Challenges in the Clinical Management of Influenza

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Disclosures

- No conflicts to report

- **Applying What is Known to Have Clinical Benefit**
  - Challenge 1: Early Diagnosis
  - Challenge 2: Starting Antiviral Treatment Early
  - Challenge 3: Improving Management of Hospitalized Patients
- **Developing new interventions for clinical management of influenza**
  - Challenge 4: Conducting Clinical Trials of Interventions to Improve Clinical Management

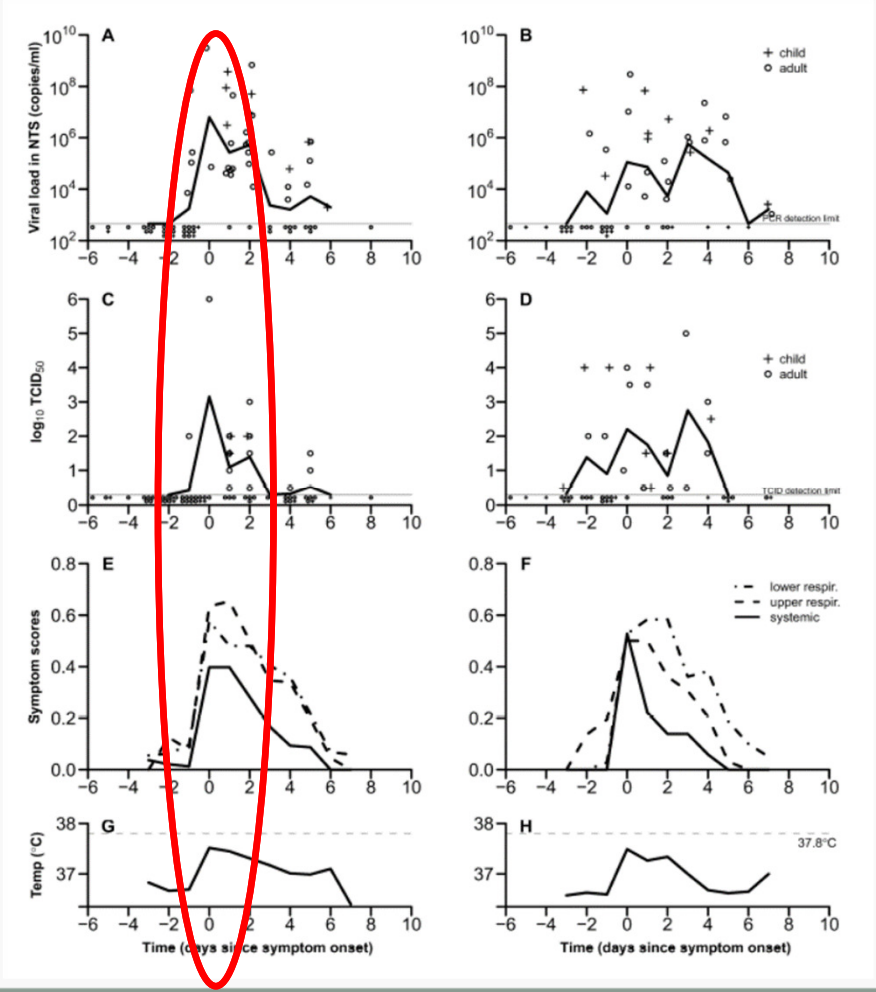
Early Antiviral Treatment is Highly Important

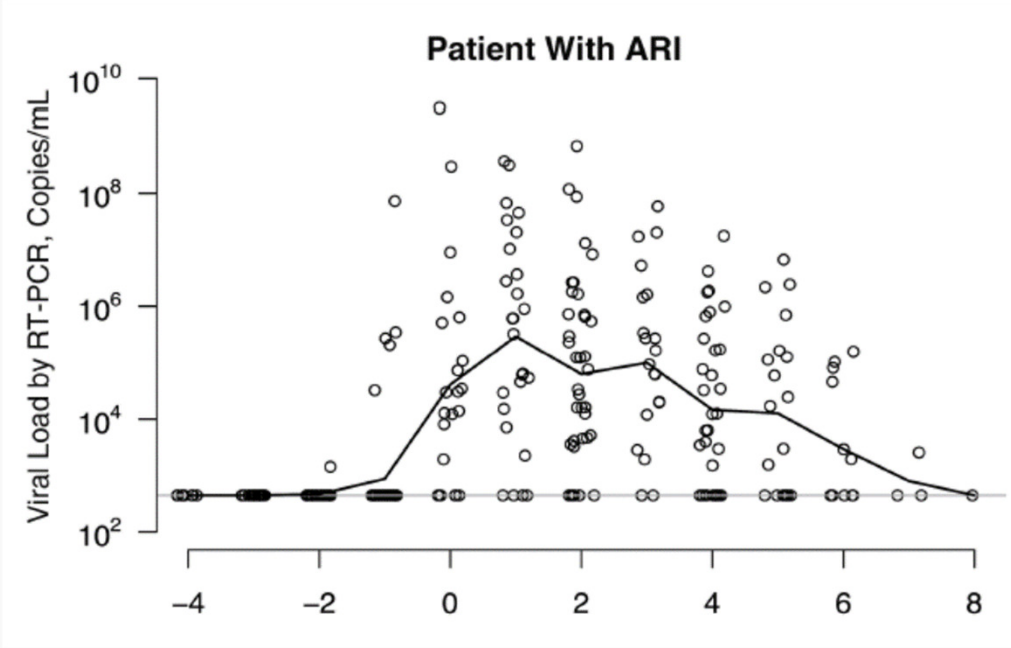
- **RCTs have shown that antiviral treatment versus placebo has significant clinical benefit when started within 48 hours after onset**
  - ➢Antiviral treatment has the greatest clinical benefit when started as close to illness as possible
  - Baloxavir (adolescents and adults)
    - **Patients treated ≤24 hours after illness onset had a significantly faster time to alleviation of symptoms** than patients treated >24-48 hours after illness onset (median difference in time to alleviation of symptoms vs. placebo: 32.8 hours compared with 13.2 hours (p<0.001)
  - Oseltamivir - Pooled meta-analysis of 5 RCTs in children
    - **Patients treated <24 hours after illness onset had significantly greater reduction in duration of illness** than starting treatment 24-48 hours after onset (-22.8 hours, 95% CI: -29.4 to -16.2 versus -4.4 hours, 95% CI: -15.5 to 6.5 hours)

