

Emerging respiratory tract infections 4



Rapid point of care diagnostic tests for viral and bacterial respiratory tract infections—needs, advances, and future prospects

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Respiratory tract infections rank second as causes of adult and paediatric morbidity and mortality worldwide. Respiratory tract infections are caused by many different bacteria (including mycobacteria) and viruses, and rapid detection of pathogens in individual cases is crucial in achieving the best clinical management, public health surveillance, and control outcomes. Further challenges in improving management outcomes for respiratory tract infections exist: rapid identification of drug resistant pathogens; more widespread surveillance of infections, locally and internationally; and global responses to infections with pandemic potential. Developments in genome amplification have led to the discovery of several new respiratory pathogens, and sensitive PCR methods for the diagnostic work-up of these are available. Advances in technology have allowed for development of single and multiplexed PCR techniques that provide rapid detection of respiratory viruses in clinical specimens. Microarray-based multiplexing and nucleic-acid-based deep-sequencing methods allow simultaneous detection of pathogen nucleic acid and multiple antibiotic resistance, providing further hope in revolutionising rapid point of care respiratory tract infection diagnostics.

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This is the fourth in a **Series** of five papers on emerging respiratory tract infections

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Introduction

Respiratory tract infections are caused by many viral and bacterial pathogens¹ and are the second most common cause of morbidity and mortality worldwide.^{2–4} Lower respiratory tract infections come second in the global burden of disease rankings after ischaemic heart disease.^{1,4} Surveillance reports⁵ from Europe show a substantial rise in the number of infections caused by antimicrobial resistant bacteria. Community acquired pneumonia,⁶ hospital-acquired pneumonia, and ventilator associated pneumonia⁷ all continue to present clinically significant diagnostic and management challenges. Additionally, the worldwide spread of multidrug resistant tuberculosis⁸ and emergence of multidrug resistant Gram-negative bacteria,^{9,10} for which few effective therapy options exist, are a major concern. Respiratory tract infections are also the most common infections in an ever increasing number of immunocompromised people¹¹ in whom a broader differential diagnosis of opportunistic microorganisms presents further diagnostic challenges.¹² Successful treatment outcomes for respiratory tract infections presenting in all types of health-care settings will only be achieved with rapid, sensitive, and specific identification of pathogens and antibiotic resistance profiles to allow effective evidence-based antimicrobial therapy and pathogen-specific infection control measures.¹³

The presence of microbial nucleic acids in respiratory tract samples has been exploited for amplification of targets to identify microbes and antibiotic resistance. In this review, we describe the available diagnostic tests for viral and bacterial causes of respiratory tract infections

Key messages

- Millions of adults and children worldwide continue to die of treatable respiratory tract infections caused by a wide range of microbial pathogens.
- The emergence of multi-antibiotic resistant bacteria and novel respiratory viruses with pandemic potential is of global concern.
- Optimum clinical management outcomes can be achieved only through rapid accurate diagnosis of the microbial cause of respiratory tract infections and initiation of appropriate antibiotic therapy.
- The presence of microbial nucleic acids in respiratory tract samples has been exploited for amplification of microbe species and antibiotic resistance specific genetic targets
- Molecular diagnostic platforms allow for rapid diagnostic tests to be modelled on automated platforms using nucleic acid amplification techniques (NAAT). The clinical dilemma surrounding the use of high sensitivity and specificity NAATs is that identification of pathogen nucleic acid from a respiratory tract sample may not necessarily attribute causation.
- Few validated NAAT tests that screen for respiratory tract infections caused by specific viral or bacterial groups are being used by diagnostic laboratories to diagnose selected pathogens, usually in combination with more traditional methods.
- Laboratories in most developing countries use traditional age-old methods for diagnosis of respiratory tract infections except for the Cepheid GeneXpert MTB/RIF assay, which is being rolled out worldwide for rapid diagnosis of tuberculosis and rifampicin resistance.
- Microarray-based multiplexing and nucleic-acid-based deep-sequencing methods for the simultaneous detection of pathogen nucleic acid and multiple antibiotic resistance provide further hope for revolutionising rapid point-of-care tuberculosis diagnostics, and they have been invaluable in identifying new viral and bacterial pathogens.
- Despite advances, a great need for rapid, point-of-care pathogen-specific, sensitive, and affordable diagnostics remains for the advancement of clinical management, infection control, and improved public health response to emerging pathogens.

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and developments in technologies that offer the potential for improving the quality, speed, and tractability of near point-of-care rapid diagnostic tests.

