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# The clinical need for the RVP test

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Twenty-five years ago medical school students learned about influenza and the common cold but they may not have heard about respiratory syncytial virus (RSV) or parainfluenza virus and certainly did not hear about coronavirus, human metapneumovirus (hMPV) or bocavirus. Today's infectious disease clinicians must be up to date in their knowledge of all the etiological agents of respiratory tract infection in order to manage their patients appropriately, and this involves learning about the new emerging respiratory viruses such as hMPV and bocavirus to say nothing about SARS and avian influenza H5N1. Such has been the evolution of infectious diseases training over the past quarter century.

The RVP test uses a sensitive multiplex PCR and fluidic micro-array to detect 20 different respiratory viruses and may be the most comprehensive and sensitive diagnostic approach for the detection of respiratory virus infections. As mentioned in earlier papers, this test detects the common cold viruses (rhinovirus and coronavirus), conventional respiratory viruses (influenza A and B, parainfluenza 1–4, RSV, and Adenovirus), and the emerging viruses detected since 2000 (human metapneumovirus [hMPV], SARS, Avian influenza H5N1, coronaviruses NL63 and HKU1). In pre-clinical and clinical trials the RVP test consistently detected between 25% and 50% more respiratory viruses detected compared with conventional diagnostic testing methods (Mahony and Chong, 2007; Mahony et al., 2007). In this paper I will present the clinical reasons for using the RVP test for diagnosing respiratory infections in patients presenting with symptoms and signs of upper or lower tract infection especially in young children presenting with acute respiratory infection (ARI).

Since most viral respiratory tract infections can present with similar symptoms and signs it is impossible to differentiate between an important respiratory infection such as influenza that would require a different management and infection control measures and a less severe infection with, say, rhinovirus by clinical presentation only. The clinician examining a patient presenting with upper tract signs and symptoms is therefore at a loss to know if his patient has influenza or a common cold, and relies on the laboratory to tell him what viral infection that patient has. Influenza is a febrile illness characterized by fever, cough, upper respiratory symptoms including sore throat, rhinorrhoea and nasal congestion, and systemic symptoms including headache, myalgia and malaise. Although this constellation of signs and symptoms is frequently seen with influenza virus infection, other clinical presentations from asymptomatic infection to viral pneumonia also occur. Most clinicians would agree that "influenza" is not a clinical diagnosis and that their clinical suspicion needs to be confirmed by the laboratory. However, having said this nearly all community physicians commonly diagnose patients with a "flu-like illness" (even SARS can present as a flu-like illness) which in principle means that the patient may have influenza or any one of a number of viruses presenting similarly to influenza (at least 18 possibilities). Because influenza is a reportable disease in many jurisdictions and dictates certain clinical management decisions as well as infection control measures particularly in a health-care setting such as a hospital or nursing home, influenza virus must be identified accurately by the laboratory. The consequences of not identifying influenza virus in a large nursing home or busy hospital ward could result in an outbreak of 10–20 infected patients within a single day, resulting in significant morbidity and mortality and lost revenue in the case of a hospital if bed closures are invoked.

Infections in infants, the elderly and the immunocompromised host can present differently than in an otherwise healthy individual and often present a challenge to clinicians and the laboratory to identify the causative agent. In addition, infections in otherwise healthy individuals can also present differently due to differences in previous exposure to the viral agent (immunity), differences in genetic makeup (immune responsiveness), and differences

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in nutritional (e.g. vitamin A) or physiological status. As mentioned above, influenza can present with a range of signs and symptoms, and most if not all respiratory viruses also present similarly with a range of clinical syndromes including rhinorrhoea, pharyngitis, laryngitis, laryngotracheobronchitis, bronchitis, bronchiolitis, pneumonitis or pneumonia. Given that both rhinovirus and influenza virus can cause rhinorrhea or a common cold and both can also cause pneumonia it is important to identify influenza virus so appropriate medications can be administered.

The second major reason for identifying specific respiratory viruses is so that the appropriate patient management can be initated where antiviral drugs or medications are available or when specific procedures are indicated. In the case of influenza there are two approved classes of antivirals that can be given viz. M2 channel inhibitors amantadine and rimantadine for influenza A, and the newer neuraminidase inhibitors oseltamivir (Tamiflu) and zanamavir (Relenza) for influenza A and B. The neuraminidase inhibitors when given prophylactically must be given within 48 hours of the onset of symptoms to be effective so a same day diagnosis is important. In children a serious complication of influenza (or other viruses) called Reye syndrome, characterized by cerebral edema and fatty liver, may develop 2–12 days after onset of infection. The risk for this syndrome is enhanced by exposure to salicylates such as aspirin, so a proper viral diagnosis is important for limiting the use of salicylates in children. Respiratory syncytial virus (RSV) is arguably the single most important respiratory virus causing acute respiratory tract infections in children and is a major cause of lower tract infection in infants causing croup, bronchiolitis and pneumonia that can be life threatening. Specific treatments are available for RSV including aerosolized ribavirin (Virazole) especially for immunocompromised infants or those that are severely ill. A humanized RSV monoclonal antibody palivizumab (Synagis) has been licensed in the USA for prophylaxis against RSV disease in high risk infants. Rhinovirus infections, which have been overlooked by the medical community for years, are also important to diagnose since they can cause serious lower tract infections and there are experimental treatments available for these infections. Companies continue to work on improved delivery to the airways using inhalers and nebulizers for dry and wet preparations. Studies have included intranasal administration of soluble ICAM-1, use of intranasal ipratropium bromide, an anticholinergic agent, intranasal imiquimod, or administration of antivirals and antimediators in combination (Hayden et al., 1996; Turner et al., 1997, 1999; Clejan et al., 2005). A picornavirus capsid binding drug, pleconaril, has been shown to have some benefit against natural colds in clinical trials (Hayden et al., 2003a). In addition, specific inhibitors of rhinovirus 3C protease have shown potency and are in clinical trials (Hayden et al., 2003b).