Dobson Lancet 2015; Hayden NEJM 2018; Malosh Clinical Infect Dis 2018

- **Early diagnosis of influenza requires:**
  - Patient seeks medical care early after symptom onset (Japanese model)
    - Clinic visit or phone consultation
  - Influenza testing is performed vs. clinical diagnosis by Clinician
    - Assumes: influenza testing is accurate
    - Assumes clinical diagnosis is accurate
  - Influenza testing at alternative sites (e.g. pharmacies)?
    - For non-high-risk patients
- **Future developments:**
  - Use of home-based influenza testing
    - Self-collected respiratory swabs (nasal swab)
    - Testing device for swab is connected to a smart phone
    - Positive result triggers message to clinician to prescribe antiviral treatment
    - High-risk patients or those with severe illness need to be examined by a clinician

Influenza Viral Shedding Peaks Within 24 Hours of Illness Onset





Lau J Infect Dis 2010; Ip Clin Infect Dis 2017

Rapid Influenza Molecular Assays Have High Sensitivity

Pooled Sensitivity to detect influenza A and B viruses versus RT-PCR (N=162 studies) (Pooled Specificity >98%)

- **Rapid antigen tests: 53-54%**
- **Rapid antigen tests with analyzer device: 77-80% (digital immunoassays)**
- **Molecular assays: 92-95%**


Annals of Internal Medicine REVIEW

Diagnostic Accuracy of Novel and Traditional Rapid Tests for Influenza Infection Compared With Reverse Transcriptase Polymerase Chain Reaction

A Systematic Review and Meta-analysis

Joanna Merckx, MD, MSc; Rehab Wali, BSc, MBBS; Ian Schiller, MSc; Chelsea Caya, MScPH; Genevieve C. Gore, MLIS; Caroline Chartrand, MD, MSc; Nandini Dendukuri, PhD; and Jesse Papenburg, MD, MSc


Clinical Infectious Diseases

REVIEW ARTICLE

IDSA hivma

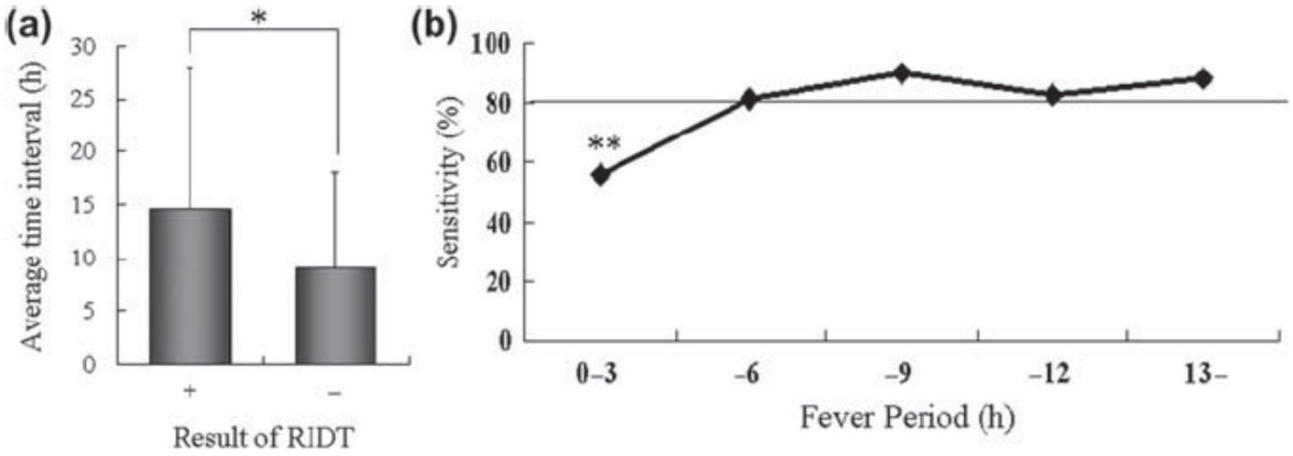
Rapid Molecular Tests for Influenza, Respiratory Syncytial Virus, and Other Respiratory Viruses: A Systematic Review of Diagnostic Accuracy and Clinical Impact Studies

