New Respiratory Viruses
What are we missing?

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Objectives
• List at least three respiratory viruses discovered in the 21st century
• Describe the general approach to discovering new viruses
• Summarize the studies that associate new viruses with respiratory illness
• Describe the situations in which you should suspect MERS
• List antiviral therapies available to treat respiratory viruses
Common Viral Respiratory Tract Infections

- URI
- Croup
- Bronchitis
- Bronchiolitis
- Pneumonia

- 12-32 million episodes of URI affecting 4 million children in U.S. annually
- $40 billion economic impact

Common Respiratory Viruses in Children

- Rhinoviruses
- Respiratory syncytial virus (RSV)
- Adenovirus
- Influenza A and B
- Parainfluenza viruses (PIV)

The new kids on the block

- Influenza H5N1 (bird flu) 1997
- Metapneumovirus (MPV) 2001
- SARS-CoV 2003
- Corona NL63 2004
- Corona HKU1 2005
- Human Bocavirus (HBoV) 2005
- polyomaviruses KI, WU 2007
- Influenza pH1N1 2009
- MERS 2012
- Influenza H7N9 2013
- HRVs QPM, NAT-001, NAT-045...
- Others
New methods for detecting infectious agents

- Consensus primer PCR
- Cloning and immunoscreening
- Random cloning and sequencing
- Representational difference analysis (RDA)
- Sequence independent single primer amplification (SISPA)

Ambrose and Clewley 2006, Rev Clin Micro 16:365-83

Agents identified by new molecular methods

- Parvovirus B19
- Hepatitis C
- Hepatitis E
- Rotavirus
- Astrovirus
- Norwalk virus
- HHV6

How will you find them?

Multiplex respiratory virus PCR testing

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Respiratory Virus</th>
<th>Upper Respiratory</th>
<th>Lower Respiratory</th>
<th>Other Respiratory</th>
<th>Upper vs. Lower</th>
</tr>
</thead>
<tbody>
<tr>
<td>Test System</td>
<td>Laboratory</td>
<td>Laboratory</td>
<td>Laboratory</td>
<td>Laboratory</td>
<td>Laboratory</td>
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<tr>
<td>Time required for result</td>
<td>5.6</td>
<td>3.5–5.9</td>
<td>15.3</td>
<td>5.8</td>
<td>8.0</td>
</tr>
<tr>
<td>Readout</td>
<td>Moderate</td>
<td>Moderate</td>
<td>Moderate</td>
<td>Low</td>
<td>Moderate</td>
</tr>
<tr>
<td>Interpretation</td>
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<td>laboratorian</td>
<td>laboratorian</td>
<td>laboratorian</td>
<td>laboratorian</td>
</tr>
</tbody>
</table>

* These data reflect the state of technology as of October 2006; manufacturers may offer their test systems in the future


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How do they relate?

- URI
- Croup
- Bronchitis
- Bronchiolitis
- Pneumonia
- Rhinoviruses
- Respiratory syncytial virus
- Adenovirus
- Influenza A and B
- Parainfluenza viruses
- Metapneumovirus
- Coronavirus
- Human Bocavirus
- MERS
- Others

Modern Koch's Postulates

- Purported agent should belong to a class of organisms known to cause similar disease
- High correlation between a disease process and both the detection and the level of the organism
- Epidemiologic studies that support a role for the agent as a cause of the syndrome
- Immune responses to indicate recent exposure to the agent correlate with disease
- Detection of the organism in the tissues affected by the disease and not in other tissues

Adapted from Fredericks and Relman, Clin Micro Rev 1996;9:18-33
Metapneumovirus

- In Paramyxoviridae/Pneumovirinae subfamily and the Metapneumovirus genus based on nucleic acid similarities
- Turkey rhinotracheitis virus was the only previous member of the Metapneumovirus genus
- RSV is pneumovirus
- There are pneumoviruses of cows, sheep, and mice

Van den Hoogen, Nat Med 2001; 7:719-724

Coronaviruses

- Corona viruses in animals and birds cause respiratory disease
- Corona viruses isolated from upper respiratory tract in 1960’s
- Corona (OC43, 229E) virus pneumonia described in infants, military recruits, elderly in 1970’s
- SARS caused by a coronavirus
- MERS is a coronavirus

What is a Bocavirus?

- Related to Bovine parvovirus and Canine minute virus (Parvoviridae, genus Bocavirus)
- Small, single-stranded DNA virus
- Entire genome approximately 5,000 nucleotides
- Animal Bocaviruses infect respiratory and GI epithelium and lymphatic system

Brieu N, J Clin Micro 2007;45:3419-20
Allendar T et al, PNAS 2005;102:12891-6
Modern Koch’s Postulates

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Metapneumovirus

- Associated with URI and LRI, particularly bronchiolitis
- Infects all ages, but very common in young children
- Causes exacerbations of asthma and COPD
- Otitis media in 60% of HMPV infected children under 3 years of age.

