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Performance of rubella suspect case definition: implications for surveillance

Acurácia da definição de caso suspeito de rubéola: implicações para vigilância

ABSTRACT

OBJECTIVE: To assess the performance of the rubella suspect case definition among patients with rash diseases seen at primary care units.

METHODS: From January 1994 to December 2002, patients with acute rash, with or without fever, were seen at two large primary health care units and at a public general hospital in the municipality of Niterói, metropolitan area of Rio de Janeiro, Brazil. Data from clinical and serologic assessment were used to estimate the positive predictive values of the definition of rubella suspect case from the Brazilian Ministry of Health and other combination of signs/symptoms taking serologic status as the reference. Serum samples were tested for anti-rubella virus IgM using commercially available enzyme immunoassays. Positive predictive values and respective 95% confidence intervals were calculated.

RESULTS: A total of 1,186 patients with an illness characterized by variable combinations of rash with fever, arthropathy and lymphadenopathy were studied. Patients with rash, regardless of other signs and symptoms, had 8.8% likelihood of being IgM-positive for rubella. The Brazilian suspect case definition (fever and lymphadenopathy in addition to rash) had low predictive value (13.5%). This case definition would correctly identify 42.3% of the IgM-positive cases, and misclassify 26.1% of the IgM-negative cases.

CONCLUSIONS: These results support the recommendation to investigate and collect clinical specimens for laboratory diagnosis of all cases of rash, for surveillance purposes. Although this strategy may increase costs, the benefits of interrupting the circulation of rubella virus and preventing the occurrence of congenital rubella syndrome should pay off.

KEYWORDS: Rubella, epidemiology. Rubella, diagnosis. Predictive value. Epidemiologic surveillance. Case definition.

RESUMO

OBJETIVO: Avaliar a acurácia da definição de caso suspeito de rubéola entre pacientes com doenças exantemáticas atendidos em unidades de saúde pública.

MÉTODOS: A população de estudo foi constituída de pacientes com doença exantemática, com ou sem febre, atendidos em serviços de saúde pública, de janeiro de 1994 a dezembro de 2002 no município de Niterói, RJ. Dados clínicos e sorológicos foram utilizados para estimar os valores preditivos positivos da definição de caso

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suspeito de rubéola do Ministério da Saúde do Brasil e outras combinações de sinais e sintomas, considerando o resultado da sorologia como referência. A detecção de IgM específica para rubéola em amostras sangüíneas foi realizada por ensaio imunoenzimático. Foram calculados os valores preditivos positivos e respectivos intervalos de confiança de 95%.

RESULTADOS: Foram estudados 1.186 pacientes com uma doença caracterizada por uma variada combinação de *rash* com ou sem febre, artropatia e linfoadenopatia. Pacientes com exantema, independentemente da presença de outros sinais e sintomas, apresentaram uma probabilidade de 8,8% de serem IgM positivos para rubéola. A definição de caso suspeito de rubéola utilizada no Brasil apresentou baixo valor preditivo positivo (13,5%). Esta definição de caso identificou corretamente 42,3% dos casos IgM positivos, e classificou de forma incorreta 26,1% dos IgM negativos.

CONCLUSÕES: Os resultados indicam que as doenças exantemáticas devem ser investigadas em conjunto para fins de vigilância epidemiológica e coleta de espécimens clínicos para o diagnóstico laboratorial. Esta estratégia aumenta os custos, mas gera benefícios na interrupção da circulação do vírus e na prevenção da síndrome da rubéola congênita.

DESCRITORES: Rubéola, epidemiologia. Rubéola, diagnóstico. Valor preditivo. Vigilância epidemiológica. Definição de caso.

