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Viral co-infections among children with confirmed measles at hospitals in Hanoi, Vietnam, 2014

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ABSTRACT

Objective: To characterize viral co-infections among representative hospitalized measles cases during the 2014 Hanoi outbreak.
Methods: Throat swabs were collected from 54 pediatric patients with confirmed measles, and molecular diagnostics performed for 10 additional viral respiratory pathogens (Influenza A/H1N1pdm09; A/H3N2 and influenza B; Parainfluenza 1, 2, 3; Respiratory Synctial Virus, RSV; human Metapneumovirus, hMPV; Adenovirus and Picornavirus).
Results: Twenty-one cases (38.9%) showed evidence of infection with other respiratory viruses: 15 samples contained measles plus one additional virus, and 6 samples contained measles plus 2 additional viruses. Adenovirus was detected as a predominant cause of co-infections (13 cases; 24.1%), followed by RSV (6 cases; 11.1%), A/H1N1pdm09 (3 cases; 5.6%), PIV3 (3 cases; 3.7%), Rhinovirus (3 cases; 3.7%) and hMPV (1 case; 1.96%).
Conclusions: Viral co-infections identified from pediatric measles cases may have contributed to increased disease severity and high rate of fatal outcomes. Optimal treatment of measles cases may require control of multiple viral respiratory pathogens.

1. Introduction

Measles is a vaccine-preventable respiratory viral illness of the Paramyxovirus family, associated with symptoms of high fever, runny nose, white spots in the mouth and a hallmark rash. Despite inclusion of measles within the national immunization programs of most countries worldwide, the disease remains a leading cause of death in young children worldwide [1].

In Vietnam, measles vaccination has been included in the National Expanded Program for Immunization (EPI) since 2001, for children from nine months to six years, and elimination targets were originally identified in 2009 for achievement in 2012 [2]. However, the disease reemerged during 2008–2010 with 7948 confirmed cases [3] and then again in May 2013, when cases were reported from 24 cities and provinces, including the major urban centers of Hanoi and Ho Chi Minh city. In 2014, Vietnam reported more than 3500 confirmed measles infections, a single hospital in Hanoi-the National Pediatric Hospital (NHP)-treated as many as 1280 measles patients, of which at least 100 cases were fatal [4].

Pneumonia is the most common severe complication of measles infection and accounts for most measles-associated death [5]. Pneumonia may be caused by measles virus alone, secondary viral infections with adenovirus or RSV, or secondary bacterial infections. Viral co-infections are known to cause increased disease severity and are a risk factor for respiratory failure [6,7]. The importance of viral respiratory co-infections during hospitalization is the challenge for infection control and rapid spread among patient rooms, which is particularly difficult under conditions of over-crowding during outbreaks.

During April 2014, the Vietnam Ministry of Health swiftly responded to the measles outbreak through mobilizing the health system to provide patient treatment and diagnosis, to verify vaccination records of school-age children, and to sponsor catch-up vaccination campaigns for children at risk. However, over-crowding conditions at major hospitals and treatment centers in Hanoi, particularly at NHP and Bach Mai hospital (BMH) were reported, with alarming increases in the number of severe pneumonia patients [4,6]. The comprehensive strategy for patient

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treatment involved triage of the most severe measles cases, particularly those with pneumonia. Determination of other microbiology-associated measles complications was performed to provide adequate treatment to reduce mortality and control measles infection in hospitals.

Our study reports descriptive data on viral etiologies associated with hospitalized measles cases presenting to two hospitals in Hanoi during the peak of outbreak case detections in April, 2014. This study was undertaken to determine the frequency of co-infecting viral pathogens, including molecular detection of ten common respiratory viruses.

2. Material and methods

2.1. Study population

During April 2014, we collected residual respiratory specimens (nasopharyngeal swabs, tracheal aspirates) for patients that had screened positive for measles by RT-PCR using standard protocols as previously described [8] in the clinical diagnostic laboratories of NHP and BMH. All samples were originated from inpatient wards (intensive care units) and were submitted to the virology department of the National Institute of Hygiene and Epidemiology (NIHE). In total, samples from 54 measles-confirmed cases with severe pneumonia were obtained (30 from NPH, 24 from BMH). The case definition of measles severe pneumonia was high fever (>38.5 °C), cough, shortness of breath, rash and fatigue.