Sloots T, J Clin Micro 2008; 42:233-43
Heikkinen T, Emerg Infect Dis 2008; 14:101-106

Metapneumovirus

<table>
<thead>
<tr>
<th>Table 1: Clinical Features of 61 Children with Human Metapneumovirus Infection of the Lower Respiratory Tract.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Feature</td>
</tr>
<tr>
<td>--------------------</td>
</tr>
<tr>
<td>Cough</td>
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<tr>
<td>Cough</td>
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<tr>
<td>Sputum</td>
</tr>
<tr>
<td>Cough</td>
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<tr>
<td>Abdominal pain</td>
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<tr>
<td>Tachypnea</td>
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<tr>
<td>Diaphoresis</td>
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<tr>
<td>Vomiting</td>
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<tr>
<td>Nausea</td>
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<tr>
<td>Abdominal distention</td>
</tr>
<tr>
<td>Anorexia</td>
</tr>
<tr>
<td>Diaphoresis</td>
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<tr>
<td>Diaphoresis</td>
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<tr>
<td>Abdominal distention</td>
</tr>
<tr>
<td>Abdominal distention</td>
</tr>
<tr>
<td>Anorexia</td>
</tr>
<tr>
<td>Diaphoresis</td>
</tr>
</tbody>
</table>


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Metapneumovirus

Coronaviruses - SARS

- Pandemic in 2003 - initial spread linked to a professor of nephrology who traveled from Guangzhou to Hong Kong
- 8000 cases with 10% mortality rate
- Significant nosocomial outbreaks
- 36 different corona viruses

- What happened to SARS?!!

Coronaviruses

- NL63 and HKU1 detected in 1-10% of people with respiratory tract disease
- Co-infections with other respiratory viruses described in up to 50% of patients

Van der Hoek L, FEMS Microbiol Rev 2006; 30:760-73
MERS-CoV

• First described in 2012 as a cause of severe community acquired pneumonia
• Sporadic cases and asymptomatic infections have continued to occur in the Arabian Peninsula
• As of May 16, 2014 there have been 572 confirmed cases of which 173 have been fatal
• Healthcare workers account for 19% of cases
• People get on planes in the Arabian Peninsula and take MERS with them


Where did MERS come from?

There are 7,000,000 camels in Somalia

MERS-Clinical Aspects

• Causes both upper and lower respiratory tract infection
• Frequently preceded by GI symptoms (nausea, vomiting, and diarrhea)
• Accompanied by renal failure in severe cases
• Incubation period 5 days (3-12 days)


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MERS-Who and how to test

- Patients with fever and pneumonia or ARDS picture
- Recent (14 days) travel to the Arabian peninsula or contact with somebody who travelled there
- An RT-PCR is available through state health departments
- Samples-NP swab, sputum, tracheal aspirate, BAL, blood, stool
- Serologic testing also available and primarily of value in cases with symptoms of more than 14 days

Suspected MERS patient-
Where do I put them?

- Airborne precautions (like TB, measles, varicella)
  - N-95 masks
  - Gowns, gloves, eye protection
- Patient should wear a face mask when airborne isolation not possible
- Home isolation for people not sick enough for hospital

Bocavirus Infections
San Diego Experience

- Retrospective analysis of samples from 1354 children, ages 0-18 years
- Nasal scraping samples submitted for diagnostic testing for respiratory viruses
- Samples without cellular elements rejected
- Duplicate positive samples from the same patient within one month not included

Arnold JC et al, Pediatrics 2007;121:e631-e637

Distribution of Viral Pathogens

- RSV 41%
- HBoV 20.7%
- Adenovirus 19.6%
- MPV 18.1%
- Parainfluenza 8%
- Influenza 4%

Arnold JC et al, Pediatrics 2007;121:e631-e637

Clinical Characteristics

Arnold JC et al, Pediatrics 2007;121:e631-e637

Linder J, Intervirology 2008
Is coinfection required for Bocavirus to cause disease?

