, EBOV, and Bundibugyo virus in non-human primates
  - Three candidate experimental vaccines will undergo evaluation
Recommendations for Clinicians
Recommendations for Clinicians: Infection Control

- If you are concerned your patient may have Ebola disease, isolate the patient in a private room at the healthcare facility
- Follow CDC guidance on PPE selection and wear, including donning/doffing
- Where possible, use dedicated (and disposable) medical equipment, limiting use of needles and other sharps
- Procedures that can increase environmental contamination with infectious material or create aerosols should be minimized
- If performing aerosol-generating procedures, follow guidance to reduce exposures (e.g., limit to essential personnel, utilize an airborne infection isolation room (AIIR) if available)
Recommendations for Clinicians: Notification

- Contact your state/local, tribal, or territorial health department and follow jurisdictional protocols for patient assessment

- As a resource for public health departments, CDC’s Viral Special Pathogens Branch is available 24/7 for consultations by calling CDC Emergency Operations Center (770-488-7100)
The findings and conclusions in this report are those of the authors and do not necessarily represent the official position of the Centers for Disease Control and Prevention.
Q&A
Influenza Update

Tim Uyeki, MD, MPH, MPP
2022-2023 U.S. Influenza Season

Influenza Positive Tests Reported to CDC by U.S. Clinical Laboratories, National Summary, October 2, 2022 – November 26, 2022

- 79% A(H3N2) viruses
- 21% A(H1N1)pdm09 viruses

New Influenza Hospital Admissions Reported to HHS Protect, National Summary, October 2, 2022 – November 26, 2022

Cumulative Rate of Laboratory-Confirmed Influenza Hospitalizations among cases of all ages, 2015-16 to 2022-23, MMWR Week 47

https://www.cdc.gov/flu/weekly/index.htm
**Preliminary In-Season Burden Estimates, 2022-2023**

CDC estimates* that, from October 1, 2022 through November 26, 2022, there have been:

- 8.7 – 19 million flu illnesses
- 4.2 – 9.5 million flu medical visits
- 78,000 – 170,000 flu hospitalizations
- 4,500 – 13,000 flu deaths

[https://www.cdc.gov/flu/about/burden/preliminary-in-season-estimates.htm](https://www.cdc.gov/flu/about/burden/preliminary-in-season-estimates.htm)
Groups at Increased Risk for Influenza Complications and Severe Illness

- Children under 2 years and adults aged 65 years and older
- **Persons with chronic medical conditions**, including pulmonary (including asthma) or cardiovascular (excluding isolated hypertension), renal, hepatic, neurologic (including persons who have had a stroke) and neurodevelopmental, hematologic, metabolic or endocrine disorders (including diabetes mellitus)
- **Persons who are immunocompromised**
- Persons with extreme obesity (BMI ≥40)
- Children and adolescents who are receiving aspirin-or salicylate-containing medications (who might be at risk for Reye syndrome after influenza virus infection)
- Residents of nursing homes and other long-term care facilities
- Pregnant persons and people up to 2 weeks postpartum
- People from certain racial and ethnic minority groups, including non-Hispanic Black, Hispanic or Latino, and American Indian or Alaska Native persons
Influenza Viral Shedding Typically Peaks Within 24 Hours of Illness Onset

- Virus can be detected in the upper respiratory tract one day before illness onset, virus levels peak within 24 hours after onset
  - Highest infectious period is within 3 days after symptom onset
- Young children can be infectious for longer periods
- Severely immunocompromised persons can be infectious for weeks or longer

Influenza viral RNA detection

Lau LL et al., J Infect Dis 2010
# Influenza Diagnostic Tests

<table>
<thead>
<tr>
<th>Test</th>
<th>Method</th>
<th>Time to Results</th>
<th>Performance</th>
<th>Notes†</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rapid diagnostic test</td>
<td>Antigen detection</td>
<td>10 min</td>
<td>Low to moderate sensitivity; high specificity</td>
<td>Negative results may not rule out influenza; most assays are approved for point-of-care use; multiplex assays can identify and distinguish among influenza A, influenza B, and SARS-CoV-2</td>
</tr>
<tr>
<td>Rapid molecular assay</td>
<td>Viral RNA detection</td>
<td>15-30 min</td>
<td>Moderately high to high sensitivity; high specificity</td>
<td>Negative results may not rule out influenza; some assays are approved for point-of-care use; multiplex assays can identify and distinguish among influenza A, influenza B, and SARS-CoV-2</td>
</tr>
<tr>
<td>Immunofluorescence assay</td>
<td>Antigen detection</td>
<td>2-4 h</td>
<td>Moderate sensitivity; high specificity</td>
<td>Negative results may not rule out influenza; requires trained laboratory personnel with fluorescent microscope in a clinical laboratory</td>
</tr>
<tr>
<td>Molecular assay</td>
<td>Viral RNA detection</td>
<td>60-80 min for some assays; up to 4-6 h for others</td>
<td>High sensitivity; high specificity</td>
<td>Negative results may not rule out influenza; multiplex assays can identify and distinguish among influenza A, influenza B, and SARS-CoV-2</td>
</tr>
<tr>
<td>Tissue cell virus culture</td>
<td>Virus isolation</td>
<td>3-10 d</td>
<td>Generally high sensitivity (can vary by virus); high specificity</td>
<td>Negative results may not rule out influenza</td>
</tr>
</tbody>
</table>

* Respiratory tract specimens should be collected as close to illness onset as possible for testing. Serologic testing requires paired acute and convalescent sera and is not recommended except for public health investigations and research. Updated information and guidance on the use of influenza diagnostic tests and interpretation of results are available at www.cdc.gov/flu/professionals/diagnosis/index.htm.

† These tests are FDA-cleared or are available through FDA EUAs for high- or moderate-complexity clinical laboratories or point-of-care use, including by Clinical Laboratory Improvement Amendments waiver.
Influenza Testing and Specimen Source

- Upper respiratory tract
  - Influenza viruses are generally detectable for 3-4 days by antigen tests, and 5-6 days by nucleic acid assays in uncomplicated disease
    - **Influenza viral replication and viral RNA detection may be prolonged with corticosteroids, immunosuppression**
    - **Highest yield: Nasopharyngeal (NP) swabs (ideally collected within 3-4 days of illness onset)**
      - Other acceptable specimens: nasal swabs, NP aspirates, nasal aspirates, combined nasal and throat swabs
  
- Lower respiratory tract
  - Prolonged influenza viral replication in severe lower respiratory tract disease
    - **Influenza viruses may be detectable in LRT specimens when cleared from the upper respiratory tract**
      - RT-PCR was negative in 10-19% of patients in upper respiratory tract specimens versus lower respiratory tract (BAL specimens) for influenza A(H1N1)pdm09 viral RNA
What Influenza Tests Are Recommended?

