Respiratory Viral Infections in Developing Countries: Common, Severe, and Unrecognized

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(See the article by Nokes et al. on pages 50–7)

Respiratory infections have a significant impact on health worldwide. The great majority of respiratory infections are of viral origin [1]. However, 10%–50% of patients will develop a secondary bacterial infection; children are mainly afflicted with acute otitis media, sinusitis, or pneumonia. In very young or older individuals or individuals with chronic medical conditions, viral respiratory infections may induce a severe illness. In the United States alone, 100,000 infants are hospitalized yearly for respiratory syncytial virus (RSV) infection [2, 3]. Epidemics of influenza and RSV infection are associated with an annual 36,000 and 11,000 deaths, respectively [4]. Since the discovery of influenza A virus in 1933, ~20 respiratory viruses have been identified. Most acute respiratory infections are caused by rhinovirus, RSV, enteroviruses, influenza A and B viruses, parainfluenza viruses, or adenovirus. During the 21st century, new emerging respiratory viruses have been detected, including severe acute respiratory syndrome coronavirus, human metapneumovirus, coronaviruses NL 63 and HKU1, and human bocavirus. Today, the etiology of acute respiratory viral infections can be determined in 80%–95% of cases [5–7].

Although respiratory viral infections are much studied in developed countries and their impact on health care is well understood, there is a gap in information on the burden of respiratory viral infections in developing countries [8]. From the public health point of view, it would be valuable to know which viruses are the most common causative agents, what their disease manifestations are, how often virus alone causes severe respiratory infection, what interplay occurs between viruses and bacteria, and how severe lower respiratory infections could be prevented.

In this issue of *Clinical Infectious Diseases*, Nokes et al. [9] report on the incidence and severity of RSV infections in a cohort of children from a rural district of Kenya, in an attempt to define the age group for which future vaccines should be targeted. The generated data are solid: the design was population-based; surveillance was active, with weekly household visits during epidemics of RSV infection and monthly visits between epidemics; and the follow-up period was sufficiently long, beginning soon after birth and continuing through 3 epidemics of RSV infection. The main finding is clear: RSV is an even more important cause of severe lower respiratory tract infections in children in developing countries than was suggested by earlier studies [10–12]. Active community surveillance is needed to determine the disease burden, because only a minority of children with severe infection are admitted to the hospital. However, the incidence figures in the present, well-planned study probably underestimate the burden of RSV infection, because only antigen detection from nasal washes was used in diagnostic testing for RSV, and its sensitivity is suboptimal [13, 14].

In accordance with textbook knowledge, the peak incidence of severe RSV infection was seen infants aged <6 months. Nevertheless, the authors estimate that more than one-half of severe infections occurred in children aged 6–30 months, partly because of frequent reinfections. These data are important for the planning of intervention strategies. In addition to data for children, data for adults are needed, because respiratory viruses have recently been found to cause substantial morbidity and mortality in the older population, and adult populations of resource-poor countries may be vulnerable to respiratory viral infections because of comorbidities.

The study by Nokes et al. [9] has some limitations. The incidence of the most severe manifestations of RSV infection cannot be determined by means of a relatively small cohort. The study does not tell which group of patients experience the

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highest mortality associated with RSV infection in the developing world; is mortality still concentrated among the youngest infants, despite severe disease also occurring in older infants, and what are the roles of malnutrition, prematurity, HIV infection, and other underlying conditions? Only 11 patients were hospitalized for severe infection, and although bacterial coinfections were not seen, the low number of cases prevents conclusions of the role of bacteria in RSV pneumonia. In the developed countries, up to 60% of children with RSV bronchiolitis have otitis media [15, 16], and in most cases, both the virus and bacteria can be detected from middle ear fluid [17]. Nokes et al. [9] do not report the incidence of RSV-associated otitis media, radiograph-confirmed pneumonia, or antibiotic use in their cohort.

The study of Nokes et al. [9] provides valuable information on RSV in the developing world, but data on other respiratory viral infections in child and adult populations would be also needed. The authors estimate that RSV caused 13% of lower respiratory tract infections in the study cohort. If, in addition to antigen detection, RT-PCR would have been used in the detection of RSV, this proportion would have been somewhat higher. Even so, 80%–85% of infections are caused by other agents—in most cases, probably by another virus. Studies on respiratory viruses in developing countries have mainly focused on influenza and RSV. Rhinoviruses and enteroviruses are the most common cause of respiratory infections in developed countries [5, 18], but remarkably few data are available on the role of these picornaviruses in respiratory tract infections in the developing world. In a study of serious infections in infants aged <90 days from the Philippines, enteroviruses were detected in 22%, RSV in 17%, and rhinovirus in 10% of cases [19]. In a study from Africa, rhinovirus and enteroviruses were rarely detected [20]. In both of these studies, picornaviruses were detected by virus culture, which is known for its poor sensitivity. Currently, PCR is the method of choice for the detection of many respiratory viruses, particularly those for which no antigen detection is available (i.e., picornaviruses, coronaviruses, and human bocavirus). If no PCR laboratory is available at the site of sample collection, specimens can be transported without any substantial decrease in detection sensitivity [21].

Progress in the development of vaccines against respiratory viral infections has been very slow. Only vaccines against influenza A and B viruses are generally available. After the discovery of RSV in 1957, it soon became clear that an effective vaccine was badly needed. The formalin-inactivated RSV vaccine developed at the National Institutes of Health during the 1960s induced virus-specific neutralizing antibodies. Paradoxically, during a subsequent RSV infection, a more-severe pulmonary disease developed, and 2 vaccine recipients died of a natural RSV infection [22]. Several types of vaccine candidates have been developed, including inactivated virus, subunit peptides, nonreplicating and replicating vectored vaccines, and live attenuated vaccines [23]. No RSV vaccine candidate, however, has entered for wide-scale clinical studies. The other major virus, rhinovirus, has >100 serotypes, and development of a vaccine is not considered to be possible at the moment. In everyday life, the only way to prevent respiratory viral infections is to understand their transmission [21, 24–26] and to try to prevent transmission through hygiene measures. This has been shown to be possible in day-care centers in a developed country [27].

It is now the time to plan studies that would determine the burden of the whole range of respiratory viruses in the developing world. The World Health Organization should have on its priority list, in addition to influenza, other major respiratory viruses, including RSV, rhinovirus, and enteroviruses. In the developing countries, 2 million children aged <5 years die annually of lower respiratory tract infections [28, 29]. We should try to learn more about the role of respiratory viruses in these severe infections to make progress in their prevention.

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