Laura M. Vos,[1] Andrea H. L. Bruning,[2] Johannes B. Reitsma,[3] Rob Schuurman,[4] Annelies Riezebos-Brilman,[4] Andy I. M. Hoepelman,[1] and Jan Jelrik Oosterheert[1]

- **Meta-analysis of Rapid Influenza Molecular Assays (N=29 studies)**
  - **Pooled Sensitivity: 87.9%**
  - **Pooled Specificity: 97.4%**

Merckx Annals of Int Med 2017; Vos Clin Infect Diseases 2019

- Patients present soon after illness onset (same day or next day)
- Potential for early influenza diagnosis by rapid testing
  - Potential for starting early antiviral treatment



Sensitivity = 80%; Specificity = 97.1% of RIDTs to detect H1N1pdm09 virus versus RT-PCR

- High RIDT sensitivity is due to early testing when viral levels are high
  - However, sensitivity was lower when presenting very early after fever onset

Harada Scand J Infect Dis 2012

- **Early antiviral treatment requires:**
  - A) **Clinician prescribes antiviral medication**
    - Educated about influenza and antiviral medications for influenza
    - Who to prioritize?
      - Target Group: **Persons at high-risk for complications** (young children, ≥65 years, pregnant women, persons with chronic medical conditions)
  - B) **Antiviral medication is widely available**
    - Supply of antivirals is sufficient
    - Costs: Who pays for antivirals?
      - No financial barriers (government health insurance, private insurance, medication is affordable)
  - C) **Patient receives antiviral treatment**
    - Patient has access to antivirals and starts treatment as soon as possible
- **How to improve access to antivirals**?
  - Make available at all outpatient clinics, emergency rooms?
  - Make available for over-the-counter use? Low cost (generic drugs)?

Influenza A(H1N1)pdm09 Viral Shedding Varies by Disease Severity

Viral Shedding is Longer with Severe Disease

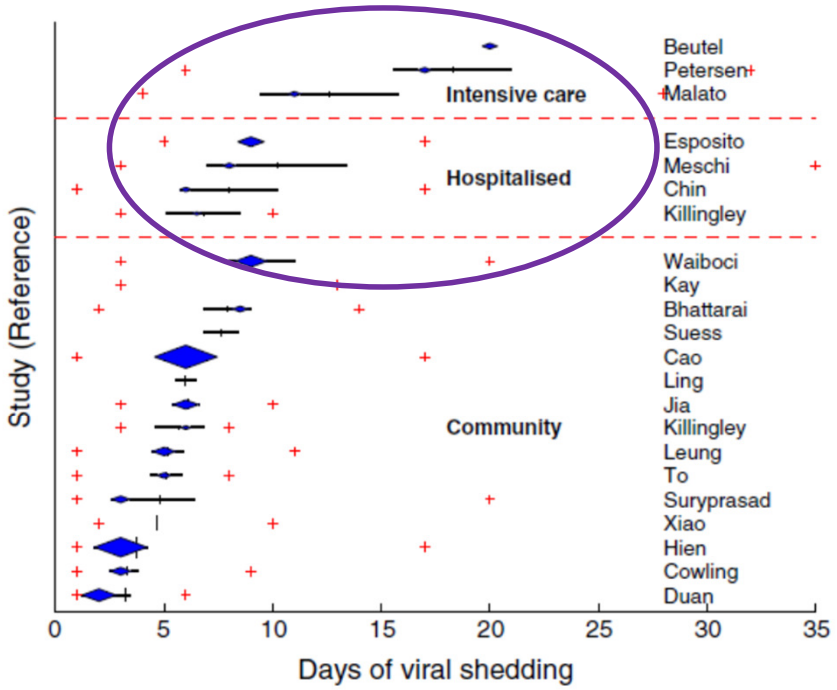


Figure 1. Shedding duration of influenza A(H1N1)pdm09 by study and patient setting. (Legend: cross = minimum and maximum; middle of diamond = median; area of diamond = study size; vertical line = mean; horizontal line = 95% confidence interval)

