Etiologies of Rash and Fever Illnesses in Campinas, Brazil

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Background. Few population-based studies of infectious etiologies of fever-rash illnesses have been conducted. This study reports on enhanced febrile-rash illness surveillance in Campinas, Brazil, a setting of low measles and rubella virus transmission.

Methods. Cases of febrile-rash illnesses in individuals aged <40 years that occurred during the period 1 May 2003–30 May 2004 were reported. Blood samples were collected for laboratory diagnostic confirmation, which included testing for adenovirus, dengue virus, Epstein-Barr virus (EBV), enterovirus, human herpes virus 6 (HHV6), measles virus, parvovirus-B19, Rickettsia rickettsii, rubella virus, and group A streptococci (GAS) infections. Notification rates were compared with the prestudy period.

Results. A total of 1248 cases were notified, of which 519 (42%) had laboratory diagnosis. Of these, HHV-6 (312 cases), EBV (66 cases), parvovirus (30 cases), rubella virus (30 cases), and GAS (30 cases) were the most frequent causes of infection. Only 10 rubella cases met the rubella clinical case definition currently in use. Notification rates were higher during the study than in the prestudy period (181 vs 52.3 cases per 100,000 population aged <40 years).

Conclusions. Stimulating a passive surveillance system enhanced its sensitivity and resulted in additional rubella cases detected. In settings with rubella elimination goals, rubella testing may be considered for all cases of febrile-rash illness, regardless of suspected clinical diagnosis.

Relatively few comprehensive population-based studies of the etiology of fever-rash illnesses have been conducted, and most of these are from the northern hemisphere [1–6]. Such studies are important to better understand the age and geographic distribution and the incidence of these etiologies. In the context of the Americas’ measles and rubella elimination goals, this information can also inform a minimum suspected measles and rubella reporting rate, which aims to ensure surveillance sensitive enough to detect circulating measles and rubella virus.

In 1994, the Region of the Americas set the goal of measles elimination (“elimination” is defined as the absence of endemic measles cases in a defined geographical area for a period of at least 12 months, in the presence of a well-performing surveillance system) by 2000. This goal was achieved in November 2002. Since then, all reported measles cases have been linked to importation from measles-endemic countries [7]. In Brazil, 2 confirmed measles cases were reported in 2003 [8] and 0 cases were reported in 2004 [9]. During 2001–2002, Brazil conducted vaccination campaigns targeting all women of childbearing age (the target age group varied by state, with 12 years the lowest and 49 years the upper age limit).
for accelerated rubella control and congenital rubella syndrome (CRS) prevention. Five hundred sixty-three cases of rubella were reported nationwide in 2003 [8] and 401 were reported in 2004 [10]. In September 2003, the Americas endorsed the rubella and CRS elimination goal by 2010 [11].

To monitor progress toward measles and rubella elimination, the Pan American Health Organization (PAHO) recommends that all countries in the region have integrated measles and rubella surveillance. In Brazil, all cases of fever and rash meeting clinical case definitions for measles (defined as fever and maculopapular rash accompanied by ≥1 of the 3 following symptoms, cough, coryza, or conjunctivitis, in any individual, regardless of age or vaccination status) or rubella (defined as fever and maculopapular rash accompanied by retroauricular, occipital, or cervical lymphadenopathy in any individual, regardless of age and vaccination status) should be notified and confirmed or discarded by laboratory testing [12, 13]. The use of specific indicators to evaluate the quality of surveillance has been proposed. The World Health Organization (WHO) has suggested an annual rate of reported suspected measles or rubella cases of ≥2 cases per 100,000 population as an indicator of the sensitivity of the surveillance system. PAHO has recently endorsed this indicator as a criterion for documentation and verification of measles, rubella, and CRS elimination in the American region [14].