INTRODUCTION

Rubella is a common cause of childhood rash (exanthema) and fever in non-immunized populations, and its public health importance relates to teratogenic effects of primary rubella infection in pregnant women.[5] The infection caused by rubella virus is usually mild, with most cases presenting as subclinical or unrecognized events.[7,18] Besides, the most common symptoms of rubella (maculopapular rash, low-grade fever, posterior cervical and suboccipital adenopathy, and arthralgia/arthritis, especially in adult females) can easily be mistaken for other rash diseases.[1,8,14,16] Therefore, a definitive diagnosis of rubella can be made only by specific laboratory methods.[18]

Mass immunization against rubella was gradually implemented by Brazilian states in primary care units between 1992 and 2000, in campaigns targeting children aged 1-11 years. By 2000, all Brazilian states had initiated routine use of combined measles, mumps, and rubella (MMR) vaccine, with one dose scheduled for 15 months of age. In 2003, the age of vaccination was changed to 12 months with a booster dose at 4-6 years of age.[12]

Although rubella surveillance in Brazil had begun in 1996 when case reporting became mandatory,[12] its effectiveness varied across the country. As part of the regional goal for measles elimination in the Americas by the year 2000, rubella surveillance was intensified in 1999 and integrated into measles surveillance. With the improvement of epidemiological surveillance of rubella and congenital rubella syndrome (CRS) outbreaks among young adults were reported during 1999-2000.[15] To prevent the occurrence of CRS, a rubella vaccination campaign targeting 12-30-year-old females nationwide was conducted in two phases during 2001-2002.[12]

Case investigation and identification of contacts are now recommended for all suspected cases of rubella.[3] Case definition is a fundamental component of disease surveillance. The current definition of rubella suspect case from the Brazilian Ministry of Health relies on the presence of maculopapular rash of acute onset, fever and retroauricular, occipital and cervical lymphadenopathy[12] to prompt further investigation and laboratory or epidemiologic confirmation.

Thus, the objective of this study was to assess the performance of the rubella suspect case definition from the Brazilian Ministry of Health among patients with rash diseases. Data gathered along nine years, in a research project of surveillance of rash diseases, provided a unique opportunity to verify the effectiveness of the set of clinical criteria to select patients thought to include rubella cases.

METHODS

A cross-sectional study was carried out. Data from

clinical and serologic assessment conducted on cases of rash were used to estimate the positive predictive values of the definition of suspect case from the Brazilian Ministry of Health[12] and of other combination of signs/symptoms taking the serologic status as a reference. Sensitivity and specificity could not be estimated since serologic tests for rubella were not available in cases without rash.

From January 1994 to December 2002, 1,186 patients with acute rash, with or without fever, were seen at two large primary health care units and at a public general hospital in the municipality of Niterói, State of Rio de Janeiro, Southern Brazil. The study population comprised patients attending the two largest primary health care units and a general hospital from the public network with a catchment area of approximately 50% of the population of the municipality of Niterói (459,451 inhabitants in 2000*). The clientele of those health units has predominantly middle and low socioeconomic status. Individuals of any age presenting spontaneously to those health units with maculopapular rash were considered eligible for the study regardless of accompanying symptoms. Cases were excluded from the study if the rash was vesiculopapular or urticariform, or if more than 30 days had elapsed after the start of rash. A standard clinical examination was performed and a clotted blood sample for serology was collected in a sterile glass tube at the time the patient was enrolled in the study.

Symptoms and signs (measured or reported fever, myalgia, malaise, headache, runny nose, conjunctivitis, arthropathy, lymphadenopathy and other symptoms) were assessed as in usual care by medical doctors at the time of enrollment. Signs, symptoms and their duration, and sociodemographic data were recorded on a form designed for the study.

All serum samples were tested for anti-rubella virus IgM using commercially available enzyme immunoassays (EIA): Rubenostika II IgM, Organon Teknika (Boxtel, Holland) (1994-1999) and Enzygnost® anti-rubella-virus/IgM, Dade Behing (Marburg, Germany) (2000-2002). Sera were also tested for measles virus IgM using an antibody capture EIA developed at the Centers for Disease Control (Atlanta, USA)[9] (1994-1998) and a commercially available EIA: Enzygnost anti-measles virus/IgM, Dade Behring (Marburg, Germany) (1999-2002), and for dengue virus IgM by an in-house EIA.[10,13] Specimens negative for rubella, measles and dengue virus IgM were also tested for anti-human parvovirus B19 IgM using an antibody capture EIA (MACEIA).[4] An indirect immunofluorescence test for human herpes virus type 6 (HHV-6) IgG[17] was also used to detect low avidity HHV-6 IgG (indicating recent primary infection) in children less than 4 years of age without an alternative diagnosis.