- **Outpatients:**
  - Rapid influenza molecular assays are recommended over rapid influenza antigen detection tests.

- **Hospitalized patients:**
  - RT-PCR or other molecular assays are recommended.
    - Antigen detection tests (rapid antigen detection tests and immunofluorescence) are not recommended should not be used unless molecular assays are not available.
  - Immunocompromised patients: Multiplex RT-PCR assays targeting a panel of respiratory pathogens, including influenza viruses are recommended.

- Do not order viral culture for initial or primary diagnosis of influenza.
- Do not order serology for influenza.
  - Results from a single serum specimen cannot be reliably interpreted, and collection of paired acute and convalescent sera 2-3 weeks apart are needed.
Co-circulation of Influenza Viruses and SARS-CoV-2

- **Co-infection with influenza A or B viruses and SARS-CoV-2**
  - Frequency appears to be uncommon (but may result in more severe disease)

- **Overlapping signs, symptoms, some differences**
  - Influenza vs. COVID-19
    - Earlier onset of complications/severe disease with influenza
    - Shorter viral shedding, period of viral RNA detection with influenza
    - Ageusia/dysgeusia, anosmia are more common with COVID-19
    - Diarrhea can occur in young children with influenza; at any age with COVID-19

- Testing for influenza A/B and SARS-CoV-2 can help guide specific antiviral treatment in persons at high risk for complications and identify co-infections

Beltran-Corellini Eur J Neurology 2020; Zayet Microbes and Infect 2020; Stowe Int J Epidemiology 2021; Pawlowski PNAS Nexus 2022
SARS-CoV-2 and Influenza Virus Co-infection Can Cause Severe Disease

- U.K. study from January 20-April 25, 2020 (N = 19,256)
  - SARS-CoV-2 and influenza virus co-infection (n = 58) was associated with 2 times higher odds of ICU admission (adjusted OR, 2.08; 95% CI, 1.17-3.70) or death (adjusted OR, 2.27; 95% CI, 1.23-4.19) compared with SARS-CoV-2 infection alone

  - N=212,446 adults; n=6,965 had other respiratory virus testing results
    - 8.4% had respiratory viral co-infections; Influenza virus: 227; RSV: 220; Adenoviruses: 136
  - SARS-CoV-2 and influenza virus co-infection was associated with 4 times higher odds of invasive mechanical ventilation (weighted OR: 4.14, 2.00-8.49; p<0.0001) versus SARS-CoV-2 infection alone (RSV, Adenoviruses: not significant)
  - SARS-CoV-2 and influenza virus co-infection was significantly associated with 2.35 times the odds of in-hospital mortality (weighted OR: 2.35, 1.07-5.12; p<0.031) versus SARS-CoV-2 infection alone
Multiplex Assays for Influenza Viruses and SARS-CoV-2

- **Multiplex Antigen Detection Assays**
  - Assays that can detect Influenza A and B and SARS-CoV-2 antigens simultaneously in respiratory specimens have received FDA Emergency Use Authorization (EUA)
    - Results in 15 minutes
    - High complexity, moderate complexity, CLIA-waived

- **Multiplex Nucleic Acid Detection Assays**
  - Assays that can detect Influenza A and B and SARS-CoV-2 nucleic acids simultaneously in respiratory specimens have received FDA EUA or De Novo 510(k) clearance or premarket approval (PMA)
    - Variable turnaround time to results (20 minutes to 8 hours)
    - High complexity, moderate complexity, CLIA-waived

Four FDA-approved antivirals are recommended:

- All have demonstrated efficacy and are FDA-approved for early treatment (<2 days of illness onset) in outpatients with uncomplicated influenza
- Neuraminidase inhibitors (NAIs):
  - **Oseltamivir** (oral, twice daily x 5 days)
  - **Zanamivir** (inhaled, twice daily x 5 days) [investigational IV zanamivir is not available in the U.S.]
  - **Peramivir** (intravenous: single dose)
- **Cap-dependent endonuclease inhibitor**: **Baloxavir marboxil** (oral: single dose)

<table>
<thead>
<tr>
<th>Antiviral Drug</th>
<th>Route of Administration</th>
<th>Recommended Ages for Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Oseltamivir</strong></td>
<td>Oral (twice daily x 5d)</td>
<td>All ages</td>
</tr>
<tr>
<td>Zanamivir</td>
<td>Inhaled (twice daily x 5d)</td>
<td>≥7 years</td>
</tr>
<tr>
<td>Peramivir</td>
<td>Intravenous (single infusion)</td>
<td>≥6 months</td>
</tr>
<tr>
<td><strong>Baloxavir</strong></td>
<td>Oral (single dose)</td>
<td>≥5 years (otherwise healthy) ≥12 years (high-risk)</td>
</tr>
</tbody>
</table>

https://www.cdc.gov/flu/professionals/antivirals/summary-clinicians.htm
CDC Antiviral Treatment Recommendations

- Focused on prompt treatment of persons with severe disease and those at increased risk of influenza complications

  Antiviral treatment is **recommended as soon as possible** for any patient with confirmed or suspected influenza who is:
  - Hospitalized (without waiting for testing results) (**oseltamivir**)
  - Outpatients with complicated or progressive illness of any duration (**oseltamivir**)
  - Outpatients at high risk for influenza complications (**oseltamivir, baloxavir**)

  Antiviral treatment can be considered for any previously healthy, non-high-risk outpatient with confirmed or suspected influenza (e.g. with influenza-like illness) on the basis of clinical judgment, if treatment can be initiated within 48 hours of illness onset; including empiric treatment (e.g. in-person visit or via telemedicine) (**any NAI or baloxavir**)

[https://www.cdc.gov/flu/professionals/antivirals/summary-clinicians.htm](https://www.cdc.gov/flu/professionals/antivirals/summary-clinicians.htm)
Oseltamivir Efficacy in Uncomplicated Influenza

RCTs have shown that oseltamivir treatment has significant clinical benefit when started within 36-48 hours after illness onset versus placebo

- Pooled meta-analysis of 5 RCTs in children (oseltamivir n=770 vs. placebo n=838)
  - Treatment started within 48 hours of onset:
    - Reduced illness duration by 18 hours overall and by 30 hours in children without asthma (-29.9 hours; 95% CI: -53.9 to -5.8 hours)
    - Reduced risk of otitis media by 34% (RR 0.66; 95% CI: 0.47-0.95)