To better understand the etiologies, distribution, and background rates of fever-rash illnesses in a community setting with low rates of measles and rubella virus transmission and to assess the usefulness and feasibility of a minimum suspected measles or rubella reporting rate as an indicator of measles-rubella surveillance sensitivity, we conducted enhanced passive surveillance for fever-rash illnesses in individuals aged <40 years during the period from 1 May 2003 through 30 May 2004 in Campinas, Sao Paulo State, Brazil.

METHODS

Study Setting
Campinas, a city of ~1 million inhabitants located 120 kilometers northwest of Sao Paulo, Brazil, was selected as a study site due to its well-functioning disease surveillance system, low rates of measles and rubella virus transmission, and proximity to a reference laboratory capable of testing for numerous infectious agents. Public health care, provided by the National Health System (Sistema Único de Saúde), is used exclusively by ~70% of the population; the remaining 30%, although eligible for NHS services, receive most health care through the private sector. In the public sector, Campinas has 78 clinics, 3 urgent care centers, and 1 hospital. In the private sector, there are 5000 practitioners employed mainly by 4 major Health Maintenance Organizations [15] and 21 hospitals. In addition, there are 2 university hospitals. Before this study, measles, rubella, and dengue surveillance existed, in accordance with national guidelines. Reporting came almost exclusively from public health providers. Surveillance quality was considered good, as demonstrated by standard performance indicators [16].

Study Implementation
The study was conducted from 1 May 2003 through 30 May 2004. Before initiating the study, meetings were held with surveillance workers and both private and public primary health care providers in Campinas. An international seminar was convened when the study was launched, and folders, posters, and CDs were distributed to health care professionals from both public and private settings invited to participate. A website through which fever-rash illnesses could be electronically reported was developed.

Information about the study was made available to the population via the media. Throughout the study, meetings were held with health care providers from private and university settings whenever they reported fewer than expected cases. Prior to the end of the study, a surveillance bulletin was distributed to all reporting sites, and a seminar targeting surveillance professionals was held to present the study’s findings.

Implementation of the study was done through the existing surveillance structure. To provide the additional workforce necessary, the municipal surveillance team was supplemented by 12 staff (1 manager, 8 nurse assistants, 2 laboratory technicians, and 1 driver). One person oversaw rash and fever surveillance in each of the 5 health districts of the city. Data were reported directly to the municipal level responsible for managing the surveillance system.

Data Collection
A standard case reporting form was used to collect demographic, clinical, and risk factor information for all nonvesicular febrile-rash illnesses in individuals aged <40 years. To facilitate private sector participation, a simplified notification form was developed for their use. Fever was defined as axillary temperature >37.8°C and rash as recent presence of generalized red lesions on the skin.

Completed forms were sent daily to the district surveillance team who identified missing information or specimens and sought collection of this information through home visits. Surveillance was passive but was supplemented by weekly or biweekly active case finding in 3 selected emergency departments and 3 urgent care clinics that had historically underreported measles and rubella cases.

Specimen Collection and Processing
The specimen collection and testing protocol assumed that some patients would receive a presumptive clinical diagnosis at the time of presentation for care, and this diagnosis was factored into the algorithm. At the time of initial presentation to the health care provider, 3–5 mL of blood was drawn for laboratory testing, unless rubella, dengue, or Rocky Mountain spotted fever (RMSF; ie, *Rickettsia rickettsii* infection) was the presumptive
clinical diagnosis. If the latter occurred, the first specimen was drawn, respectively, on the fifth, sixth, or seventh day after rash onset. Oropharyngeal swabs were collected up to 5 days after rash onset from all patients with cough and coryza and transported in viral transport media vials for enterovirus and adenovirus testing. Persons with suspected group A streptococci (GAS) infection had oropharyngeal swabs transported in activated carbon media. A second convalescent-phase blood sample was collected from all reported cases 3–4 weeks after rash onset, when any missing clinical and epidemiologic data were also collected during home visits.

Whole-blood and oropharyngeal samples were refrigerated at 4°C and sent every other day to 1 of the 2 municipal reference laboratories in Campinas, where blood samples were centrifuged. Samples were shipped 3–5 times weekly from these reference laboratories to the Instituto Adolfo Lutz Laboratory in São Paulo, where oropharyngeal swabs were centrifuged and blood and oropharyngeal samples were further processed and tested.

