QUESTIONS?

Please contact your rep or our Client Services Team for assistance.
OBJECTIVES

Overview of Upper Respiratory Tract Infections (URTI's)

Discuss unique characteristics of URTI's

Discuss clinical impact of fast and accurate diagnosis of URTI's

SUMMARY

URTI's significantly impact our healthcare system

Clinical presentations are similar while management options vary based on viral or bacterial etiology

Comprehensive, fast and accurate testing is necessary to treat patients more appropriately
OVERVIEW

Overview of Upper Respiratory Tract Infections (URTI's)

Discuss unique characteristics of URTI's

Discuss clinical impact of fast and accurate diagnosis of URTI's

COLLECTION PROCEDURE

• Measure distance from patient’s nostril to nasopharynx. Do not advance swab deeper than the length.
• Gently insert swab along the base of one nostril [straight back, not upwards] and continue along floor of nasal passage until reaching nasopharynx.
• Rotate swab 2-3 times and hold in place for 5 seconds.
• Place swab in tube containing viral transport medium. Break off excess length at score mark to permit capping of tube.
• Perform nasopharyngeal wash/aspirate.

SHIPPING PROCEDURE

• Complete Paradigm Laboratories requisition form.
• Label transport tube with two patient identifiers, date and collection time.
• Please store specimen at room temperature. DO NOT REFRIGERATE.
• Place specimen in FedEx Clinic Pak and send using the provided pre-printed FedEx Air Bills to Paradigm Laboratories.
OVERVIEW

Upper Respiratory Tract Infections

- Symptoms may last up to 14 days with an average of 7 to 11 days1
- False negative results from a respiratory virus can increase the cost of patient care by $2,300 when compared to a true positive2
- 1,026,476 hospitalizations in the US due to upper respiratory tract infections between 1998 and 2006


Increased cost of patient care resulting from false negative results

CMS QUALITY MEASURES

Respiratory changes can lead to many risk factors and impact reportable Outcome-Based Quality Measures

- Symptoms may cause:
  - Fatigue/debility
  - Poor appetite
  - Diarrhea
  - Bowel/urinary incontinence

- Effects on Outcomes:
  - Falls
  - Pressure sores
  - Increased need for ADL assistance
  - Use of catheter

- CMS CASPER:
  - Impact Outcome-Based Quality Measures
### Pathogens

Respiratory tract infections can be the result of one of many viral or bacterial pathogens.

<table>
<thead>
<tr>
<th>Viruses</th>
<th>Bacteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Adenovirus</td>
<td>• Mortadella pertussis</td>
</tr>
<tr>
<td>• Coronavirus HKU1, NL63, 229E, OC43</td>
<td>• Chlamydophila pneumoniae</td>
</tr>
<tr>
<td>• Human Metapneumovirus</td>
<td>• Mycoplasma pneumoniae</td>
</tr>
<tr>
<td>• Human Rhinovirus/Enterovirus</td>
<td></td>
</tr>
<tr>
<td>• Influenza A, A/H1, A/H3, A/H1-2009, B</td>
<td></td>
</tr>
<tr>
<td>• Parainfluenza 1, 2, 3, 4</td>
<td></td>
</tr>
<tr>
<td>• Respiratory Syncytial Virus</td>
<td></td>
</tr>
</tbody>
</table>

Detect a broader range of pathogens, including coinfections

- In a comparison between Multiplex PCR and a leading competitor’s assays, 78.6% of patients tested positive for a respiratory infection by Multiplex PCR compared to 23.4% by the competitor’s assay. This discrepancy was largely attributed to the higher number of targets detected by Multiplex PCR using a single assay versus the competitor’s five assays.

- In 192 patient specimens, Multiplex PCR detected 155 pathogens not included in the competitor’s assays in addition to identifying more coinfections (28 vs 3).

Improve patient isolation and cohorting

- Accurately identifying etiologic agents can inform isolation and cohorting to minimize cross infection.