Viral Shedding Duration is Similar in Children and Adults

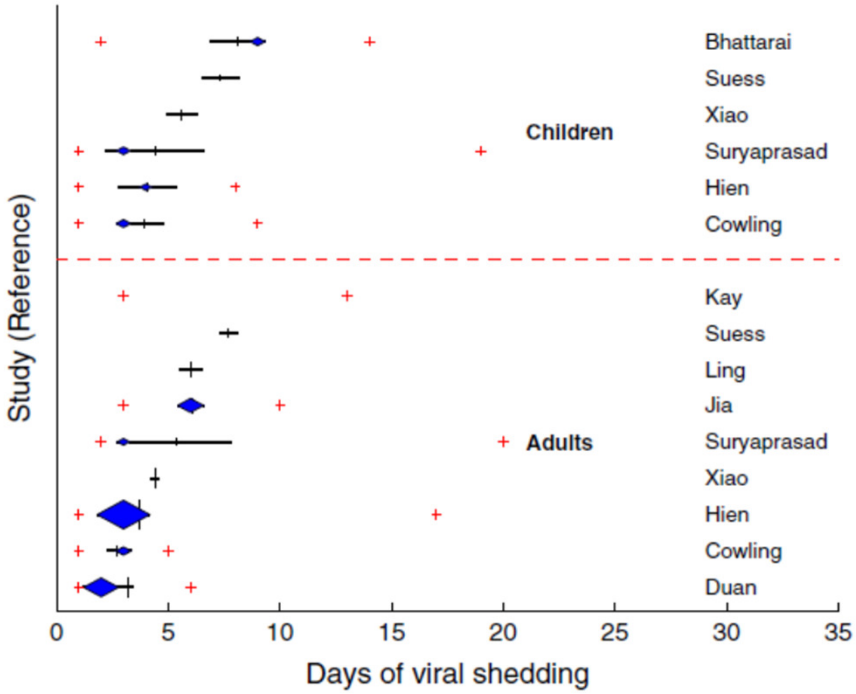


Figure 2. Shedding duration of influenza A(H1N1)pdm09 in studies of community-based cases, by study and age group.

Fielding Influenza and Other Respiratory Viruses 2014

- **Observational studies report highest clinical benefit when antiviral treatment is started as soon as possible in hospitalized influenza patients**
  - Meta-analysis of neuraminidase inhibitor (NAI) treatment for influenza A(H1N1)pdm09 (most received oseltamivir, N = 29,234) reported survival benefit of early compared with later or no treatment
    - **NAI treatment started on the day of admission was associated with a 19% overall reduction in duration of hospitalization** (aIRR, 0.81 [95% CI, 0.78-0.85]; median decrease, 1.19 days [IQR, 0.85–1.55 days]), compared with no or later initiation of NAI treatment
  - One observational study (N = 699) reported that **starting NAI treatment within 6 hours after hospital admission was associated with shorter duration of hospitalization** versus starting antiviral treatment later ($p<0.001$)
- Infectious Diseases Society of America (IDSA) and CDC recommend:
  - **Start oseltamivir treatment for hospitalized patients with suspected influenza as soon as possible without waiting for influenza testing results**

➢ **How can this recommendation be implemented at hospitals?**

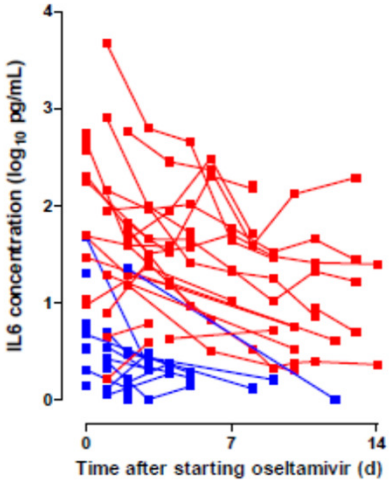
➢ **Protocols with checklists to start antiviral treatment in the Emergency Department**

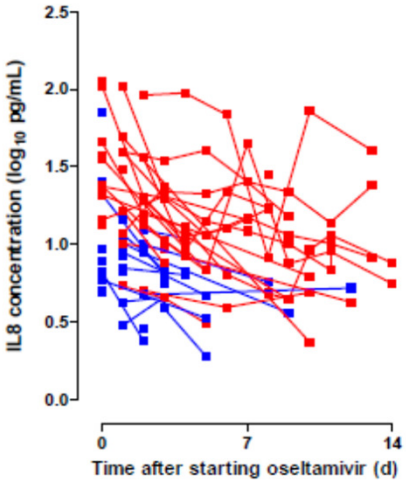
Muthuri Lancet Respiratory Dis 2014; Venkatesan J Infect Dis 2019; Katzen Clinical Infect Dis 2018; Uyeki Clinical Infect Dis 2019