**Laboratory Procedures**

Serum specimens were tested in the laboratory for serological evidence of the following etiologies of febrile-rash illnesses: adenoviruses, dengue virus, Epstein Barr virus (EBV), enteroviruses (coxsackieviruses B1–B6; echoviruses 4, 6, 9, 11, and 30; enteroviruses 70 and 71; and polioviruses 1–3), human herpes virus 6 (HHV6), measles virus, parvovirus B19, *R. rickettsii*, and rubella virus. Oropharyngeal swabs were tested for GAS bacterial culture or for enteroviruses and adenoviruses viral culture.

Testing for adenovirus, enterovirus, and RMSF could only be performed when both acute- and convalescent-phase serum specimens were available. Testing for GAS was only performed when an oropharyngeal swab was available (in addition to serum samples).

The sequence in which specimens were tested followed a flow diagram (Figure 1) determined by the patient’s clinical findings, Brazil’s disease control priorities, and disease epidemiology. In summary, all samples were tested initially for measles, rubella, and dengue viruses, in that order, except when a different presumptive clinical diagnosis was suspected by the health care professional. In those cases, testing for the presumptive condition was done first, followed by testing for measles, rubella, and dengue viruses. If all results were negative, samples were further tested for HHV6 if case patients were aged <2 years or for parvovirus B19 if case patients were aged ≥2 years. If those test results were negative, case-by-case clinical, epidemiologic, and laboratory data were assessed by a group of professionals who convened periodically to determine the sequence of further testing.

Case patients with rash and fever beginning 7–14 days after vaccination with measles- and rubella-containing vaccine were tested for both measles and rubella, and cases were classified as postvaccine rash if measles or rubella immunoglobulin (Ig) M antibody was detected between the eighth to 30th day (measles) or eighth to 56th day (rubella) after vaccination, respectively. [17].

When serum from a patient tested positive for 2 different diseases, it was considered that one of these tests must have yielded a false-positive result. Each case was therefore individually evaluated, and demographic and epidemiologic variables were considered for final classification of etiology. A description of tests performed, commercial kits used, and their reported sensitivities and specificities for diagnosis of the various infectious diseases considered is presented in Table 1.

**Notification Rates**

Notification rates for rash and fever illness during the study period were compared with rates of suspected measles and rubella cases notified during the prestudy period (January 1999–December 2002). Notification rates by presumptive diagnosis, age group, and source of notification (private vs public) were calculated. Final etiologies by age group are presented.

**Costs of Surveillance System**

Incremental costs of VigiFex enhanced surveillance was estimated during the study period. Cost of implementation of VigiFex in addition to routine surveillance prior to the study period was estimated.
Clinical Characterization of Reported Cases

Clinical characterization of all reported cases of rash and fever illness was performed, considering clinical information recorded in the case reporting form. The number of cases that would meet the Brazilian standard case definitions for measles or rubella was identified.

Database and Data Analysis

Microsoft Access databases were developed for collection of epidemiologic and laboratory data and were updated weekly. These databases were merged weekly. Data were analyzed using Epi Info 2002 [32].

RESULTS

Patient Characteristics

From 1 May 2002 through 30 May 2003, 1248 rash and fever illness cases in individuals aged <40 years were reported; 657 case patients (52.6%) were male, and 837 (67.1%) were children aged <4 years.