- Pooled meta-analysis of 9 RCTs in adults (oseltamivir n=1565 vs. placebo n=1295)
  - Treatment started within 36 hours of onset:
    - Reduced illness duration by 25.2 hours (-25.2 hours; 95% CI: -36.2 to -16.0 hours)
    - 44% Reduced risk of lower respiratory tract complications occurring >48 hours after treatment requiring antibiotics (RR: 0.56; 95% CI: 0.42 to 0.75; p=0.0001)
Baloxavir Efficacy in Uncomplicated Influenza

RCTs have shown that baloxavir treatment has similar clinical benefit to oseltamivir and significant clinical benefit versus placebo when started within 48 hours after illness onset

- RCTs in adolescents and adults (aged ≥12 yrs)
  - Treatment started ≤48 hours of onset (baloxavir vs. placebo vs. oseltamivir):
    - Single-dose baloxavir (n=456) significantly reduced illness duration by a median of 26.5 hours vs. placebo (n=231) in non-high-risk persons (95% CI, 72.6 to 87.1 hours; p<0.001)
    - Median time to alleviation of symptoms was similar for baloxavir and oseltamivir (n=377)
    - Single-dose baloxavir (n=388) significantly reduced illness duration by a median of 29 hours vs. placebo (n=386) in persons with ≥1 high-risk condition (95% CI 14·6 to 42·8; p<0.0001)
    - Median time to improvement of symptoms was similar for baloxavir and oseltamivir
      - Baloxavir significantly reduced median time to improvement of influenza B symptoms by 27 hours versus oseltamivir (95% CI: 6.9 to 42.3 hours; p=0.025)

Hayden NEJM 2018; Ison Lancet Infect Dis 2020
Special Populations

CDC Recommendations

• Pregnant People
  ➢ For treatment of pregnant people and up to 2 weeks postpartum, oral oseltamivir is preferred
    • Baloxavir is not recommended for treatment of pregnant people or breastfeeding mothers
      ▪ No efficacy or safety data for baloxavir in pregnant or lactating people
      ▪ Substantial evidence of oseltamivir safety for pregnancy and birth outcomes

• Immunocompromised persons
  ▪ Prolonged influenza viral replication is a possibility, with emergence of antiviral resistant viruses during/after treatment
    • Monitoring for antiviral resistance is advised
    • Infection prevention and control precautions are recommended to reduce nosocomial transmission risk
  ➢ Neuraminidase inhibitor treatment is recommended
  ➢ Baloxavir is not recommended (risk of resistance emergence)

https://www.cdc.gov/flu/professionals/antivirals/summary-clinicians.htm
Oseltamivir Recommended for Hospitalized Patients

- Oseltamivir treatment (oral or enterically-administered) is recommended as soon as possible for hospitalized patients with confirmed or suspected influenza (without waiting for testing results)
  - Based on observational studies
    - No completed fully-enrolled placebo-controlled RCTs of oseltamivir treatment
    - Starting oseltamivir at admission is associated with:
      - Reduced hospital length of stay in adults and children, and may reduce mortality risk in adults
- Inhaled zanamivir and oral baloxavir are **not recommended** because of limited data
- Insufficient data for peramivir treatment of hospitalized influenza patients
  - For patients who cannot tolerate or absorb oral or enterically-administered oseltamivir (e.g. gastric stasis, malabsorption, or gastrointestinal bleeding), intravenous peramivir is an option
Oseltamivir treatment and duration of hospitalization

- (N=18,309; hospitalized adults, 36 countries; 2009-2011)
  - NAI treatment (mostly oseltamivir) started on the day of admission was associated with a 19% overall reduction in duration of hospitalization compared with no or later initiation of NAI treatment (aIRR, 0.81 [95% CI, 0.78-0.85]; median decrease, 1.19 days [IQR, 0.85–1.55 days]) (N=18,309)

- (N = 699; hospitalized adults, U.S.; 2009-2014)
  - Starting NAI (mostly oseltamivir) treatment within 6 hours after hospital admission was associated with shorter duration of hospitalization versus starting antiviral treatment later (p<0.001). Median LOS = 2.8 days (IQR 1.8-4.1) versus 3.9 days (IQR 2.1-6.6) for treatment started 6-24 hours after admission (p=0.0002)

- (N=55,799 hospitalized children, U.S.; 2007-2020); median age 3.6 years; 59.5% were treated with oseltamivir within one day of admission.
  - Children treated with oseltamivir <2 days after admission was associated with shorter length of stay (median 3 vs. 4 days), lower odds of 7-day hospital readmission (3.5%vs 4.8%; adjusted odds ratio [aOR], 0.72; 95%CI, 0.66-0.77), fewer late ICU transfers (2.4%vs 5.5%; aOR, 0.41; 95%CI, 0.37-0.46), and lower odds of the composite outcome of death or ECMO use (0.9%vs 1.4%; aOR, 0.63; 95%CI, 0.54-0.73).

Venkatesan J Infect Dis 2019; Katzen Clinical Infect Dis 2018; Walsh JAMA Pediatrics 2022
Conclusions

• **Molecular assays are recommended for influenza testing**
  - Rapid molecular assays for outpatients; rapid molecular and other molecular assays for hospitalized patients (including multiplex assays)
  - Multiplex assays (influenza A/B, SARS-CoV-2, RSV) can help guide clinical management when the community prevalence of co-circulating respiratory viruses is high

• **Antiviral treatment is recommended as soon as possible for persons at high-risk for complications and for those with severe disease**
  - Outpatients: high-risk persons (ideally <2 days of illness onset), progressive or severe disease (regardless of time since onset)
  - Inpatients: Oseltamivir treatment is recommended as soon as possible

- Please promote influenza vaccination!
  - For persons ≥65 years: high-dose, recombinant, or adjuvanted influenza vaccine
RSV Update

Meredith McMorrow, MD
Update on the 2022-23 RSV Season and Overview of Pediatric Respiratory Disease Surveillance & Healthcare Utilization

Infectious Diseases Society of America
December 3, 2022

Meredith McMorrow, MD, MPH, FAAP
Team Lead, Enhanced Surveillance Platforms
Coronavirus and Other Respiratory Viruses Division (proposed)
RSV is the leading cause of hospitalization in U.S. infants

- Most (68%) infants are infected in the first year of life and nearly all (97%) by age 2\(^1\)
- Premature infants born at <30 weeks gestation had hospitalization rates ~3x higher than term infants\(^2\)
  - Preterm infants have higher rates of ICU admission, mechanical ventilation\(^3\)
  - Average cost of hospitalization in infant <29 weeks ~4x higher than for term infant\(^3\)
- 79% of children hospitalized with RSV aged <2 years had no underlying medical conditions\(^2\)
- 2-3% of all infants will be hospitalized for RSV\(^2,4\)

\(^1\)Glezen et al, Arch Dis Child, 1986; \(^2\)Hall et al, Pediatrics, 2013; \(^3\)McLaurin et al, J Perinatol, 2016; \(^4\)Langley & Anderson, PIDJ, 2011
RSV is frequently diagnosed by rRT-PCR using commercially available assays.