- In 192 patient specimens, Multiplex PCR detected 155 pathogens not included in the competitor’s assays in addition to identifying more coinfections (28 vs 3). Ruling out infections such as influenza can verify if strict isolation procedures are needed for urgent surgeries.

MULTIPLEX PCR PROVIDES ACCURATE RESULTS TO IMPROVE PATIENT MANAGEMENT

In 192 patient specimens, Multiplex PCR detected 155 pathogens not included in the competitor’s assays in addition to identifying more coinfections (28 vs 3).
SIGNS & SYMPTOMS

Respiratory bacteria and viruses have very similar symptoms but are treated differently.

Unfortunately, no amount of antibiotics will get rid of your cold. The best way to treat most colds, coughs or sore throats is plenty of fluids and rest. For more advice talk to your doctor or pharmacist.

<table>
<thead>
<tr>
<th>Pathogen</th>
<th>Sensitivity</th>
<th>Specificity</th>
<th>Prospective</th>
<th>Retrospective</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adenovirus</td>
<td>98.9%</td>
<td>100.0%</td>
<td>98.9%</td>
<td></td>
</tr>
<tr>
<td>Coronavirus HKU1</td>
<td>95.6%</td>
<td>n/a</td>
<td>99.9%</td>
<td></td>
</tr>
<tr>
<td>Coronavirus NL63</td>
<td>95.6%</td>
<td>n/a</td>
<td>100.0%</td>
<td></td>
</tr>
<tr>
<td>Coronavirus 229E</td>
<td>100.0%</td>
<td>100.0%</td>
<td>99.9%</td>
<td></td>
</tr>
<tr>
<td>Coronavirus 043</td>
<td>94.8%</td>
<td>n/a</td>
<td>99.5%</td>
<td></td>
</tr>
<tr>
<td>Human metapneumovirus</td>
<td>71.7%</td>
<td>n/a</td>
<td>96.8%</td>
<td></td>
</tr>
<tr>
<td>Human rhinovirus/enterovirus</td>
<td>71.7%</td>
<td>n/a</td>
<td>96.8%</td>
<td></td>
</tr>
<tr>
<td>Influenza A</td>
<td>100.0%</td>
<td>100.0%</td>
<td>99.9%</td>
<td></td>
</tr>
<tr>
<td>Influenza A H1</td>
<td>n/a</td>
<td>100.0%</td>
<td>100.0%</td>
<td></td>
</tr>
<tr>
<td>Influenza A H3</td>
<td>n/a</td>
<td>100.0%</td>
<td>100.0%</td>
<td></td>
</tr>
<tr>
<td>Influenza A H1-2009</td>
<td>88.9%*</td>
<td>100.0%</td>
<td>99.9%</td>
<td></td>
</tr>
<tr>
<td>Influenza B</td>
<td>n/a</td>
<td>100.0%</td>
<td>100.0%</td>
<td></td>
</tr>
<tr>
<td>Parainfluenza virus 1</td>
<td>100% *</td>
<td>97.1%</td>
<td>99.9%</td>
<td></td>
</tr>
<tr>
<td>Parainfluenza virus 2</td>
<td>87.4%*</td>
<td>100.0%</td>
<td>99.9%</td>
<td></td>
</tr>
<tr>
<td>Parainfluenza virus 3</td>
<td>95.6%</td>
<td>100.0%</td>
<td>99.9%</td>
<td></td>
</tr>
<tr>
<td>Parainfluenza virus 4</td>
<td>100% *</td>
<td>100.0%</td>
<td>99.9%</td>
<td></td>
</tr>
<tr>
<td>Respiratory syncytial virus</td>
<td>100.0%</td>
<td>n/a</td>
<td>89.1%</td>
<td></td>
</tr>
<tr>
<td>Bordetella pertussis</td>
<td>100% *</td>
<td>94.6%</td>
<td>99.9%</td>
<td></td>
</tr>
<tr>
<td>Chlamydophila pneumoniae</td>
<td>100% *</td>
<td>100% †</td>
<td>100.0%</td>
<td></td>
</tr>
<tr>
<td>Mycoplasma pneumoniae</td>
<td>100% *</td>
<td>94.4%</td>
<td>100.0%</td>
<td></td>
</tr>
</tbody>
</table>

* Due to low prevalence in the prospective study, clinical sensitivity for these pathogens was based on less than 10 positive samples. † Spiked Chlamydophila pneumoniae samples were used to test retrospective sensitivity.