The mean interval between symptom onset and presentation to health care was 4.6 days (range, 0–30 days). At the time of initial presentation, 1244 case patients (99.7%) had specimens collected; 4 (0.3%) case patients refused to have blood drawn but had oropharyngeal swabs collected. Acute-phase serum specimens were collected for 1244 (99.7%) of 1248 cases; of these patients, 1132 (90.7%) had convalescent-phase serum specimens collected. However, acute- and convalescent-phase serum samples were collected within adequate timing from 915 case patients (73.5%), with the convalescent-phase serum collected a mean of 21 days (median, 17 days; range, 14–60 days) after the first specimen. Oropharyngeal specimens were collected for 244 (41.4%) of 590 case patients with respiratory symptoms. Vaccination cards were available for 1123 case patients (90%). Of these, 650 (57.8%) had been vaccinated against rubella and 679 (60.5%) against measles, whereas 443 (39.5%) had not been previously vaccinated for measles or rubella.

Overall Notification

The notification rate for all fever-rash illnesses during the study period was 181 cases per 100 000 population aged <40 years. Age-specific notification rates of fever-rash illness ranged from 2644 cases per 100 000 population among those aged <1 year to 24.6 cases per 100 000 population among those aged 30–39 years (Table 2). Prestudy period (1999–2002) notification rates of suspected measles plus suspected rubella in the population aged <40 years in Campinas varied from 38.1 cases per 100 000 population in 1999 to 82.3 cases per 100 000 population in 2000.

### Table 1. Differential Diagnosis and Laboratory Testing Conducted, VigiFex Surveillance Study, Campinas, Brazil, 2003–2004

<table>
<thead>
<tr>
<th>Infectious agent</th>
<th>Test description</th>
<th>Sample(s)</th>
<th>Kit manufacturer</th>
<th>Sensitivity/specificity, %</th>
<th>Reference(s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dengue virus</td>
<td>Capture ELISA IgM</td>
<td>Blood</td>
<td>PanBio</td>
<td>94.7/100</td>
<td>[18]</td>
</tr>
<tr>
<td>Measles virus</td>
<td>ELISA IgM, IgG, and capture IgM</td>
<td>Blood</td>
<td>Behring</td>
<td>88.6/98.7 (IgM)</td>
<td>[19–21]</td>
</tr>
<tr>
<td>Rubella virus</td>
<td>ELISA IgM</td>
<td>Blood</td>
<td>Organon Teknika</td>
<td>100/98 (IgM)</td>
<td>[22]</td>
</tr>
<tr>
<td>Parvovirus B19</td>
<td>ELISA IgM and IgG</td>
<td>Blood</td>
<td>Biotrin</td>
<td>78–90/84.5–99 (IgM)</td>
<td>[23–25]</td>
</tr>
<tr>
<td>Adenovirus</td>
<td>IgG seroconversion through indirect immunofluorescence</td>
<td>Blood and oropharyngeal swab</td>
<td>ATCC</td>
<td>80–85/100</td>
<td>[26]</td>
</tr>
<tr>
<td>Human herpes virus 6</td>
<td>Indirect immunofluorescence reaction IgM</td>
<td>Blood</td>
<td>Biotrin</td>
<td>Not defined</td>
<td></td>
</tr>
<tr>
<td>Epstein-Barr virus</td>
<td>ELISA IgM (VCA) and IgG (EBNA)</td>
<td>Blood</td>
<td>Biomerieux</td>
<td>95/89 (IgM)</td>
<td>[27]</td>
</tr>
<tr>
<td>Rickettsia rickettsii</td>
<td>Indirect immunofluorescence reaction—seroconversion</td>
<td>Blood</td>
<td>CDC</td>
<td>99.2/100 (IgG)</td>
<td>[28]</td>
</tr>
<tr>
<td>Enterovirus</td>
<td>Cellular culture neutralization reaction and viral isolation and indirect immunofluorescence with monoclonal antibodies for identification</td>
<td>Blood and oropharyngeal swab</td>
<td>ATCC strains and Chemicon monoclonal antibodies</td>
<td>93/99</td>
<td>[29, 30]</td>
</tr>
<tr>
<td>Group A Streptococcus</td>
<td>Culture</td>
<td>Oropharyngeal swab</td>
<td>Copan Venturi Transystem</td>
<td>90–95/100</td>
<td>[31]</td>
</tr>
</tbody>
</table>

**NOTE.** ATCC, American Type Culture Collection; CCA, viral capsid antigen; EBNA, Epstein-Barr virus nuclear antigen; ELISA, enzyme-linked immunosorbent assay; Ig, immunoglobulin.