There are rapid antigen detection kits available for use in POC settings:
- Variable sensitivity and specificity
- CLIA waiver may be limited to certain age groups

For high-risk infants and young children, palivizumab may be administered monthly during the RSV season per AAP guidance.

Treatment of RSV is with supportive care.
Weekly percent positive for viruses detected in the National Respiratory and Enteric Virus Surveillance System (NREVSS), March 2020 to November 18, 2022

Report was last updated on: 11/17/2022

All results presented are from nucleic acid amplification tests which represent >90% of the diagnostic tests reported to NREVSS. The last three weeks of data may be less complete.

NREVSS is an abbreviation for the National Respiratory and Enteric Virus Surveillance System. For more information on NREVSS, please visit National Respiratory and Enteric Virus Surveillance System | CDC.

SARS-CoV-2: Severe acute respiratory syndrome coronavirus type 2

Flu: Influenza virus types are combined but reported by type and subtype depending on the testing capabilities of each contributing laboratory.

RSV: Respiratory syncytial virus. Types A and B are not shown separately in this report.

RV/EV: Rhinovirus or enterovirus. These results are generally clinically indistinguishable and reported in a combined category via NREVSS.

PIV: Parainfluenza virus types 1 through 4 are combined for this report. However, laboratories report these data individually.

HCoV: Human coronavirus types HKU1, OC43, 229E and NL63 are combined for this report. However, laboratories report these data individually.

R Adenovirus: All adenovirus detections reported to NREVSS from respiratory specimens (for example, nasal pharyngeal swabs). There are >100 adenovirus types. Most commercial laboratory tests do not distinguish type without further identification.

HMPV: Human metapneumovirus types A and B are not reported separately from NREVSS.
RSV weekly percent positive by HHS region - National Respiratory and Enteric Virus Surveillance System (NREVSS), July 2, 2022 to November 18, 2022
Weekly test positivity for ED/Inpatient Children in the New Vaccine Surveillance Network (NVSN), January 1, 2022 to November 18, 2022

- Network of 7 pediatric medical centers
- Year-round active surveillance for acute respiratory infection
- All participants tested for multiple respiratory viruses by PCR
- >10,000 children enrolled annually
Weekly Rates of RSV-Associated Hospitalizations among Children Ages <18 years by Surveillance Season – RSV-NET, 2018-2022

Date are subject to reporting lag. Rates presented likely underestimate actual rates of RSV hospitalization as cases are defined as those with a positive test, and not all patients might be tested for RSV. Rates are unadjusted and do not account for changing testing practices over time. Data for May and June 2022 are incomplete.
Percentage of pediatric inpatient and ICU beds occupied, February 15, 2022 to November 23, 2022, United States and HHS Regions

Source: Unified Hospital Data - Analytic Dataset, based on reporting from all hospitals (N = 5,307).

Data fields for pediatric inpatient and ICU beds and occupancy are required for reporting as of Feb 2, 2022. Data in this graphic begins on Feb 15, 2022 to account for delays in initial reporting of these fields.

<table>
<thead>
<tr>
<th>Region</th>
<th>Current 7-Day Average % Pediatric Inpatient Occupancy</th>
<th>Current 7-Day Average % Pediatric ICU Occupancy</th>
</tr>
</thead>
<tbody>
<tr>
<td>US</td>
<td>76.69%</td>
<td>80.25%</td>
</tr>
<tr>
<td>Northeast</td>
<td>77.50%</td>
<td>85.84%</td>
</tr>
<tr>
<td>Eastern</td>
<td>69.66%</td>
<td>81.02%</td>
</tr>
<tr>
<td>Mid-Atlantic</td>
<td>81.12%</td>
<td>89.01%</td>
</tr>
<tr>
<td>Southeast</td>
<td>70.32%</td>
<td>76.89%</td>
</tr>
<tr>
<td>Midwest</td>
<td>74.25%</td>
<td>75.79%</td>
</tr>
<tr>
<td>Southwest</td>
<td>84.91%</td>
<td>85.34%</td>
</tr>
<tr>
<td>Central Plains</td>
<td>76.19%</td>
<td>82.43%</td>
</tr>
<tr>
<td>Rocky Mountain</td>
<td>81.81%</td>
<td>72.42%</td>
</tr>
<tr>
<td>Pacific Southwest</td>
<td>80.63%</td>
<td>78.64%</td>
</tr>
<tr>
<td>Pacific Northwest</td>
<td>75.36%</td>
<td>79.23%</td>
</tr>
</tbody>
</table>
Weekly U.S. Emergency Department (ED) Visits in Patients with Acute Respiratory Illness*, Ages 0-1, 2-4, 5-11, and 12-17 Years, Dec 30, 2018, to Nov 26, 2022, National Syndromic Surveillance Program

*The CDC Broad Acute Respiratory Discharge Diagnosis (DD) v1 definition identifies ED visits with general respiratory infections (e.g., influenza, respiratory syncytial virus, or COVID-19) as well as general respiratory illness such as cough or pneumonia. These are identified in discharge diagnoses. Counts limited to the subset of NSSP facilities with consistent reporting to NSSP and with high quality diagnosis codes throughout the time period.

Data are Provisional Until Officially Released by the CDC - For Internal Use Only (FIUO) - For Official Use Only (FOUO) - Sensitive But Unclassified (SBU) - Not for Further Distribution
Weekly U.S. Emergency Department (ED) Visits with Diagnosed RSV and RSV-like Illness*, Ages 0-1, 2-4, 5-11, 12-17, 18-64, and 65+ Years, Dec 30, 2018, to Nov 26, 2022, National Syndromic Surveillance Program

*CDC Respiratory Syncytial Virus v1 definition includes visits with RSV, bronchiolitis, or syncytial virus in the chief complaint and visits with diagnosed RSV. Counts limited to the subset of NSSP facilities with consistent reporting to NSSP and with high quality diagnosis codes throughout the time period.