- 26%
- 83-90%
- 95%
- 16.1%

- Arnold et al
- Fry et al
- Allander et al
- Bonzel

- Bocavirus may require co-infection for helper functions of other viruses
- Bocavirus may only replicate well in rapidly replicating cells stimulated by other viruses


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Human Metapneumovirus

- Coinfection with RSV more likely to lead to ICU care than infection with either virus alone
- Low rate of detection in asymptomatic children

- Van den Hoogen 0/400
- Williams 1/86

Table 1: Prevalence of HRV infections in human populations by age group

<table>
<thead>
<tr>
<th>Age group</th>
<th>Infection rate (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0-1 year</td>
<td>4.3</td>
</tr>
<tr>
<td>1-2 years</td>
<td>5.2</td>
</tr>
<tr>
<td>3-5 years</td>
<td>11.9</td>
</tr>
<tr>
<td>6-12 years</td>
<td>12</td>
</tr>
<tr>
<td>&gt;12 years</td>
<td>12</td>
</tr>
</tbody>
</table>

King, L, Clin Micro 2004;42:141-55

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Coronaviruses

- Detected in 1-10% of people with acute respiratory tract infection
- Viral shedding for 3 weeks or longer
- Croup 6-fold more likely in in NL63-positive children than in NL63-negative children

Bocavirus in asymptomatic children

- 0/96 (0%) children < 2 years of age
  (Kesaler O, J Infect Dis 2006: 194:1276-82)
- 0/68 (0%) children < 5 years of age
  (Brieu N, Pediatr Infect Dis J, 2008)
- 3/280 (1%) hospitalized control children
  (Fry et al, J Infect Dis 2007)
- 13/152 (8.6%) children <1 year of age
- 43/100 (43%) children <4 years of age
  (Longtin J et al, Emerging Infect Dis 2008:14:217)

Is Bocavirus causing respiratory disease?

- Evaluation of 1171 hospitalized patients in Thailand with pneumonia
- HBoV detected in 4.5% of patients with pneumonia (83% < 5 years of age)
- HBoV detected in only 1% of 280 age- and season-matched controls
- Coinfection with common respiratory viruses found in 83% of patients
- 4x increased risk of pneumonia in HBoV coinfected patients but not in those only infected with HBoV
  (Fry et al, J Infect Dis, 2007;195:1038-45)
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Adapted from Fredericks and Relman, Clin Micro Rev 1996;9:18-33

HMPV

- 90% seroprevalence by 5 years of age

Wolf D, J Infect Dis 2003;188:1865-67

Bocavirus Seroeprevalence

<table>
<thead>
<tr>
<th>Age Group</th>
<th>No. of samples with antibody against HMPV</th>
<th>No. of samples with antibody against Bocavirus</th>
<th>% Prevalence</th>
</tr>
</thead>
<tbody>
<tr>
<td>0-4 mo</td>
<td>15</td>
<td>5</td>
<td>57.19%</td>
</tr>
<tr>
<td>5-9 mo</td>
<td>15</td>
<td>5</td>
<td>57.14%</td>
</tr>
<tr>
<td>10-14 mo</td>
<td>15</td>
<td>5</td>
<td>57.14%</td>
</tr>
<tr>
<td>15-19 mo</td>
<td>15</td>
<td>5</td>
<td>57.14%</td>
</tr>
<tr>
<td>20-24 mo</td>
<td>15</td>
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<td>25-29 mo</td>
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<tr>
<td>30-34 mo</td>
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<td>35-39 mo</td>
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<td>40-44 mo</td>
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<td>45-49 mo</td>
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<td>50-54 mo</td>
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<tr>
<td>55-59 mo</td>
<td>15</td>
<td>5</td>
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<tr>
<td>60-64 mo</td>
<td>15</td>
<td>5</td>
<td>57.14%</td>
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<tr>
<td>65-69 mo</td>
<td>15</td>
<td>5</td>
<td>57.14%</td>
</tr>
<tr>
<td>70+ mo</td>
<td>15</td>
<td>5</td>
<td>57.14%</td>
</tr>
<tr>
<td>Total</td>
<td>225</td>
<td>50</td>
<td>76.40%</td>
</tr>
</tbody>
</table>

Endo R, J Clin Micro 2007;45:3121-3223

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Others

- Polyoma viruses KIV, WUV
- Found in 1-3% of samples from patients with respiratory tract disease
- Co-infection in as many as 70%
- Found in a similar percentage of asymptomatic controls
- Rhinoviruses
- Hendra and Nipah virus
- Mimivirus

Can I treat these?- antiviral therapy

- Well established for influenza
- Cidofovir/Brincidofovir (CMX001) used to treat adenovirus infections in transplant patients
- Ribavirin/steroids +/- lopinavir/ritonavir used for SARS
- Ribavirin interferon for SARS and MERS
- Nitazoxanide for MERS (induces interferon)
- Convalescent plasma or monoclonal antibodies for SARS/MERS
- Oral, IV, aerosolized ribavirin for RSV in immunocompromised patients
- Monoclonal antibody and siRNA for RSV
- Ribavirin for parainfluenza
- DAS181 sialidase for parainfluenza and influenza

Some Remaining Questions

- Are all of these new viruses really a pathogens?
- How often are these new viruses detected in adults with respiratory disease or in healthy individuals?
- What is the role of co-infection?
- What else is out there?