As mentioned above RSV needs to be accurately diagnosed not only in children, who are at the highest risk of getting severe disease, but also in transplant patients since RSV can be life threatening in the immunocompromised host. If severely immunocompromised patients are given anti-rejection medication to prevent rejection of organs and subsequently develop RSV infection then immunosuppressive therapy must be halted or modified immediately. Accurate diagnosis of RSV in bone marrow transplant patients is also important since treatment with a combination of ribavirin plus palivizumab has been shown to improve the outcome of severe RSV infection in this population (Whimbey et al., 1995).

The third major reason to identify respiratory viruses relates to unnecessary medical procedures. Death has sometimes resulted from unnecessary procedures performed in patients for whom RSV was not considered. Bronchoscopy, lung biopsy, or overly aggressive therapy with corticosteroids and bronchodilators for presumed asthma can all pose a danger to these patients, and some of these management decisions are best made with an accurate viral diagnosis. Identification of viruses in patients with ARI can alter patient management by reducing the unnecessary use of antibiotics, blood work or other medical procedures. The correct diagnosis of viral ARI can also eliminate unnecessary blood work for bacterial workup (WBC differential and neutrophil counts). As the cost of antibiotics continues to rise and their indiscriminant use draws increasing attention in the context of their contribution to the development of bacteria with increased antibiotic resistance, an accurate and timely diagnosis of viral respiratory tract infection can help reduce the unnecessary use of antibiotics in patients with bacterial infections. This carries with it not only a cost saving to the health-care system but a positive impact on the growing problem of antibiotic resistance in bacteria.

The advent of multiplex PCR and its application to the diagnosis of viral respiratory tract infections has indicated recently that dual and even triple respiratory tract infections occur in both children and adults. In some studies up to 45% of respiratory infections were found to be dual infections (Kuypers et al., 2005). In our hands 5–10% of respiratory virus infections diagnosed by the RVP test have been dual infections and a few triple infections have been detected (Mahony et al., 2007). Clinical studies are currently under way using the RVP test to determine the clinical significance of these dual respiratory infections.

Making the correct diagnosis of a respiratory virus infection is also important in the context of respiratory outbreak management and in the event of a novel respiratory virus appearing in the human population for the first time. Respiratory outbreaks in the community often go undiagnosed with no etiological agent being detected. This is because suboptimal or insensitive methods are used or specific viral agents may not be tested for. In North America it is estimated that in one quarter to one third of respiratory outbreaks no etiological agent is ever detected.

Use of the RVP test would certainly assist the public health authorities in investigating respiratory outbreaks given the large number of viruses that it can detect. The RVP test has helped with the diagnosis of nursing home outbreaks of hMPV and rhinovirus and obviated the need for oseltamivir prophylaxis. Use of the RVP test in outbreak situations will also increase our understanding of the epidemiology of outbreaks in the community and assist the public health authorities in developing appropriate control measures. The RVP test may also be useful in the event of a new outbreak of SARS, H5N1 influenza or a new agent since it can be used to rule out the "common agents" and therefore indicate the possibility that a new agent is circulating.

Finally a case can be made that adoption of the RVP test by clinical laboratories will be cost effective. We have conducted a cost–benefit and cost–consequence study in our institution and although the RVP test may cost more than DFA plus shell vial culture, the small additional cost to the laboratory is far offset by the savings in health-care dollars to the hospital when the cost of unnecessary medications and producers (antibiotics, corticosteroids, blood work, etc.), infection control practices (isolation and bed closures) and public health recommendations for unnecessary influenza prophylaxis are factored into the equation. In addition to cost savings there are also consequences (discomfort associated with unnecessary procedures) that have an associated cost for the individual patient. Along these same lines, the benefit of clinicians being able to reassure anxious parents that their child has a self-limiting viral infection that is treatable with an antiviral agent or will resolve without complications has a benefit to the family. Given the choice of knowing or not knowing whether a patient has a viral respiratory tract infection, most clinicians in today's litiginous society would want to know if the patient had a viral infection so that he or she could provide the best clinical management for the patient.

## 1. Conflict of interest statement

Stockholder, honoraria, patent applications (Luminex).

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