Multiplex PCR Respiratory Panel [instruction booklet]. Dallas, Texas: Trilogy Diagnostics; 2012: p. 3.
WHAT DOES THE MULTIPLEX PCR RESPIRATORY PANEL TEST FOR?

Detect 20 upper respiratory tract pathogens, including those responsible for influenza, the common cold and whooping cough

**DETECT 17 VIRUSES**
- Human rhinovirus/enterovirus
- Adenovirus
- Coronavirus (HKU1, NL63, 229E, OC43)
- Parainfluenza (1, 2, 3, 4)
- Human metapneumovirus
- Respiratory syncytial virus

**DETECTS 3 BACTERIA**
- Chlamydophila pneumoniae
- Mycoplasma pneumoniae
- Mortadella pertussis


SIGNS & SYMPTOMS

Coughing
Nasal Discharge
Congestion
Wheezing
Fever
Headache
Myalgia
Fatigue/debility
Poor appetite
Diarrhea
UNIQUE CHARACTERISTICS OF UPPER RESPIRATORY TRACT INFECTIONS

MULTIPLEX PCR: A COMPREHENSIVE TEST THAT PROVIDES FAST AND ACCURATE RESULTS

- Fast\(^1,2\)
- Accurate\(^1\)
- Comprehensive\(^1\)

DFA=direct fluorescent antibody; RT PCR=reverse transcriptase polymerase chain reaction.

Multiple PCR is the best option for fast, accurate and comprehensive results.
ADENOVIRUS

Highest incidence: late summer to early winter

Affected demographic: all ages, immunocompromised

Non-enveloped DNA viruses with seven species (A to G)

Categorized by hemagglutination and approximately 55 serotypes

Adenovirus species B, C, and E cause acute respiratory disease

Outbreaks occur in institutional settings (e.g. military training, long-term care facilities and pediatric tertiary-care hospitals)

Shed for long periods of time and persists on surfaces in an infective state

1. Multiplex RIB Respiratory Panel [Instruction booklet]. Dallas, Texas: Trilogy Diagnostics; 2012: p. 4

A FAST AND ACCURATE DIAGNOSIS CAN REDUCE MISUSE OF ANTIBIOTICS

Death rate for patients with ARIs was two-fold higher than for those without ARIs

The misuse of antibiotics costs the US healthcare system over $20 billion each year

US households lost approximately $35 billion in 2000 to antibiotic-resistant infections, including lost wages, extended hospital stays and premature deaths

Delayed treatment of influenza can result in complications including pneumonia and exacerbations of underlying pulmonary and cardiac disease

From 2008 to 2013, death rates due to influenza and pneumonia exceeded the epidemic threshold multiple times

Annual cost of antibiotic misuse in the U.S.

$20 bil

Number of species/serotypes

7/55

From 2008 to 2013, death rates due to influenza and pneumonia exceeded the epidemic threshold multiple times

†From 2008 to 2013, death rates due to influenza and pneumonia exceeded the epidemic threshold multiple times

CORONAVIRUS

• Highest incidence: winter and spring¹
• Affected demographic: children and adults¹
• First isolated in the 1960’s²
• Most common coronaviruses that infect people include variants 229E, OC43, HKU1, NL63⁴⁻⁶
• Associated with croup and exacerbation of asthma²⁻⁶
• Outbreaks occur in institutional settings (e.g. military training, long-term care facilities and pediatric tertiary-care hospitals) ²⁻⁴
• Periodicity of epidemics for strains 229E and OC43: 2-3 years²