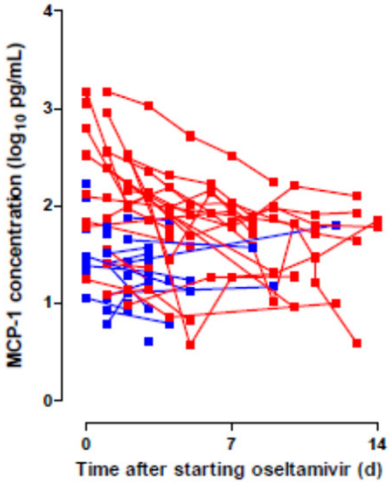
- **Other potential therapies** (virus-targeted)
  - **Convalescent plasma**
    - One case-control study in Hong Kong adults (n = 20) admitted to an intensive care unit within 7 days of influenza illness onset reported that **convalescent plasma treatment** (neutralizing Ab titer ≥160) **had significantly lower mortality** than non-treated controls (n=73) (20% vs. 54.8%, p<0.01), and significantly reduced respiratory tract influenza A(H1N1)pdm09 viral load and IL6, IL10, and TNFα levels (p<0.05)
  - **Hyperimmune IVIG**
    - One Phase III double blinded placebo-controlled RCT in hospitalized adults within 7 days of influenza illness onset reported a single dose of hyperimmune IVIG (n=156) **did not show benefit at Day 7** compared to saline control (OR:1·25, 95% CI 0·79–1·97; p=0·33)
  - **High-titer Immune Plasma**
    - One phase III double blinded placebo-controlled RCT in hospitalized children and adults within 6 days of influenza illness onset reported that high-titer plasma (HAI titer ≥1:80) **did not show clinical benefit at day 7** vs. low-titer plasma (HAI titer ≤1:10) controls (OR: 1.22, 95% CI: 0.65-2.29, p=0.54)
- **Immunotherapy with monoclonal antibodies (mAbs)**
  - No studies to date have shown significant clinical benefit of mAbs for treatment of outpatients versus placebo or for hospitalized patients + oseltamivir vs. oseltamivir alone

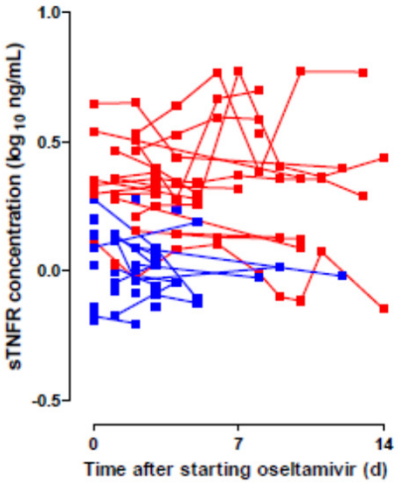
Hung Clin Infect Dis 2011; Davey Lancet Respir Med 2019; Beigel Lancet Respir Med 2019; Beigel Antiviral Res 2019

Proinflammatory Responses are Higher and Longer with Influenza Pneumonia









Lower respiratory tract disease

Upper respiratory tract illness

Lee Antiviral Therapy 2011; Lee CHEST 2010; Lee PLoS ONE 2021

- **Combination Anti-inflammatory and Antiviral Treatment**
  - **Azithromycin + Oseltamivir**
    - One small open-label RCT in hospitalized adults in Hong Kong <5 days of influenza illness onset showed that azithromycin + oseltamivir (n=25) **significantly reduced cytokines** IL-6, CXCL8, IL-17, CXCL9 versus oseltamivir alone (n=25) [trend of reducing CRP]
  - **Clarithromycin + Naproxen (Cox-1 inhibitor NSAID)+ Oseltamivir**
    - One phase IIb/III open-label RCT in hospitalized adults (mainly elderly) in Hong Kong ≤3 days of influenza illness onset reported that **clarithromycin-naproxen-oseltamivir** (n=107) was associated with lower 30-day mortality (0.9% vs. 8.2%) and shorter hospital stay (median 1 vs. 2 days), and was **independently associated with lower 30-day mortality** (OR, 0.06, 95% CI: 0.004-0.94, p=0.04) compared with oseltamivir alone (n=110)
  - **Celecoxib (Cox-2 inhibitor NSAID) + Oseltamivir**
    - One double blind RCT in hospitalized adults in Hong Kong with influenza A(H3N2) virus infection reported celecoxib-oseltamivir (n=60) had **significantly lower 28-day mortality** (p=0.037), lower IL-6 and IL-10 levels (p<0.05), and lower disease progression from day 1 to 3 (p<0.01) vs. oseltamivir (n=60).

Lee Antiviral Therapy 2017; Hung CHEST 2017; Hung Abstract 00815 29th ECCMID Conference 2019

- **Corticosteroids**
  - **Observational studies suggest corticosteroids can prolong influenza virus replication or viral RNA detection**
    - More common with high-dose corticosteroids
  - Meta-analyses of observational studies
    - **Suggest corticosteroids increase mortality and risk of secondary infections, in patients with influenza pneumonia or ARDS**
      - But no differences when adjusted analyses were performed vs. no corticosteroids
      - Some observational studies suggest harm with high-dose, but not lower dose corticosteroids
    - One RCT of prednisone 50mg po x 7 days versus placebo for community-acquired pneumonia in Swiss adults reported no difference in clinical improvement (but very few influenza patients were enrolled: n=11 vs n = 13)

➢ **No well-powered RCTs of corticosteroid treatment of influenza**

Landsbury Crit Care Med 2020; Ni Crit Care 2019; Ye CMAJ 2020; Zhou Sci Reports 2020; Wirz Europ Resp J 2016; Yang Clin Microbiol Infect 2015