Clinical and public health diagnostics

When patients with respiratory tract infections present at any point of care, diagnostic tests should be available to simultaneously differentiate bacterial (including tuberculosis), viral, and other microbial causes to achieve the best possible treatment outcomes. At present, patients presenting with acute respiratory tract infections are started on empiric antimicrobial treatment for presumed acute bacterial infection rather than therapy directed at the causal organism.¹⁴ The major drawback in the clinical management of respiratory tract infections worldwide nowadays is the absence of standardised, rapid, accurate, specific point-of-care diagnostic tests able to screen for major pathogen groups, to enable identification of the causative organisms, and to ascertain antimicrobial susceptibilities.¹³ Present advances in molecular technologies offer a unique opportunity to address this unmet need.¹⁵

New lethal viruses and bacteria causing respiratory tract infections, several with epidemic potential, have emerged in the past 10 years, threatening global health security and attracting widespread media and political attention. These include the severe acute respiratory syndrome coronavirus (SARS-CoV [2003]),¹⁶ swine-origin influenza A (H1N1pdm2009),¹⁷ Middle East respiratory syndrome coronavirus (MERS-CoV [2012]),¹⁸ multi drug resistant and extensively-drug resistant tuberculosis,¹⁹ pan-drug resistant Gram-positive and Gram-negative bacteria,^{7,9,10} antiviral resistant cytomegalovirus strains in immunocompromised patients,²⁰ and azole-resistant fungi.²¹ Other newly emergent respiratory pathogen threats that merit close monitoring for expanding epidemic potential include avian influenza A H7N9,²² influenza A swine H3N2v and H1N1v variant,²³ human adenovirus 14p1,²⁴ and rhinovirus group C,²⁵ each of which have caused localised outbreaks of great concern.

Whenever a previously unknown potentially lethal microorganism causing respiratory tract infection emerges, clinicians, microbiologists, and public health officials are expected to work synergistically together with national and global health systems to respond to the threat. This response has many components: rapid diagnosis and identification of similar cases; case control studies to determine reservoirs, modes of transmission, and risk factors; collection of individual and case cluster data and reports; ascertainment of transmission patterns; isolation, identification, and characterisation of the specific pathogen, and establishment of Koch's postulates if possible; and development of pathogen-specific diagnostics and genome sequencing to monitor the evolution and transmission patterns. These collaborative activities are essential for the identification of the specific microorganism, guidance of appropriate targeted therapy, monitoring of response to treatment, prediction of

prognosis, guidance of infection control measures, and public health surveillance and control recommendations. Rapid, accurate diagnostic laboratory tests are crucial in the public health management of respiratory tract infections caused by new potentially lethal pathogens.

Point-of-care and near-patient testing

The requirements for ideal point-of-care and near-patient testing for respiratory tract infections are similar (table 1) but may differ according to specific needs of the health-care setting. Several diagnostic platforms and tests have great potential to improve management of respiratory tract infections.^{26,27} Furthermore, these are becoming increasingly important in response to outbreaks of respiratory tract infections caused by zoonotic pathogens, which jump the species barrier and have epidemic potential.^{28–30} Several commercial diagnostic tests and platforms that incorporate the above technologies and promise to substantially reduce turnaround times for diagnosis of a host of microbial infections, including those of the respiratory tract, are on the market or in development (table 2). Typically, these are on automated or semiautomated systems or kits that integrate sample preparation, pathogen detection, and identification of antimicrobial resistance genes, providing an automated read-out of results. These tests and platforms are the most advanced systems requiring the least possible user input throughout the process and are capable of detecting several pathogens simultaneously. Depending on the test, single or multiple pathogens, or antimicrobial resistances may be detected. Such systems can offer not only an improved speed of diagnosis but also increased sensitivity of detection. However, the development of such tests and their successful implementation into clinical practice requires further development.^{31–33}

Where the accuracy of results is high with multiplex tests, the desirable characteristics for providing both diagnostic and epidemiological information become convergent, and routine diagnostic laboratories can consider fulfilling a public health role.³⁴ Molecular multiplex tests need to be transported outside the laboratory as point-of-care tests in busy tertiary care, outpatient clinical settings, or rural areas in developing countries. From this point, the basic requirements of a method may diverge: for field studies, the adopted amplification technology may need to be something more suited to situations where power supply cannot be guaranteed, such as isothermal amplification. For all point-of-care tests, operational simplicity allowing use by non-laboratory trained staff and accurate interpretation of raw signal data are key factors.

Evolution of diagnostics for respiratory tract infections

Before the advent of laboratory tests, the practice of medicine was an art, and making a diagnosis of respiratory infection relied entirely on the taking of

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