1. Multiplex PCR Respiratory Panel [instruction booklet]. Dallas, Texas: Trilogy Diagnostics; 2012: p. 4

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A FAST AND ACCURATE DIAGNOSIS CAN REDUCE MISUSE OF ANTIBIOTICS

According to the Institute of Medicine, antibiotic resistance is one of the key microbial threats to health in the US

Implications of Antibiotic Resistance

• Increase mortality and morbidity from untreatable diseases
• Increases risk of global spread of pathogens
• Results in longer, more frequent hospital stays
• Limits drug options at a time when pharmaceutical companies are developing fewer antimicrobials
• Increases cost of research for new drugs

A FAST AND ACCURATE DIAGNOSIS CAN REDUCE MISUSE OF ANTIBIOTICS

• Each year, over 10,000,000 courses of antibiotics are prescribed for viral conditions¹
• An estimated 55% of antibiotic prescriptions for ARTIs are unnecessary²
• 63% of all patients with an ARTI received an antibiotic, including 29% who received a narrow-spectrum agent and 34% who received a broad-spectrum agent²

Estimated percentage of unnecessary antibiotics prescribed for ARTIs

55%

HUMAN RHINOVIRUS/ENTEROVIRUS

• Highest incidence: fall and spring¹
• Affected demographic: all ages³
• Human rhinovirus and enterovirus are genetically similar and hard to differentiate²
• 100 known serotypes of rhinovirus²
• 89 serotypes of enterovirus³
• Rhinovirus known for causing the common cold²


ARTI=acute respiratory tract infection; URTI=upper respiratory tract infection.

A FAST AND ACCURATE DIAGNOSIS CAN REDUCE MISUSE OF ANTIBIOTICS

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ARTI=acute respiratory tract infection; URTI=upper respiratory tract infection.

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A FAST AND ACCURATE DIAGNOSIS CAN REDUCE MISUSE OF ANTIBIOTICS

ARTI=acute respiratory tract infection; URTI=upper respiratory tract infection.
HUMAN METAPNEUMOVIRUS

• Highest incidence: fall and spring
• Affected demographic: all ages
• Discovered in 2001
• Common cause of bronchiolitis in infants and young children
• Two genotypes [A and B] do not differ in severity of illness

Discovered in 2001

A FAST AND ACCURATE DIAGNOSIS CAN REDUCE MISUSE OF ANTIBIOTICS

An accurate diagnosis reduces overprescribing of antibiotics and prevents antibiotic resistance

Antibiotic Prescriptions for Adults with Nonpneumonic Acute Respiratory Tract Infections, by Diagnosis

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>Narrow-Spectrum Antibiotics</th>
<th>Broad-Spectrum Antibiotics</th>
</tr>
</thead>
<tbody>
<tr>
<td>Common Cold &amp; URTI (n=473)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sinusitis (n=478)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Otitis Media (n=110)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Acute Bronchitis (n=432)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Other URTI (n=219)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&gt;1 ARTI (n=269)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Overall (ARTI n=1981)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

% of Patient Visits

<table>
<thead>
<tr>
<th>0</th>
<th>35</th>
<th>70</th>
<th>105</th>
<th>140</th>
</tr>
</thead>
<tbody>
<tr>
<td>12</td>
<td>29</td>
<td>12</td>
<td>29</td>
<td>12</td>
</tr>
</tbody>
</table>

1. Multiplex PCR Respiratory Panel [Instruction booklet]. Dallas, Texas: Trilogy Diagnostics; 2012: p. 4

ARTI=acute respiratory infection; URTI=upper respiratory tract infection.
CASE 3: JESSICA D.

Jessica D is a singer. She has an important performance coming up but has not been feeling well for the last two days and requests to be put on antibiotics.