The positive predictive values of the suspect case definition from the Brazilian Ministry of Health[12] and of other specified combinations of signs/symptoms were estimated by the proportion of those patients who were found to be seropositive for rubella. Confirmed rubella cases taken as reference had at least one serum sample testing positive for rubella IgM, regardless of the clinical picture and the time of disease. Data analysis was stratified by age to account for differences in clinical presentation of rubella in children and adults, and by time period, acknowledging the two distinct phases of surveillance and control of rash diseases in Brazil. Ninety-five percent confidence intervals for the estimates were constructed. Data were analyzed using Epi Info 6.04d.

Informed consent was obtained for all participants and from the parents or guardians of patients younger than 18 years of age. The study was approved by the hospital's Institutional Review Board.

RESULTS

A total of 1,186 patients presenting exanthematous disease with variable combinations of rash with fever, arthropathy and lymphadenopathy were studied from January 1994 to December 2002. There were few losses due to failure in venopuncture or inadequate blood samples, but no refusals. Laboratory confirmed diagnosis was achieved in 673 (56.7%) cases investigated: dengue fever (354 cases, 52.6%), human parvovirus B19 (120 cases, 17.8%), rubella (104 cases, 15.5%), HHV-6 (63 cases, 9.4%), and measles (32 cases, 4.7%). No diagnosis was established in 513 (43.3%) cases that were seronegative for rubella, measles, dengue, parvovirus and HHV-6. That proportion was lower among individuals with one day of rash (22%). In fact, for cases without laboratory confirmation, the proportion of cases with one day of rash was lower (7%) compared to those with serological confirmation (18%). Altogether, 47% of the participants had blood samples drawn within two to five days of rash. Among patients without laboratory diagnosis 53.4% were less than 15 years old and 59.2% were female subjects, whereas those with serologic confirmation had 49.5% below 15 years and 58.4% of female subjects. Patients were

*Instituto Brasileiro de Geografia e Estatística [homepage da Internet]. Cidades@. Disponível em http://www.ibge.gov.br/cidadesat [acesso em 10 ago 2005]

Table 1 - Positive predictive value (PPV) and 95% confidence interval of different combinations of exanthema with other signs and symptoms. Niterói, Brazil, 1994-2002.

Age	Below 15 years			15 or more years			All ages
Signs and Symptoms	Rubella	Total S/S	PPV ±1.96 SE	Rubella	Total S/S	PPV ±1.96 SE	PPV ±1.96 SE
Ex. + fever + arthropathy + lymphadenopathy	2	18	0.111 ±0.145	17	81	0.210 ±0.089	0.192 ±0.078
Ex. + lymphadenopathy	26	237	0.110 ±0.040	39	180	0.217 ±0.060	0.156 ±0.035
Ex. + fever + lymphadenopathy	19	187	0.102 ±0.043	25	139	0.180 ±0.064	0.135 ±0.037
Ex. without fever	15	135	0.111 ±0.053	18	138	0.130 ±0.056	0.121 ±0.039
Ex. + fever+ [arthropathy or lymphadenopathy or conjunctivitis]	34	320	0.106 ±0.034	34	351	0.096 ±0.031	0.101 ±0.023
Ex. + arthropathy	7	73	0.096 ±0.068	35	300	0.117 ±0.036	0.113 ±0.032
Ex. + fever + [arthropathy or lymphadenopathy]	42	526	0.080 ±0.023	53	513	0.103 ±0.026	0.091 ±0.017
Ex. + fever + arthropathy	4	59	0.068 ±0.064	23	248	0.093 ±0.036	0.088 ±0.032
Ex. + fever	37	472	0.078 ±0.024	34	441	0.077 ±0.025	0.078 ±0.017
Ex. without arthropathy	42	531	0.079 ±0.023	19	282	0.067 ±0.029	0.075 ±0.018
Ex. without lymphadenopathy	23	367	0.063 ±0.025	16	402	0.040 ±0.019	0.051 ±0.016
Ex. without fever, arthropathy and lymphadenopathy	0	72	0.000 -	0	66	0.000 -	0.000 -
Exanthema	49	604	0.081 ±0.022	55	582	0.095 ±0.024	0.088 ±0.016

Ex.: Exanthema; S/S: Signs and symptoms; SE: Standard error

divided in rubella (104 cases) and non rubella (1,082 cases) to assess the performance of the rubella suspect case definition (Table 1).