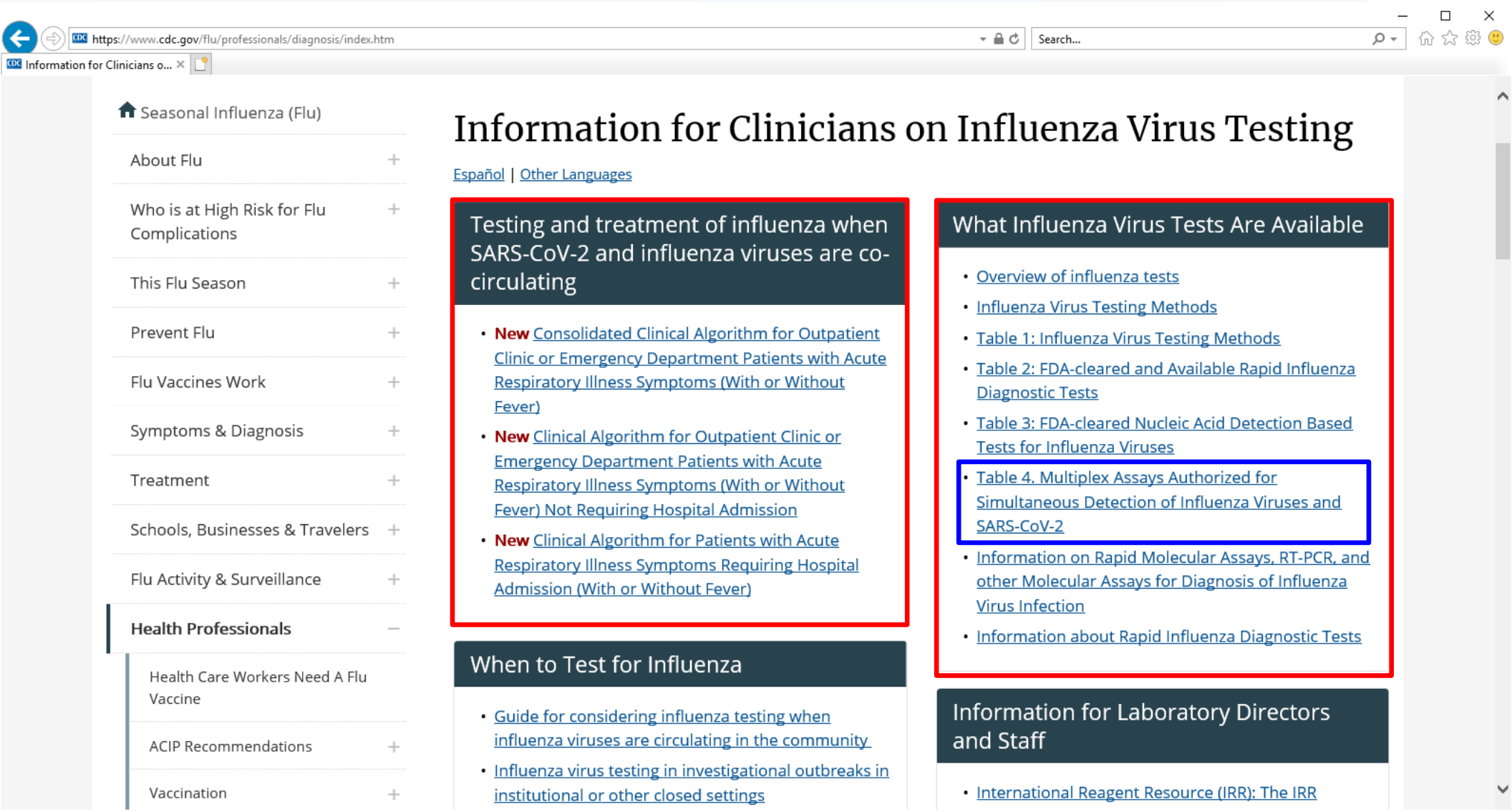
- **Community-acquired bacterial co-infections (e.g. pneumonia) are a well-known complication of influenza**
  - Most common pathogens: *Staphylococcus aureus* (MRSA, MSSA), *Streptococcus pneumoniae*, Group A *Streptococcus*
    - Optimal antibiotic management is a gap, especially for critically ill patients
- Hospital-acquired co-infections are complications in critically ill influenza patients
  - Multi-antibiotic resistant bacterial infections, fungal infections
    - How to prevent or reduce risk?
- Nosocomial influenza virus transmission is always a challenge
  - Transmission from healthcare workers, visitors, other patients
    - How to prevent or reduce risk?