*a* For secondary infections, the sensitivity is 55.7%.

*b* Sensitivity depends on previous antimicrobial use and other conditions of the sample tested.

### Clinical Characterization of Reported Cases

Clinical characterization of all reported cases of rash and fever illness was performed, considering clinical information recorded in the case reporting form. The number of cases that would meet the Brazilian standard case definitions for measles or rubella was identified.

### Database and Data Analysis

Microsoft Access databases were developed for collection of epidemiologic and laboratory data and were updated weekly. These databases were merged weekly. Data were analyzed using Epi Info 2002 [32].
(Figure 2), with a mean rate in the period of 52.3 cases per 100,000 population aged <40 years.

**Notification by Initial Presumptive Clinical Diagnosis**

Notification rates of rash and fever illnesses by presumptive clinical diagnosis are presented in Table 3. Presumptive clinical diagnoses before laboratory testing with the highest notification rates were HHV6 (44.2 cases per 100,000 population aged <40 years), GAS (43.0 cases per 100,000 population aged <40 years), rubella (27.1 cases per 100,000 population aged <40 years), and dengue (16.9 cases per 100,000 population aged <40 years). The notification rate for suspected measles or rubella was 31.6 cases per 100,000 population aged <40 years (Table 3 and Figure 2).

**Etiology of Rash and Fever Illness**

Overall, 519 (41.7%) of 1,132 rash-fever cases had an etiologic diagnosis determined by laboratory, with the highest proportions with a laboratory-confirmed diagnosis among children aged <1 year (59.0%) and among persons aged 30–39 years (53.7%) (Table 2). Children aged <10 years accounted for 455 (87.7%) of cases with an identified etiology (Table 2). The most common laboratory-determined etiologies were HHV6 (312 cases), EBV (66 cases), parvovirus (30 cases), rubella virus (30 cases), GAS (30 cases), and dengue virus (22 cases) (Table 4).

No cases of measles were confirmed, supporting Brazil’s achievement of measles elimination. Two hundred two rash and fever cases were reported as suspected rubella, of which 8 were laboratory-confirmed. An additional 22 rubella cases were detected through laboratory testing, for a total of 30 cases. Two of these 22 additional cases actually met Brazil’s clinical case definition for rubella and thus should have been reported as suspected rubella. These 2 cases were diagnosed as dengue infection. The majority (n = 18) of diagnosed rubella cases (n = 30) occurred in children aged <4 years (60.3%).

**Table 2. Notification Rate of Rash and Fever Illnesses and Laboratory-Confirmed Diagnosis by Age Group, VigiFex Surveillance Study, Campinas, Brazil, 2003–2004**

<table>
<thead>
<tr>
<th>Age group, years</th>
<th>Population</th>
<th>Number of notified cases (n)</th>
<th>Notification rate per 100,000 population</th>
<th>Number (%) of notified cases with laboratory-confirmed diagnosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>≤1</td>
<td>14,937</td>
<td>396</td>
<td>2,644.44</td>
<td>233 (59.0)</td>
</tr>
<tr>
<td>1–4</td>
<td>63,028</td>
<td>442</td>
<td>701.28</td>
<td>167 (37.8)</td>
</tr>
<tr>
<td>5–9</td>
<td>78,381</td>
<td>213</td>
<td>2,71.75</td>
<td>55 (25.8)</td>
</tr>
<tr>
<td>10–14</td>
<td>85,266</td>
<td>51</td>
<td>59.81</td>
<td>10 (19.6)</td>
</tr>
<tr>
<td>15–19</td>
<td>93,913</td>
<td>32</td>
<td>34.07</td>
<td>11 (34.4)</td>
</tr>
<tr>
<td>20–29</td>
<td>187,414</td>
<td>74</td>
<td>39.48</td>
<td>21 (28.4)</td>
</tr>
<tr>
<td>30–39</td>
<td>166,453</td>
<td>41</td>
<td>24.63</td>
<td>22 (53.7)</td>
</tr>
<tr>
<td>Total</td>
<td>689,392</td>
<td>1,248</td>
<td>181</td>
<td>519 (41.7)</td>
</tr>
</tbody>
</table>