2.2. Sample processing

Nucleic acids were extracted using Qiagen viral RNA Mini Kit (Qiagen CA, USA). For each sample, 140 μL of VTM were processed according to the manufacturer instructions, eluted in 60 μL of Qiagen AVE buffer. Real time RT-PCR were used to screen for influenza A and B through detection of *M* gene, followed by subtyping by HA-specific RT-PCR [1,9]. Subsequently, all samples negative for influenza were screened by real time RT-PCR for parainfluenza (PIV) 1, 2, 3; hRSV; hMPV; adenoviruses, and by conventional RT-PCR for detection of rhinovirus. All tests were performed according to standard procedures as currently performed within the national surveillance program for Severe Acute Respiratory Illness previously described [9–12].

3. Results

The measles cases included in this study originated from 54 children with a median age of 11.5 months (range from 2 months to 4 years old), including 20 children <9 months old (37.0%) and 34 children >9 months (63.0%). 38 of the cases were boys (70.4%) and 16 were girls (29.6%). Samples from twenty-nine cases were collected within 5 days of hospital admission, eighteen samples were collected from 6 to 10 d post-admission, and seven samples were collected after 11 or more days of hospitalization.

Of the 54 measles confirmed samples that were tested for 10 other respiratory viruses, 15 (27.8%) were confirmed positive for a single additional viral pathogen. These comprised 2 (3.7%) cases of influenza A/H1N1pdm09 viruses; 8 (14.8%) cases of adenovirus; 4 (7.4%) RSV and 1 (1.9%) rhinovirus (Table 1).

Table 1
Detection of multiple viral infections in measles confirmed cases with severe pneumonia in Hanoi, April 2014.

Co-infection	Respiratory viruses positive
One additional virus	15/54 (27.8%)
A/H1N1pdm09	2 (3.7%)
Adenovirus	8 (14.8%)
RSV	4 (7.4%)
Rhinovirus	1 (1.9%)
Two additional viruses	6/54 (11.1%)
Adeno + A/H1N1pdm09	1 (1.9%)
Adeno + hMPV	1 (1.9%)
Adeno + RSV	1 (1.9%)
Adeno + PIV3	2 (1.9%)
RSV + Rhino	1 (1.9%)
Total	21/54 (38.9%)

Six measles-confirmed cases (11.1%) were identified as having co-infection with two additional viral pathogens: among these, co-infections with adenovirus and A/H1N1pdm09/hMPV/RSV/PIV3 were determined for 5 patients and one patient was found co-infected with RSV and rhinovirus (Table 1). We did not find either influenza A/H3 nor influenza B, nor any cases of PIV1 and PIV2 among the measles-confirmed samples.

The proportion of measles cases co-infected with one or two other respiratory viruses were 38.9% (21 patients). Adenovirus was identified in thirteen samples (61.9%), including eight cases (38%) of single co-infection and five cases (23.8%) of double viral co-infections (Table 1, Figure 1).

The adenovirus was the most frequently co-infections, identified in 13 samples, with children aged (2–15) months, median age of 7.8 months. The second most frequent viral co-infection was RSV, identified in 6 samples (28.6%), with children aged (6–24) months, median age of 12.2 months, including 4 cases of single co-infection and 2 cases of double viral co-infection identified in older children (Figure 1). A/H1N1pdm09 co-infections identified in 3 samples, with children aged (9–18) months, median age of 12.0 months. Rhinovirus co-infections identified in 2 samples, with children aged (6–24) months, median age of 15.0 months. hMPV co-infections identified in 1 samples, with children aged 6 months. PIV3 co-infections identified in 2 samples, with children aged (7–15) months, median age of 11.0 months.

Among 18 measles cases determined to have one or two additional co-infecting viruses, 13 were collected from 6 to 10 d post hospital admission (72.2%), 4 samples in 29 were taken

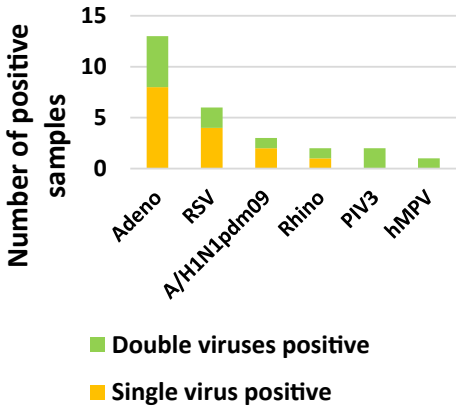

Figure 1. Incidence of respiratory viruses infections.