- Age 33
- Chief complaint:
  - Severe congestion
  - Runny nose
  - Sore throat
  - Temperature 98°F
- History of present illness:
  - Symptoms started 2 days ago, starting with a runny nose then progressed into sinus congestion and loss of voice, secretions clear, no thick or colored mucus

How would you approach diagnostic testing in this patient? What advantages would a fast, accurate diagnosis provide?

INFLUENZA A & B

- Highest incidence: winter
- Affected demographic: all ages
- Dominant type varies annually due to antigenic shift and drift
- 5-20% of the population effected during flu season
- Increased mortality when coupled with viral or bacterial pneumonia complications
- 4 antiviral medications available (amantadine, rimantadine, zanamivir and oseltamivir)

1. Multiplex PCR Respiratory Panel [instruction booklet]. Dallas, Texas: Trilogy Diagnostics; 2012: p. 4
PROPORTIONS OF INFLUENZA SUBTYPE INFECTIONS IN U.S.

Table 2. Proportions of influenza subtype infections in the U.S. (as reported by CDC)

<table>
<thead>
<tr>
<th>FLU SEASON</th>
<th>INFLUENZA</th>
<th>% OF INFLUENZA A</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>H1</td>
<td>H1N1</td>
</tr>
<tr>
<td>2013-2014</td>
<td>85%</td>
<td>0%</td>
</tr>
<tr>
<td>2012-2013</td>
<td>70%</td>
<td>0%</td>
</tr>
<tr>
<td>2011-2012</td>
<td>86%</td>
<td>0%</td>
</tr>
<tr>
<td>2010-2011</td>
<td>74%</td>
<td>0%</td>
</tr>
<tr>
<td>2009-2010</td>
<td>99%</td>
<td>1%</td>
</tr>
<tr>
<td>2008-2009</td>
<td>89%</td>
<td>13%</td>
</tr>
<tr>
<td>2007-2008</td>
<td>71%</td>
<td>28%</td>
</tr>
<tr>
<td>2006-2007</td>
<td>79%</td>
<td>62%</td>
</tr>
<tr>
<td>2005-2006</td>
<td>82%</td>
<td>8%</td>
</tr>
</tbody>
</table>

A FAST AND ACCURATE DIAGNOSIS CAN IMPROVE CARE FOR ELDERLY PATIENTS

Respiratory infections, such as RSV, HMPV, and influenza are difficult to differentiate in older adults due to similar clinical presentations and seasonal patterns.

**TIMELINESS**
Timely antiviral treatment can improve patient outcomes and reduce mortality
Early use of antivirals is associated with rapid viral clearance, fewer symptoms, reduced progression to pneumonia and reduced mortality.

**ACCURACY**
Sensitivity of rapid tests and viral culture is lower among older patients.
Accurate diagnostic tests are required to verify illnesses that cannot be confirmed by symptoms or current tests.


HMPV=human metapneumovirus; RSV=respiratory syncytial virus.
CASE 2: VICTOR H.

Victor is brought into the ER by his niece. She explains that he has been disoriented and has eaten very little over the past 2 days.

- Age 66
- Symptoms:
  - Cough
  - Diarrhea
  - Temperature 98.8 F
- Medications:
  - Oral diabetic treatment
  - Antihypertensive agent

How would you approach diagnostic testing in this patient? What advantages would a fast, accurate diagnosis provide?