+The most recent week of data may be incomplete

Data are Provisional Until Officially Released by the CDC - For Internal Use Only (FIUO) - For Official Use Only (FOUO) - Sensitive But Unclassified (SBU) - Not for Further Distribution
Laboratory-Confirmed COVID-19-Associated Hospitalization, March 7, 2020, to November 12, 2022

The Coronavirus Disease 2019 (COVID-19)–Associated Hospitalization Surveillance Network (COVID-NET) conducts population-based surveillance for laboratory-confirmed COVID-19-associated hospitalizations in children (persons younger than 18 years) and adults. The current network covers nearly 100 counties in the 10 Emerging Infections Program states (CA, CO, CT, GA, MD, MN, NM, NY, OR, and TN) and four additional states through the Influenza Hospitalization Project (IA, MI, OH, and UT). The network represents approximately 10% of US population (~32 million people). Cases are identified by reviewing hospitals, laboratory, and admissions databases and infection control logs for patients hospitalized with COVID-19. Laboratory confirmation is dependent on clinician-ordered SARS-CoV-2 testing. Therefore, the unadjusted rates provided are likely to be underestimates as COVID-19-associated hospitalizations can be missed due to test availability and provider or facility testing practices. COVID-NET hospitalization data are preliminary and subject to change as more data become available. In particular, case counts and rates for recent hospital admissions are subject to lag. As data are received each week, prior case counts and rates are updated accordingly. All incidence rates are unadjusted.

*Starting the week of May 29, 2022, Iowa data are removed from weekly rate calculations. Source: COVID-NET hospitalization data through November 12, 2022; https://covid.cdc.gov/covid-data-tracker/#covidnet-hospitalization-network
National Percentage of Deaths due to Pneumonia, Influenza, and COVID-19 in Children <18 years – National Center for Health Statistics Mortality Surveillance System, October 2021 – October 18, 2022
Summary

- We continue to see high levels of pediatric respiratory illness due to multiple viruses
- Nationally, the rate of rise for RSV is decreasing and several HHS Regions have peaked and are seeing reductions in RSV detections
- Early increases in seasonal influenza have been reported in most regions of the US, with the highest levels of activity in the Southcentral and Southeast regions of the country
- Public health response
  - Prevention focus on vaccines for influenza, COVID-19
  - Diagnostics, important to determine etiology, guide therapy
Data Sources

Unified Hospital Dataset

- Includes all acute care hospitals in United States
- Data are collected as aggregate daily number of admissions among patients 0–17 years that does not allow for finer age disaggregation

Coronavirus Disease 2019-Associated Hospitalization Surveillance Network (COVID-NET)

- Population-based surveillance system that collects data on laboratory-confirmed COVID-19-associated hospitalizations among children and adults
- Network of >250 acute-care hospitals in 14 states
- Updated weekly (Wednesdays, with data posted publicly every Thursday)

Respiratory Syncytial Virus (RSV) Hospitalization Surveillance Network (RSV-NET)

- Population-based surveillance system that collects data on laboratory-confirmed COVID-19-associated hospitalizations among children and adults
- Collects and reports data from acute-care hospitals across 75 counties in 12 states
- Typical surveillance season is October 1–April 30. Surveillance extended into summer 2021 and 2022 due to atypical increases in rates of hospitalization
Data Sources - Continued

New Vaccine Surveillance Network (NVSN)

- Active, population-based surveillance network at 7 pediatric medical centers
- Year-round acute respiratory illness surveillance in inpatients, ED, and outpatient clinics
- Participants tested for multiple respiratory viruses by multiplex PCR assays

National Syndromic Surveillance Program (NSSP)

- Electronic patient encounter data received from emergency departments, urgent and ambulatory care centers, and laboratories
- Tracks symptoms, signs and clinical diagnoses of emergency department patients in near real-time
- ARI definition pulls only from discharge diagnoses, including diagnosed RSV. RSV definition pulls from both chief complaint text direct mentions of RSV (included if the record says "RSV," "bronchiolitis" or "syncytial virus.") and the diagnosis.

Influenza Hospitalization Surveillance Network (FluSurv-NET)

- Population-based surveillance system that collects data on laboratory-confirmed influenza-associated hospitalizations among children and adults through a network of acute care hospitals in 14 states.
- FluSurv-NET also provides demographic and clinical information including age, sex and underlying medical conditions among persons hospitalized with flu. Data gathered are used to estimate age-specific hospitalization rates on a weekly basis and to describe characteristics of persons hospitalized with influenza illness.
Data Sources - Continued

National Respiratory and Enteric Virus Surveillance System (NREVSS)

• Passive, laboratory-based surveillance from ~300 commercial, hospital, and state/local public health laboratories
• Weekly reporting of total tests (PCR, antigen, etc.) performed and positive tests by virus
• Testing is clinician-directed and includes patients of all ages
Use of COVID-19 Convalescent Plasma

Carlos H. Villa, MD, PhD
COVID-19 Convalescent Plasma

CDC/IDSA Clinician Call
December 3, 2022

Carlos H. Villa, MD PhD
Office of Blood Research and Review, CBER/FDA
Carlos.villa@fda.hhs.gov
Convalescent Plasma (CP)

• CP is plasma collected from patients who have recovered from an infection
  – COVID-19 convalescent plasma (CCP) contains antibodies to SARS-CoV-2

• Antibodies in CP can be used as ‘passive’ immune therapy
  – Historically considered most effective when high titer is administered early

• Neutralizing antibodies likely an important mechanism of action
  – Optimal characteristics of antibody repertoire unknown (e.g., IgG vs IgM, isotype, epitopes, etc.)

April 2020 – Early SARS-CoV-2 Pandemic

- Available pathways at the time:
  - Traditional INDs / Randomized Controlled Trials (RCT)
  - Single Patient Emergency IND
  - Expanded Access INDs
    - National EAP sponsored by Mayo Clinic

- Based on preliminary reports, a neutralizing antibody titer of ≥1:160 was recommended but not required
  - Various assays/cutoffs used in clinical trials

- FDA provided guidance on manufacturing of CCP (https://www.fda.gov/media/136798/download, updated several times since initial issuance)

- CCP donors must meet FDA blood donor eligibility criteria

Regulatory History of EUA

• 8/2020: Emergency Use Authorization (EUA) of CCP for the treatment of hospitalized patients with COVID-19
  – Limited data from RCTs, observational studies, and national expanded access protocol (EAP); EUA noted that additional RCT data were needed
  – Exploratory analyses of EAP were based on neutralization ID$_{50}>250$ as ‘high titer’ ([https://www.ncbi.nlm.nih.gov/pmc/articles/PMC9082011/](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC9082011/))