- **Co-infection with influenza A or B viruses and SARS-CoV-2 can occur**
  - Documented in case reports, case series
  - Frequency, severity, and risk factors are unknown
- **Overlapping signs, symptoms, some differences with either infection**
  - Incubation period is shorter with influenza (1-3 days) than COVID-19 (2-14 days)
  - Viral shedding, period of viral RNA detection is generally shorter for influenza
  - Ageusia/dysgeusia, anosmia are more common with COVID-19 than influenza
  - Diarrhea can occur in young children with influenza; at any age with COVID-19
  - Timing of onset of complications/severe disease is earlier with influenza
- High-risk groups for influenza and COVID-19 are similar
  - Young children are at high-risk for influenza complications

Cuadrado-Payan Lancet 2020; Azekawa ID Cases 2020; Ma Int J Infect Dis 2020; Ding J Med Virology 2020; Wu Emerg Inf Dis 2020; Beltran-Corellini Eur J Neurology 2020; Zayet Microbes and Infect 2020

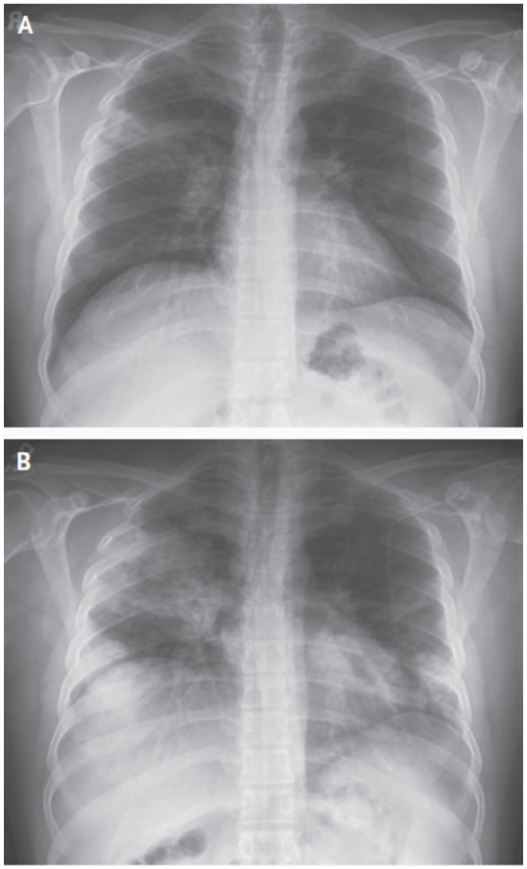
- **Implications**
  - **Testing is needed to distinguish influenza from COVID-19**
    - **Consider influenza virus infection, SARS-CoV-2 infection, co-infection**
  - **Treatment issues**
    - Approved antiviral medications for influenza have no effect on COVID-19
      - Oseltamivir, baloxavir have no in-vitro activity against SARS-CoV-2
        - No drug interactions with remdesivir
    - Corticosteroids may prolong influenza viral replication in the upper and lower respiratory tracts (e.g. dexamethasone treatment of severe COVID-19)
      - Corticosteroids may increase risk of hospital-acquired infection
    - Community-acquired bacterial co-infection appears more common with influenza than COVID-19 (MRSA, MSSA, pneumococcus, group A *Strept*)

