

STATE-OF-THE-ART DIAGNOSTICS FOR RESPIRATORY INFECTIONS

Epidemiology & Burden

Pneumonia is an infection of the lungs that can be caused by viruses, bacteria, and fungi. It is the leading infectious cause of death in children younger than 5 years old worldwide. In 2010, there were 120 million episodes of pneumonia (14 million of which progressed to severe episodes) in children younger than 5 years. Global Pneumonia mortality was estimated to be 1.575 million.

Seasonal variability can be classified into at least three groups:

- The majority of pathogens (CoVs, Flu A, Flu B, hMPV, the PIVs, and RSV) follow the classical “respiratory” season (Oct-Mar) and increase by more than 10-fold above their baseline detection rate except PIV3 which peaks in the summer months, and has a winter peak that is only detected regionally.
- HRV/EV is detected in a high percentage of tests over time, (minimum of 10% in winter) and experiences moderate peaks of two to three fold outside the respiratory season baseline, in the early fall and spring.
- The bacteria and adenovirus are present at a relatively constant rate throughout the year.

Table 1: The major causes of pneumonia. Source: Adapted from WHO fact sheet 2016.

Major causes	Pneumonia	Atypical Pneumonia
Bacterial	<i>Streptococcus pneumoniae</i> , <i>Haemophilus influenzae</i> , and <i>Moraxella catarrhalis</i> .	<i>Mycoplasma pneumoniae</i> , <i>Chlamydia spp</i> , <i>Legionella</i> , <i>Coxiella burnetii</i>
Viral	adenoviruses, respiratory syncytial virus, Coronaviruses, influenza viruses and Parainfluenza viruses	Human metapneumovirus, parainfluenza viruses
Fungus	<i>Pneumocystis jirovecii</i> and <i>Histoplasma sp.</i> in immune-compromised patients	

Diagnostic Methods

Table 2: Diagnostic methods for respiratory infections

(Ref : Marimón, J. M. and J. M. Navarro-Marí. *Enfermedades infecciosas y microbiología clínica (English ed.)* 2017)

BACTERIAL RESPIRATORY INFECTIONS		
Methods	Advantages	Disadvantages
Culture	-can test antibody sensitivity -genotypic characterization of isolates possible	-poor performance (eg. Strep A) -difficult and slow to grow (eg: Legionella) -time consuming for seroconversion in the serological diagnosis
Antigenic detection by immunochromatographic test (ICT)	-easy to use -rapid results (15min) - specificity (Strep A: ~ 95%; <i>S pneumoniae</i> : 95-99%) -reduces bias in visual reading of result (immunofluorescence ICT)	-low sensitivity (Strep A:85%; <i>S pneumoniae</i> :60-70%) -can detect only C carbohydrate in the GAS cell wall (Strep A) and serogroup O1 urinary antigen for <i>L. pneumophila</i> -cross reactivity may occur
Immunofluorescence	-results obtained in an hour	-low sensitivity (60%)
Nucleic acid tests (NAT)	-high sensitivity & specificity -rapid response time -seroconversion & detection of urinary antigen (<i>L. pneumophila</i>)	-expensive -takes 1-2 hrs to perform -qualified staff and specialization needed
VIRAL RESPIRATORY INFECTIONS		
Culture	-better performance -can test antibody sensitivity	-expensive -difficult to grow -time consuming
Antigen detection by ICTs	-simplicity in administration -rapid implementation (10-20min) -easy reading -sensitivity high to detect RSVs than influenza	-less sensitive than IF -can detect only RSV and/or Influenza A & B
Immunofluorescence (IF)	-sensitive -wide range of respiratory viruses (RVs) can be detected	-lab equipment needed -subjectivity in interpretation -high dependence on sample quality -time required to obtain results
NAT	-can detect “multiplexes”/ majority of possible viruses -time (15-90min) -minimal work load -reliable results -capable of detecting asymptomatic excretion/very low viral loads of dubious clinical significance	-multiplex NAATs are expensive -can be received only for highly specialized situations

Unmet diagnostics needs

- Diagnostics capable of quantitation to identify colonization vs. infection
- Point-of-care diagnostics as a low throughput NAAT in a primary & secondary care setting
- Diagnostics capable of distinguishing bacterial vs. viral infections and provide antibiotic sensitivities

References:

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- WHO Fact sheet. Pneumonia. 2016. Available at <http://www.who.int/mediacentre/factsheets/fs331/en/>.
- Zumla, A., et al. "Rapid point of care diagnostic tests for viral and bacterial respiratory tract infections— needs, advances, and future prospects." *The Lancet Infectious Diseases* 14(11): 1123-1135.