• 2/4/2021: Revised EUA to high titer CCP early in the course of disease
  – Transfusion to hospitalized patients late in the course of illness not associated with clinical benefit in immune competent patients

• 12/26/2021: Revised EUA to high titer CCP for treatment of COVID-19 in patients with immunosuppressive disease or receiving immunosuppressive treatments

Clinical Review Memo: [https://www.fda.gov/media/155159/download](https://www.fda.gov/media/155159/download)
Letter of Authorization: [https://www.fda.gov/media/141477/download](https://www.fda.gov/media/141477/download)
Evolution of Tests Acceptable for use in the Manufacture of CCP

• Original EUA (8/2020) included one serologic test to be used as a manufacturing test to qualify CCP as either ‘high’ or ‘low’ titer

• FDA encouraged submission of data to include additional manufacturing tests
  – Only considered tests with an existing EUA for detection of anti-SARS-CoV-2 antibodies
  – Originally considered both qualitative and semi-quantitative tests if submitted data supported an acceptable cut-off value
Evolution of Tests Acceptable for use in the Manufacture of CCP

• Test list revised in the 12/2021 EUA reissuance
  – Only tests with semi-quantitative or quantitative intended use
  – 95% confidence that at least 85% of qualified units would have ID50 neutralization titers of at least 1:250
  – Currently includes 7 tests:
    • 5 tests authorized for semi-quantitative detection of anti-SARS-CoV-2 antibodies
    • 1 test authorized for semi-quantitative detection of total neutralizing antibodies
    • 1 test authorized for quantitative detection of anti-SARS-CoV-2 antibodies
Challenges in Qualification of CCP

• Collections of CCP began early in the pandemic, but development and implementation of serologic tests for anti-SARS-CoV-2 antibodies lagged
  – Flexibility on up-front titer requirement allowed early collections, but led to lack of standardized approach
• No single, central sponsor/manufacturer developing CCP meant different establishments and studies were taking different approaches to CCP qualification
  – US has hundreds of licensed and registered blood establishments
• Serologic surrogates are imperfect correlates of neutralizing activity
• Minimal data on viral strain sequences were available for either donors or recipients
Neutralizing Antibodies

• Many variables between neutralization tests:
  – Type of virus (e.g., wild-type virus [inc. different strains], lentiviral pseudo-virus, VSV pseudo-virus, among others)
  – ‘Blocking’-based surrogates also potentially an option
  – Readouts (e.g., luciferase reporter, GFP expression, immunofluorescence)
  – Expression of other proteins involved in viral entry (e.g., TMPRSS2)

• Titers in a given neutralization test can vary several fold from another test

• Many neutralization tests are more complex or laborious than tests typically performed by blood establishments
  – Unlikely to be feasible at throughput needed for manufacturing large numbers of CCP units
  – Many different testing platforms in use in the blood industry
Serologic correlates

- Positive correlation between serologic titers and neutralization titers, but relationship is highly variable
- Serologic correlates allow high throughput identification of donations more likely to contain high neutralization titers
- Serologic correlates may vary by target antigen (e.g., anti-S1, anti-RBD, anti-NC), antibody class (IgG vs. IgM vs. ‘total’), or isotype specificity (e.g., IgG1 vs IgG2)
- Measures only one variable in a heterogeneous product (content of other antibodies, coagulation factors, among others)
- Characteristics of an individual donors’ immune responses will differ
  - Generally, no available information on donor infection (e.g. severity of disease, timing of illness/recovery), strain-specificity, or cross-variant binding and neutralization
Considerations in Immunosuppressed

- Data in this population are generally limited to small subgroup analyses of RCTs, matched-control observational studies, and case series.
- While noting this limitation, review of studies at the time of EUA reissuance found that the potential benefit of CCP in the immunosuppressed population, including relatively later in the course of illness, appeared to be larger than in immunocompetent patients, and EUA criteria were met in both the inpatient and outpatient setting.
Additional Considerations

• Manufacturing, study, and use of CCP is challenged by heterogeneity in donors, emerging variants, and lack of centralized approach to collection and testing

• It remains difficult to precisely characterize the biologic activity of CCP collected from a given donor and have assurance of potency against variants in a potential recipient

• Available evidence indicates that CCP donors who were previously vaccinated, but have recovered from recent infection, are more likely to have higher titers and relatively improved cross-variant binding and neutralization
  – Polyclonality offers theoretical benefit with respect to immune escape variants
ADDITIONAL RESOURCES:


Q&A
Masking to Prevent RTI Transmission in Health Care Settings

Alex Kallen, MD, PhD
Chanu Rhee, MD, MPH, FIDSA
Meghan A. Baker, MD, ScD, FIDSA
CDC Source Control Recommendations in Healthcare Settings

Alex J. Kallen, MD, MPH
Chief of the Prevention and Response Branch
Division of Healthcare Quality Promotion
U.S. Centers for Disease Control & Prevention
Mask Use in Healthcare Settings

• Will not cover use for care of patients with known respiratory infections as part of TBP
• Masks provide protection and source control
• Most important:
  • People in healthcare settings who wish to wear a mask to protect themselves (outside of situations already recommended – e.g., TBP) should be allowed to wear the most protective mask that fits well and that they can wear consistently

Respiratory Hygiene and Cough Etiquette

• Included as part of Standard Precautions in the 2007 Guideline for Isolation Precautions

  • “During periods of increased prevalence of respiratory infections in the community (e.g., as indicated by increased school absenteeism, increased number of patients seeking care for a respiratory infection), offer masks to coughing patients and other symptomatic persons upon entry into the facility or medical office.

    • Some facilities may find it logistically easier to institute this recommendation year-round as a standard of practice.”