PARAINFLUENZA VIRUSES

- Highest incidence: fall, spring and summer¹
- Affected demographic: infants, young children, immunocompromised; all ages for PIV4¹
- Differentiated from influenza in 1950’s²
- 4 subtypes PIV 1-4
- Periodic epidemics of 1 to 2 years alternating between PIV 1 and 2²
- Half of all croup cases are caused by PIV 1 with epidemics occurring in the fall²
- Outbreaks of PIV 3 in neonatal ICU’s with epidemics occurring in spring and summer²

1. Multiplex PCR Respiratory Panel [Instruction booklet]. Dallas, Texas: Trilogy Diagnostics; 2012: p. 4-5
RESPIRATORY SYNCYTIAL VIRUS

- Highest incidence: winter
- Affected demographic: children, young adults
- Number one cause of severe respiratory disease among infants
- Acute bronchiolitis is a major cause of hospitalization
- Treatment with monoclonal antibody against fusion protein shown to reduce risk in infants


UNMET NEEDS IN DIAGNOSING AND TREATING RESPIRATORY INFECTIONS

Uncertain diagnosis is one of the primary reasons that physicians do not prescribe antivirals

**TIMELINESS**

Influenza treatment should be initiated within 48 hours after symptom onset.

Timely treatment is associated with shorter hospitalizations among critically ill children, faster resolution of illness, less parental work absenteeism and reduced risk of developing otitis media


**ACCURACY**

The choice of influenza antiviral may depend on the viral subtype

Accurate diagnosis of the influenza subtype can inform treatment decisions

CASE 1: ERIN M.

It is mid-October. Erin presents to the ER with a fever and general body aches. Her mother tells you that she has not yet received a flu vaccine.

- Age 3
- Chief complaint:
  - Low energy
  - Dry coughs
  - Body aches
  - Temperature 100.3 F
- History of present illness:
  - Symptoms started 1 day ago, started with minor body aches then progressed into fever and coughs
- Other information: recent URTI outbreaks at daycare

How would you approach diagnostic testing in this patient? What advantages would a fast, accurate diagnosis provide?

BORTADELLA PERTUSSIS

- Highest incidence: no peak season
- Affected demographic: all ages
- Commonly known as “whooping cough”**
- Vaccine-induced immunity shown to decrease after 5-10 years
- Variable symptoms manifesting “2 weeks after initial onset”
- Treatable with several antibiotics
- Nationally reportable to public health organizations**

---

**CHLAMYDOPHILA PNEUMONIAE**

- Highest incidence: winter
- Affected demographic: older children, young adults, immunocompromised
- Common cause of community acquired atypical pneumonia
- Outbreaks in schools, military barracks and nursing homes

**Outbreaks in schools, military barracks & nursing homes**

**MOLECULAR DIAGNOSTIC OPTIONS MAKE CLINICIANS CHOOSE BETWEEN SPEED AND ACCURACY**

<table>
<thead>
<tr>
<th>Test Type</th>
<th>Speed/ Turnaround time, hands-on time</th>
<th>Accuracy/ Sensitivity/ Specificity</th>
<th>Comprehensive</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rapid Test DFA</td>
<td>Fast 1, 2</td>
<td>Accurate 1</td>
<td>Simultaneously identifies multiple pathogens</td>
</tr>
<tr>
<td>Viral Culture</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Molecular Tests (RT-PCR)</td>
<td>Fast 1, 2</td>
<td>Accurate 1</td>
<td></td>
</tr>
</tbody>
</table>

Molecular tests currently provide the best option for timeliness, comprehensiveness and accuracy.

**Notes:**


**References:**


**DFA=direct fluorescent antibody; RT-PCR=reverse transcriptase polymerase chain reaction.**
MYCOPLASMA PNEUMONIAE

- Highest incidence: summer¹
- Affected demographic: older children and young adults¹
- Periodic outbreaks every 3-7 years²
- Common cause of community acquired atypical pneumonia³,⁴
- Incubation time approximately 1-4 weeks⁴

CLINICAL IMPACT - FAST & ACCURATE DIAGNOSIS OF UPPER RESPIRATORY TRACT INFECTIONS

WHY PROPER DIAGNOSIS IS IMPORTANT

Accurate and fast diagnosis may:
• Improve patient management
• Prevent secondary spread of infection
• Prevent the use of unnecessary antibiotics
• Reduce costs of unnecessary tests
• Provide more timely and effective treatment
• Shorten hospital stays