**NOTE.** Diagnosis was considered preliminary for cases with positive human herpes virus 6 test results.

**Figure 2.** Annual notification rates of confirmed rubella/measles cases, all rash and fever illness, and other etiologies meeting the rubella or measles case definition in Campinas, Brazil, per 100,000 population aged <40 years, 1999–2004.
Of the 4 postvaccine rash cases identified, 1 was rubella and 3 were associated with measles vaccine. Four cases had positive laboratory results for both HHV6 and another etiology (parvovirus and EBV, 2 each) in the first serum sample drawn. For these patients, final diagnosis was reached by considering the patient’s age and the test results for the convalescent-phase serum samples. Six cases of rash were classified as allergic reactions to antibiotics on clinical grounds.

The distribution of fever-rash illness etiologies varied by age group (Table 4). Among children aged <5 years, HHV6 was the most common etiology. Among children aged 5–9 years, EBV followed by parvovirus, HHV6, and GAS were the most frequent etiologies. Dengue was the most common etiology among adults aged ≥30 years (Table 4). The number of reported cases of HHV6 and EBV was higher during August–October.

Among young adults aged 20–29 years, rubella was the most frequent etiology, which is consistent with the rubella virus circulation pattern in Brazil in that period.

Clinical Characterization of Reported Cases

Of 1012 reported cases with presumptive diagnoses other than measles or rubella, 727 (71.8%) met the suspected measles case definition, 293 (29%) met the suspected rubella case definition, and 181 (17.8%) met the suspected case definitions for both measles and rubella. Considering cases that would have met the clinical case definition for either measles or rubella, the suspected measles notification rate was 105.2 cases per 100 000 population aged <40 years, and the suspected rubella notification rate was 42.5 cases per 100 000 population aged <40 years during the study period (Figure 2).

Reporting by Sector

During the study period, the proportion of rash and fever illnesses reported by the private sector rose from 1.6% to 6.1% and the proportion reported by the university sector rose from 5.2% to 28%, while the proportion reported by the public sector decreased from 93.9% to 72.0%, compared with the prestudy period. However, the absolute number of rash and fever cases notified by the public sector increased from an annual peak of 445 in 2000 to 821 during the study period.

Costs of Surveillance System

The incremental cost of the study VigiFex surveillance was US$229 895, of which human resources accounted for US$117 946 (51.3%) and laboratory tests for US$73 720 (32%). Considering a total of 1248 rash and fever cases reported, this represents an additional cost of US$184 per case.

DISCUSSION

This article reports the largest study, to our knowledge, of etiologies of fever-rash illness in the published literature. This study was conducted in a highly measles- and rubella-immunized population, as were other studies [1, 3, 5]. In general, disease etiologies were similar to those in previous studies, although their distribution varied. The proportion of cases with any laboratory-confirmed diagnosis was similar to that reported by Ramsay et al [1] in England (48%) and Davidkin et al [3] in Finland (41%) but lower than that found by Oliveira et al [5] in another region of Brazil (71%). However, the distribution of etiologies differed. Our study found that 2.5% of cases were
Table 4. Notified Cases and Final Diagnosis by Age Group During VigiFex Surveillance Study, Campinas, Brazil, 2003–2004