COVID-19 Healthcare Infection Control Guidance

• Accounted for potential for asymptomatic transmission of SARS-CoV-2; broadened use of source control beyond just those with symptoms of infection

• Recommended universal masking in highest risk periods (i.e., when community transmission levels are high)
  • “When SARS-CoV-2 Community Transmission levels are high, source control is recommended for everyone in a healthcare setting when they are in areas of the healthcare facility where they could encounter patients....
  • When SARS-CoV-2 Community Transmission levels are not high, healthcare facilities could choose not to require universal source control. However, even if source control is not universally required, it remains recommended for individuals in healthcare settings who:
    • Have suspected or confirmed SARS-CoV-2 infection or other respiratory infection (e.g., those with runny nose, cough, sneeze); or
    • Had close contact (patients and visitors) or a higher-risk exposure (HCP) with someone with SARS-CoV-2 infection, for 10 days after their exposure; or
    • Reside or work on a unit or area of the facility experiencing a SARS-CoV-2 outbreak; universal use of source control could be discontinued as a mitigation measure once no new cases have been identified for 14 days; or
    • Have otherwise had source control recommended by public health authorities”

Infection Control: Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) | CDC
CDC’s Core Practices

• Originally compiled by the Healthcare Infection Control Practices Advisory Committee

• Fundamental standards of care that should be implemented in all settings where healthcare is delivered

• Standard Precautions: 5.e. Minimizing Potential Exposures
  • “During periods of higher levels of community respiratory virus transmission*, facilities should consider having everyone mask upon entry to the facility to ensure better adherence to respiratory hygiene and cough etiquette for those who might be infectious. Such an approach could be implemented facility-wide or targeted toward higher risk areas (e.g., emergency departments, urgent care, units experiencing an outbreak) based on a facility risk assessment.
  • *Examples of potential metrics include, but are not limited to, increase in outbreaks of healthcare-onset respiratory infections, increase in emergency department or outpatient visits related to respiratory infections.”

https://www.cdc.gov/infectioncontrol/guidelines/core-practices/index.html
Disclosures

Dr. Rhee

- Royalties
  - UpToDate (Procalcitonin chapter)

- Committee Membership
  - IDSA Sepsis Task Force
  - Technical Advisory Panel Member for CMS Sepsis Outcome Measure Development

- Editorial
  - Associate Editor, *Clinical Infectious Diseases*
  - Editorial Board, *Critical Care Medicine* and *Critical Care Explorations*

- Consulting Fees
  - Pfizer (Lyme disease surveillance)
  - Cytovale (Sepsis diagnostics)

Dr. Baker

- Honorarium
  - Albright Stonebridge Group

- Committee Membership
  - SHEA Guidelines Committee

No financial conflicts related to this presentation
Why is Masking Important to Prevent Nosocomial Spread of Respiratory Viruses?
Masks Provide Source Control and Protection

https://www.science.org/doi/10.1126/science.abc6197
Mask Source Control Applies to All Respiratory Viruses

Respiratory virus shedding in exhaled breath and efficacy of face masks

123 individuals infected by at least one respiratory virus provided exhaled breath samples, randomized to face mask vs no face mask

Reduced viral RNA in droplets and aerosols in masked participants

Similar findings for influenza and rhinovirus

Leung NH, Nat Med 2020; 26:676-680
Most COVID-19 Is Spread by People without Symptoms

Johansson, JAMA Network Open 2021;4(1):e2035057

CDC modeling study of sources of transmission

- Symptomatic (41%)
- Pre-Symptomatic (35%)
- Asymptomatic, Never Develop Symptoms (24%)

59% of transmissions from asymptomatic individuals
Viral Load Relative to Symptom Onset

Cevik M, BMJ 2020; 372:m3862
Influenza Transmission Has Many Similarities

Asymptomatic transmission and high community burden of seasonal influenza in an urban and a rural community in South Africa, 2017–18 (PHIRST): a population cohort study

1,116 participants from 225 households in South Africa prospectively underwent twice weekly NP swab surveillance for influenza by PCR between 2017-2018

- Transmission rate with ≥2 symptoms: 17%
- Transmission rate with no symptoms: 6%
- 27% of secondary cases acquired from asymptomatic index cases

Cohen C, Lancet Glob Health 2021; 9:e863-874
Other Respiratory Viruses Are Often Asymptomatic Too

Frequent Asymptomatic Respiratory Syncytial Virus Infections During an Epidemic in a Rural Kenyan Household Cohort

Respiratory syncytial virus evaluation among asymptomatic and symptomatic subjects in a university hospital in Sao Paulo, Brazil, in the period of 2009-2013

Rates of asymptomatic respiratory virus infection across age groups

Munywoki PK, J Infect Dis 2015; 212:1711-8
Moreira LP, Influenza Other Respir Viruses 2018; 12:326-330
Galanti M, Epidemiol Infect 2019; 147:e176
Implications

- During periods of high community prevalence, healthcare personnel risk spreading SARS-CoV-2 and other respiratory viruses to each other and to vulnerable patients in healthcare settings **even if they are fastidious about avoiding work with URI symptoms**
And “Presenteeism” in HCWs is Common

>50% of HCWs reported acute respiratory illness during influenza seasons

68-95% of HCWs reported working at least 1 day while symptomatic

- Most commonly because symptoms were mild

Jiang L, *ICHE* 2019; 40:889-896
Kuster SP, *ICHE* 2021; 43:268-273
Patients with Occult Infections Can Also Infect HCWs (even with universal patient testing)

- 14 patients and 38 staff members affected by cluster
- Cluster occurred despite universal patient testing on admission
  - Index case had 2 negative PCR tests
Most Hospital-Acquired HCW Infections Are From Other HCWs

Prospective study involving detailed interviews and contact tracing for 1,208 HCWs who tested positive for SARS-COV-2

- **Definite Community**: 45.4% (n=548)
- **Likely Community**: 11.7% (n=141)
- **Hospital (Patient, Inappropriate PPE)**: 1.0% (n=12)
- **Hospital, Employee (No Mask Lapse)**: 4.1% (n=49)
- **Hospital, Employee (Mask Lapse)**: 1.2% (n=15)
- **Mixed Community and Hospital**: 0.9% (n=11)
- **Covid Patient with Appropriate PPE**: 8.0% (n=97)
- **No Known Exposures**: 27.7% (n=335)

**57% Community Source**
- (70% household contacts)

**6% Hospital Source**
- (84% from employees)

**1% Mixed Source**

**36% Unknown**
- (78% with no known COVID-19 contacts)

Most infections likely from community; most hospital-acquired infections were from other staff rather than patients.

