

The Virome of the Human Respiratory Tract

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KEYWORDS

- Virus • Infection • Lung • Culture independent • Chronic lung disease • Diagnostics
- High-throughput sequencing

KEY POINTS

- Culture-independent molecular assays detect viral pathogens with great sensitivity and can be used to define the virome in the upper and lower respiratory tract.
- The respiratory tract virome is defined by very common pathogens (rhinoviruses, paramyxoviruses) as well as viruses that occur less frequently and those with unknown pathogenicity.
- Viruses with the potential for pathogenicity are detected in both symptomatic and asymptomatic people.
- Monitoring emerging respiratory pathogens is important, and high-throughput sequencing can be used as a tool to complement epidemiologic studies and to design diagnostics.
- In the future, comprehensive pathogen detection and host response may be coupled to create better assays for research studies and diagnostics.

INTRODUCTION

Viral infections of the respiratory tract are very common. In a recent study of 26 households in Utah that were followed weekly over 1 year, modern molecular methods were used to detect respiratory viruses in the anterior nares.¹ This study found that children less than 5 years old had about 12 viral episodes in the respiratory tract each year, whereas adults averaged about 6 per year. These numbers are higher than previous studies,² which is likely explained by the use of molecular assays instead of culture- and serology-based tests and the discovery of new respiratory viruses in intervening years that would not have been assessed in older studies.

Modern molecular methods for virus detection are highly sensitive and specific. Polymerase chain reaction (PCR) assays are also rapid and generally inexpensive. High-throughput nucleic

acid sequencing (HTS) methods are slower but have the potential to be more comprehensive because there is no need to select specific targets beforehand, and the method can detect genomes with substantial sequence variation compared with known reference genomes (Fig. 1). With these tools in hand, we can begin to think about characterizing the virome of the respiratory tract, herein defined as all of the viruses in the respiratory tract that can infect and replicate in human cells, which includes known pathogens and viruses with unknown pathogenicity. We have begun to learn about the virome of the respiratory tract through studies of patients with acute infections, chronic lung diseases, and undergoing lung transplantation, among others. The author reviews some of these studies in addition to recent technological developments, which will improve characterization of the respiratory virome and diagnostics in coming years.

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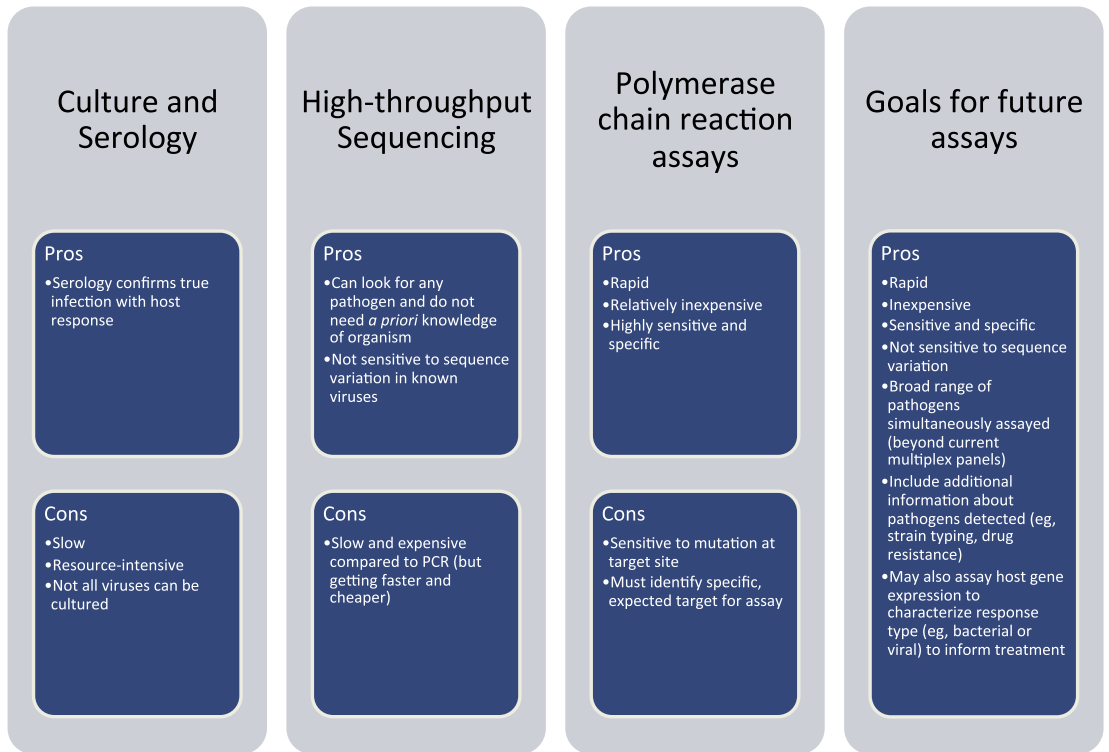


Fig. 1. Methods for characterizing viruses in the respiratory tract. Current molecular methods, such as PCR and HTS, have clear advantages over older methods (culture and serology) in terms of cost, speed, and sensitivity. Future assays for research and diagnostics will be aimed at capturing and improving on the best features of the current methods.

OVERVIEW OF THE VIROME IN THE RESPIRATORY TRACT

Defining the virome in the respiratory tract and understanding the implications of the viruses detected are significant challenges. The work is complicated by several factors. First, the lower airway is not easily accessible and sometimes requires invasive sampling. For instance, bronchoalveolar lavage samples are often only available from symptomatic individuals who are having lavage performed for diagnostic testing and not from asymptomatic controls. Second, a study of the viruses in the lungs of patients with cystic fibrosis (CF) showed that the viral populations were distinct in different regions of the lung.³ This variation within the respiratory tract and lung means it can be difficult to get a clear, or complete, view of the virome. Third, only recently have relatively unbiased approaches to identifying viruses become available in the form of HTS assays. With that said, a great deal of progress has been made in defining the human virome in the respiratory tract (summarized in [Table 1](#)).

The Virome in Patients with Respiratory Tract Infections and Controls

One cost-effective approach to broadly identify viruses associated with the respiratory tract is to pool samples and screen for a comprehensive set of viruses. The downside to this approach is that one cannot determine the frequency at which any individual virus occurs among patients. However, as characterization of the respiratory tract virome using molecular methods is a relatively new area of exploration, these studies can be useful in order to determine if viruses beyond the common, known respiratory pathogens are detected.

In one study, 210 adults and children with severe lower respiratory tract infections were sampled.⁴ Nasopharyngeal aspirates were collected and samples were combined, creating 13 pools of 8 to 24 samples per pool. Virus particles were enriched, and DNA and RNA viruses were assessed using HTS. Thirty-nine viral species were observed in these samples, giving a broad view of the scope of the respiratory tract virome during infection. Based on read counts, the most abundant viruses in the data set were the paramyxoviruses

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