<table>
<thead>
<tr>
<th>Age group, years</th>
<th>Measles virus</th>
<th>Rubella virus</th>
<th>Parvo-virus-B19</th>
<th>HHV-6</th>
<th>Enterovirus</th>
<th>Adenovirus</th>
<th>Epstein Barr virus</th>
<th>Post-vaccine</th>
<th>Kawasaki syndrome</th>
<th>Rickettsia rickettsii</th>
<th>Leptospirosis</th>
<th>Allergic reaction to anti-biotics</th>
<th>Group A Streptococcus</th>
<th>Dengue virus</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;1</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td>216</td>
<td>4</td>
<td>2</td>
<td>2</td>
<td>0</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>2</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>1–4</td>
<td>0</td>
<td>14</td>
<td>9</td>
<td>79</td>
<td>2</td>
<td>4</td>
<td>35</td>
<td>4</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td>19</td>
<td>0</td>
</tr>
<tr>
<td>5–9</td>
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<td>9</td>
<td>9</td>
<td>9</td>
<td>1</td>
<td>1</td>
<td>22</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td>9</td>
<td>2</td>
</tr>
<tr>
<td>10–14</td>
<td>0</td>
<td>2</td>
<td>1</td>
<td>2</td>
<td>1</td>
<td>0</td>
<td>3</td>
<td>0</td>
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<td>0</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td>0</td>
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<tr>
<td>15–19</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>0</td>
<td>0</td>
<td>2</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td>0</td>
<td>2</td>
<td>0</td>
<td>3</td>
</tr>
<tr>
<td>20–29</td>
<td>0</td>
<td>7</td>
<td>5</td>
<td>1</td>
<td>1</td>
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<td>1</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>5</td>
</tr>
<tr>
<td>30–39</td>
<td>0</td>
<td>2</td>
<td>4</td>
<td>3</td>
<td>0</td>
<td>1</td>
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<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>12</td>
</tr>
<tr>
<td>TOTAL</td>
<td>0</td>
<td>30</td>
<td>30</td>
<td>312</td>
<td>9</td>
<td>7</td>
<td>66</td>
<td>4</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>6</td>
<td>3</td>
<td>22</td>
</tr>
</tbody>
</table>

**NOTE.** Data are number of cases. ELISA, enzyme-linked immunosorbent assay; Ig, immunoglobulin.

- Behring ELISA Ig M, IgG, and capture IgM.
- Organon Teknika IgM.
- Biotrin ELISA IgM and IgG.
- Indirect immunofluorescence reaction. This test cannot distinguish between acute and latent HHV6 infection.
- Cellular culture neutralization reaction, viral isolation, indirect immunofluorescence with monoclonal antibodies (ATCC strains with Chemicon monoclonal antibodies).
- American Type Culture Collection IgG seroconversion through indirect immunofluorescence or viral isolation.
- bioMérieux ELISA IgM viral capsid antigen (VCA) and IgG Epstein-Barr virus nuclear antigen (EBNA).
- For measles, defined as measles IgM detected in rash patient 8–30 days after measles vaccination; for rubella, defined as rubella IgM detected in rash patient 8–52 days after rubella vaccination.
- Clinical diagnosis by attending physician.
- United States Centers for Disease Control (US CDC) indirect immunofluorescence reaction seroconversion.
- PanBio ELISA IgM.
- Culture.
- PanBio Capture ELISA IgM.
- Clinical diagnosis. Four cases had used amoxicillin a mean of 1.3 days (range, 1–2 days) prior to rash onset.
attributable to parvovirus B19, compared with 9%–19% in other studies, whereas 25% of our cases were attributed to HHV-6 in contrast to the 2%–12% reported elsewhere [1, 3–5]. Nonetheless, the age distributions of both HHV-6 and parvovirus cases were similar to those previously described [1, 3].

Our findings may reflect regional and temporal variations in febrile-rash illnesses; however, they may also be influenced by testing limitations. We diagnosed HHV6 using IgM indirect immunofluorescence. However, HHV-6 is a ubiquitous infection that may be acute or latent, and establishing a link between HHV-6 and acute rash and fever illness remains a challenge because there is no gold-standard diagnostic test that can distinguish between latent infection and active viral replication [33, 34]. Viral isolation is the only test that can reliably distinguish between these 2 states; however, it lacks sensitivity and is not practical on a population basis [35].