Rhee C, ASHE 2021; 1:e65
Masking reduces healthcare onset respiratory tract infections
Universal Masking and HCW COVID-19 Infections

Substantial decrease in HCW infection rates at Mass General Brigham healthcare system after universal masking implemented

Wang, JAMA 2020; 324:703-704
Concise Communication

Absence of nosocomial influenza and respiratory syncytial virus infection in the coronavirus disease 2019 (COVID-19) era: Implication of universal masking in hospitals

5-hospital system with 3100 beds in Hong Kong

Feb-April 2020 (with universal masking for COVID-19) → 0 nosocomial cases of influenza/RSV

Wong SC, ICHE 2021; 42:218-221
Overall decrease in RVIs from 10.3% in pre-mask period to 4.4% in mask period (p<0.001)

Sung, *Clin Infect Dis* 2016; 63:999-1006
The Type of Mask Matters

- People who reported always wearing a mask in indoor public settings less likely to test positive for COVID-19
- Matched case-control study, 1828 people, compared people with similar characteristics

Andrejko et al. MMWR. Feb 2022 bit.ly/MMWR7106
But the RCT Data on N95 vs Medical Masks are Messy

- Suggests medical masks prevent doubling in infection hazard, heterogeneity by country
- Limitations: Lack of control for possible acquisition through community exposure, exposure to patients with unrecognized COVID, differences in self-reported adherence, cross-group contamination, and inclusion of infections not temporally associated with COVID care
BMJ Open  Downsides of face masks and possible mitigation strategies: a systematic review and meta-analysis

*Meta-analysis of 11 RCTs and observational studies comparing masks vs any other interventions or controls*

**Reported downsides and adverse effects of wearing masks**
- Discomfort and skin irritation
- Psychological (loneliness)
- Negative patient perceptions of provider empathy
- Impaired communication
- Mask contamination
- Sense of dyspnea

Adverse effects generally worse with N95 respirators vs medical masks

Bakhit M, *BMJ Open* 2021; 11:e044364
Masking in Healthcare Settings: CDC Guidance

- Didn’t CDC recently say that we don’t need to wear masks in healthcare facilities anymore?
  
  ➢ Not quite!

- CDC recommends using **Community Transmission Levels** to inform this decision
  - Based on new COVID-19 cases per 100,000 people AND positivity rate over last 7 days
  - *Only consider relaxing universal masking in healthcare settings when community transmission levels are NOT high*

- Different than **COVID-19 Community Levels** that are used for non-healthcare settings to inform indoor masking recommendations
  - Based on new COVID cases, % of hospital beds occupied by COVID-19 patients, and number of new COVID-19 admissions
  - More liberal than guidance for healthcare settings
Community Transmission Levels vs Community Levels

Community Transmission

<table>
<thead>
<tr>
<th>Community Transmission in US by County</th>
<th>Total</th>
<th>Percent</th>
<th>% Change</th>
</tr>
</thead>
<tbody>
<tr>
<td>High</td>
<td>1244</td>
<td>38.61%</td>
<td>-8.04%</td>
</tr>
<tr>
<td>Substantial</td>
<td>1058</td>
<td>32.84%</td>
<td>6.58%</td>
</tr>
<tr>
<td>Moderate</td>
<td>745</td>
<td>23.12%</td>
<td>1.8%</td>
</tr>
<tr>
<td>Low</td>
<td>175</td>
<td>5.43%</td>
<td>-0.28%</td>
</tr>
</tbody>
</table>

Community Levels

Will likely get worse as we head into the winter
Other Considerations

- Even when SARS-CoV-2 community transmission levels are not high, consider masking:
  - After high risk exposure
  - Reside or work on a unit with an outbreak
    - Consider N95 respirator over standard medical masks
  - If the individual or household member is at increased risk of severe disease
  - When caring for patients who are moderately or severely immunocompromised or vulnerable (oncology/BMT, NICU and other ICUs)
  - When community rates of non-SARS-CoV-2 viruses are high
Summary

- **Masking in healthcare settings reduces nosocomial transmission of respiratory viruses**
  - Patient Protection via Source Control of HCWs
    - Many infected HCWs are asymptomatic/presymptomatic or work with mild symptoms
  - HCW Protection via Protection from Patients and Source Control of Other HCWs
    - Patients may have occult infections even with aggressive testing
    - Most hospital-based transmission are HCW-to-HCW

- **These benefits do need to be weighed against the downsides and negative consequences of masking**
  - Comfort, psychological (patient and HCW), communication

- **Apart from CDC’s COVID-19 Community Transmission Levels, masking can be informed by considerations of high-risk scenarios and patient populations as well community rates of other respiratory viruses**
Thank You!

For all the lives we touch
Clean hands protect our patients.
Always perform hand hygiene and help others do the same.

crhee@bwh.harvard.edu
mbaker1@bwh.harvard.edu
Q&A
Selected Resources

Dr. Uyeki
- https://www.cdc.gov/flu/weekly/index.htm
- https://www.cdc.gov/flu/highrisk/index.htm
- https://www.cdc.gov/flu/professionals/antivirals/summary-clinicians.htm

*IDSA Influenza Clinical Practice Guidelines: https://academic.oup.com/cid/article/68/6/e1/5251935?login=true

Dr. Villa
- https://www.fda.gov/media/136798/download
- https://www.ncbi.nlm.nih.gov/pmc/articles/PMC9082011/
- https://www.fda.gov/media/155159/download
- https://www.fda.gov/media/141477/download

Additional References Relevant to COVID-19 Convalescent Plasma
Selected Resources

**Dr. Kallen:**
- [https://www.cdc.gov/infectioncontrol/guidelines/core-practices/index.html](https://www.cdc.gov/infectioncontrol/guidelines/core-practices/index.html)

**Drs. Rhee and Baker**
- [https://www.science.org/doi/10.1126/science.abc6197](https://www.science.org/doi/10.1126/science.abc6197)

**Program Links:**
- This webinar is being recorded and can be found with the slides online at [https://www.idsociety.org/cliniciancalls](https://www.idsociety.org/cliniciancalls)
An online community bringing together information and opportunities for discussion on latest research, guidelines, tools and resources from a variety of medical subspecialties around the world.

Specialty Society Collaborators

- American Academy of Family Physicians
- American Academy of Pediatrics
- American College of Emergency Physicians
- American College of Obstetricians & Gynecologists
- American College of Physicians
- American Geriatrics Society
- American Thoracic Society
- Pediatric Infectious Diseases Society
- Society for Critical Care Medicine
- Society for Healthcare Epidemiology of America
- Society of Hospital Medicine
- Society of Infectious Diseases Pharmacists

www.COVID19LearningNetwork.org
@RealTimeCOVID19
#RealTimeCOVID19
FOR WHOM?
- Clinicians who have questions about the clinical management of COVID-19

WHAT?
- Calls from clinicians will be triaged by CDC to a group of IDSA volunteer clinicians for peer-to-peer support

HOW?
- Clinicians may call the main CDC information line at 800-CDC-INFo (800-232-4636)
- To submit your question in writing, go to www.cdc.gov/cdc-info and click on Contact Form
THANK YOU

We want to hear from you!
Please complete the post-call survey.

A recording of this call, slides and the answered Q&A will be posted at
www.idsociety.org/cliniciancalls
-- library of all past calls available --

Contact Us:
Dana Wollins (dwollins@idsociety.org)
Deirdre Lewis (dlewis@idsociety.org)