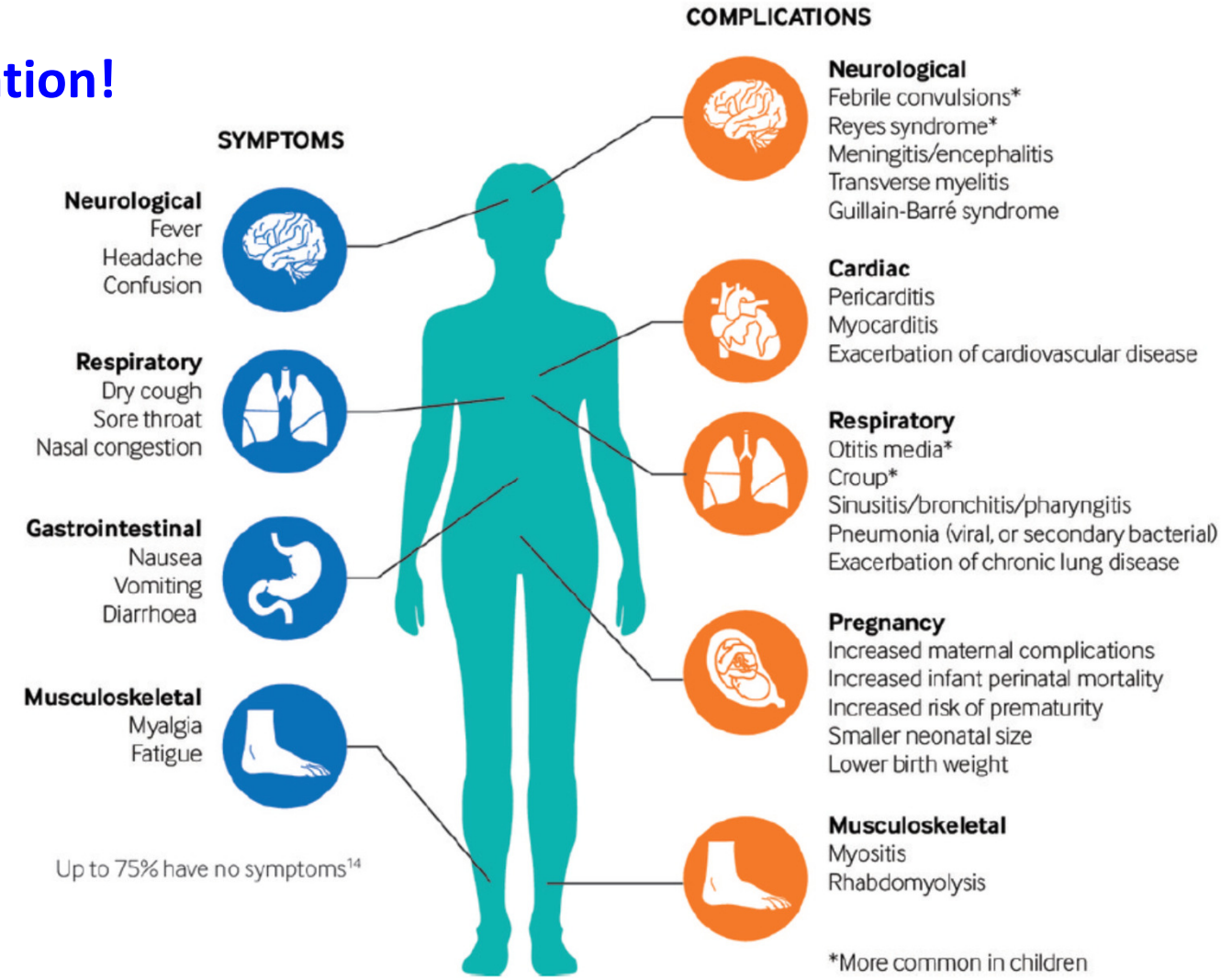
Tan Bioorganic Chem 2020; Choy Antiviral Research 2020; Langford Clin Microbiol Infect 2020; Adler Lancet Microbe 2020; Vaughn Clin Infect Dis 2020; Zhou Sci Reports 2020;Lee Clin Infect Dis 2008; Gianella Clin Microbiol Infect 2010; Lee J Infect Dis 2009


https://www.cdc.gov/flu/professionals/diagnosis/index.htm
Search...
Information for Clinicians o...
Seasonal Influenza (Flu)
About Flu
Who is at High Risk for Flu Complications
This Flu Season
Prevent Flu
Flu Vaccines Work
Symptoms & Diagnosis
Treatment
Schools, Businesses & Travelers
Flu Activity & Surveillance
Health Professionals
Health Care Workers Need A Flu Vaccine
ACIP Recommendations
Vaccination
Information for Clinicians on Influenza Virus Testing
Español | Other Languages
Testing and treatment of influenza when SARS-CoV-2 and influenza viruses are co-circulating
New Consolidated Clinical Algorithm for Outpatient Clinic or Emergency Department Patients with Acute Respiratory Illness Symptoms (With or Without Fever)
New Clinical Algorithm for Outpatient Clinic or Emergency Department Patients with Acute Respiratory Illness Symptoms (With or Without Fever) Not Requiring Hospital Admission
New Clinical Algorithm for Patients with Acute Respiratory Illness Symptoms Requiring Hospital Admission (With or Without Fever)
What Influenza Virus Tests Are Available
Overview of influenza tests
Influenza Virus Testing Methods
Table 1: Influenza Virus Testing Methods
Table 2: FDA-cleared and Available Rapid Influenza Diagnostic Tests
Table 3: FDA-cleared Nucleic Acid Detection Based Tests for Influenza Viruses
Table 4. Multiplex Assays Authorized for Simultaneous Detection of Influenza Viruses and SARS-CoV-2
Information on Rapid Molecular Assays, RT-PCR, and other Molecular Assays for Diagnosis of Influenza Virus Infection
Information about Rapid Influenza Diagnostic Tests
When to Test for Influenza
Guide for considering influenza testing when influenza viruses are circulating in the community
Influenza virus testing in investigational outbreaks in institutional or other closed settings
Information for Laboratory Directors and Staff
International Reagent Resource (IRR): The IRR

- **Conducting Clinical Trials of Interventions to Improve Clinical Management**
  - Although more has been learned about managing COVID-19 patients in 2020 than in many years of influenza clinical research, many key questions remain
  - The biggest challenge is how will randomized clinical trials of new investigational therapeutics, immunomodulators, and other supportive care interventions (e.g. prone positioning, high-flow nasal oxygen, non-invasive ventilation) be implemented?
    - **International platforms for collaborative adaptive clinical trials** (e.g. REMAP CAP)
    - **We need better antivirals, combination antiviral and anti-inflammatory/immunomodulator therapy, RCTs of low-dose corticosteroids**
    - **We need agreement on definitions of disease severity, and endpoints**
  - **We need to start with standardizing clinical management of influenza**

Thank you for your attention!





Uyeki NEJM 2009; Ghebrehewet BMJ 2016