We identified 3 school-based clusters of GAS. Treatment of GAS can prevent rheumatic heart disease, a documented cause of economic burden in Brazil [36].

Almost three-quarters of the rubella cases detected through laboratory testing were not suspected on clinical grounds, in most part because they did not meet the case definition. Of 30 patients with confirmed rubella, 20 did not present with lymphadenopathy, which is included in the rubella case definition. These data demonstrate that clinical case definition for rubella in Brazil [12, 13] and recommended by WHO [37] may lack sensitivity for settings with rubella and CRS elimination goals.

To our knowledge, this is also the only study designed to assess the value and feasibility of a recommended minimum reporting rate for suspected measles and rubella as a surveillance indicator in settings of measles and rubella elimination. Our study found a notification rate for all febrile-rash illness of 181 cases per 100,000 population aged <40 years.

The overall notification rate of suspected measles (4.6) or rubella (27.1) cases by presumptive clinical diagnosis was 31.6 cases per 100,000 population aged <40 years. Notification rates of suspected measles and rubella cases that would meet the standardized clinical case definitions were 105.2 and 42.5 cases per 100,000 population aged <40 years, respectively. All of the aforementioned reporting rates far exceeded the proposed indicator of ≥2 suspected measles or rubella cases per 100,000 population adequately investigated to monitor surveillance sensitivity [14]. Although the feasibility of meeting this benchmark has been questioned in diverse settings, our findings demonstrate that implementing enhanced surveillance was feasible at a reasonable additional cost in a setting with a well-structured surveillance system of a developing country with an intermediate per-capita income level.

In fact, our data raise the question of whether a reporting rate of 2 cases per 100,000 population is sensitive enough to detect virus circulation in regions where measles elimination has been achieved and where rubella and CRS elimination is in progress, such as the Americas. Additional assessments that consider surveillance data from other countries will be needed to assess whether this benchmark is adequate.

This study highlights the importance of incorporating the private sector into surveillance activities. The expansion of notification to all rash and fever illnesses and outreach efforts to private health care facilities during VigiFex resulted in a marked increase in notifications, particularly from private and university facilities. However, the proportion of total notifications coming from them remained low, and their participation throughout the study was difficult to maintain.

More than 30% of the incremental costs associated with enhanced surveillance implemented in this study were related to expenses for necessary laboratory tests. Approximately 20% of all laboratory costs were used to purchase diagnostic material for enterovirus and HHV-6. It may not be feasible to recommend routine testing for all fever-rash cases as broadly as was done in this study because of the high costs and difficulties associated with this method.

This study had several limitations. Because it was confined to a 13-month period, the average contribution of specific diseases with multiyear epidemic cycles, such as dengue, to rash-fever illness in Campinas may have been either over- or underestimated.

Furthermore, some persons with cases of fever-rash illness undoubtedly remained at home; because this study was facility based, these cases would have gone undetected. As previously mentioned, the proportion of cases that could truly be attributed to HHV-6 is questionable due to the limitations of the HHV-6 testing available.

CONCLUSIONS AND RECOMMENDATIONS

Variations in measles and rubella case definitions and the stage of control will likely influence measles and rubella detection rates through surveillance. Because the current clinical case definition for rubella lacks sensitivity, rubella testing may be considered for all cases of febrile-rash illness, regardless of suspected clinical diagnosis, in settings with rubella elimination goals. Because enhanced surveillance allowed the identification of disease clusters that would otherwise remain undetected, making outbreak-associated GAS a notifiable disease in the country should be considered.

Reaching the currently recommended febrile-rash illness notification rate is achievable and affordable. Additional evaluation will be needed after data are made available from countries using this indicator in the context of measles elimination.

Finally, our findings suggest that stimulating a well-functioning surveillance system through enhanced rash and fever surveillance would allow reporting of potential measles cases and additional rubella cases that may have gone unnoticed considering current clinical surveillance case definitions and regular rubella and measles surveillance.
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**References**