Patients of all ages presenting with rash, regardless of other signs and symptoms, had 8.8% probability of being IgM positive for rubella (Table 1). The combination with at least one of the symptoms fever, lymphadenopathy or arthropathy did not increase substantially the positive predictive value (PPV). Individuals aged 15 years or more with lymphadenopathy in addition to rash were the most likely to have rubella IgM antibodies (21.7%).

The suspect case definition from the Brazilian Ministry of Health (fever and lymphadenopathy in addition to rash) had low predictive values for both age groups studied: 10.2% in patients below 15 years and 18% in those with 15 or more years. Overall, this suspect case definition would correctly identify 42.3% of the IgM-positive cases of rash, and misclassify 26.1% of the IgM-negative cases of rash. However, assuming a 50% sensitivity of rash for rubella, most cases both in children and in adults would not be detected by this combination of signs and symptoms.

The combination fever and arthropathy or lymphadenopathy, which combined with rash is the case definition recommended by the World Health Organization,[18] also achieved low PPV (9.1%) in both age groups. Besides, 944 (87.2%) of the 1,082 IgM-negative cases with rash also presented those symptoms (false positives).

Rash with fever (regardless of other signs/symptoms) was found in 67.3% of rubella IgM-positive cases, but also in 77.8% of the other rash diseases. The latter would constitute false positives if rash with fever was used to indicate putative rubella cases in this setting.

The performance of the rubella suspect case definition recommended by the Centers of Disease Control and Prevention (rash, fever and one of the following: lymphadenopathy, arthropathy or conjunctivitis)[3] was also assessed. The overall PPV found (10.1%) was not much better than the results ob-

Table 2 - Positive predictive value (PPV) of different combinations of exanthema with other signs and symptoms, according to the study period. Niterói, Brazil, 1994-2002.

Study period	1994-1997						1998-2002		
Age	Below 15 years			15 or more years			All ages*		
Signs and Symptoms	Rubella	Total S/S	PPV ±1.96 SE	Rubella	Total S/S	PPV ±1.96 SE	Rubella	Total S/S	PPV ±1.96 SE
Ex. + fever + arthropathy + lymphadenopathy	2	6	0.333±0.377	13	40	0.325±0.145	4	53	0.075±0.071
Ex. + lymphadenopathy	25	77	0.325±0.105	31	90	0.344±0.098	8	247	0.032±0.022
Ex. + fever + lymphadenopathy	18	59	0.305±0.117	20	66	0.303±0.111	5	199	0.025±0.022
Ex. without fever	15	43	0.349±0.142	13	45	0.289±0.132	5	184	0.027±0.023
Ex. + fever + [arthropathy or lymphadenopathy or conjunctivitis	33	110	0.300±0.086	26	132	0.245±0.073	9	425	0.021±0.014
Ex. + arthropathy	7	24	0.292±0.182	26	104	0.250±0.083	9	243	0.037±0.024
Ex. + fever + [arthropathy or lymphadenopathy]	40	158	0.253±0.068	31	179	0.173±0.055	10	688	0.015±0.009
Ex. + fever + arthropathy	4	18	0.222±0.192	17	82	0.207±0.088	6	206	0.029±0.023
Ex. + fever	33	139	0.237±0.071	27	159	0.170±0.058	10	611	0.016±0.010
Ex. without arthropathy	42	159	0.264±0.069	19	105	0.181±0.074	-	548	- ±0.000
Ex. without lymphadenopathy	23	105	0.219±0.079	9	114	0.079±0.050	7	550	0.013±0.009
Ex. without fever, arthropathy and lymphadenopathy	-	72	- -	-	66	- -	-	1	- -
Exanthema	48	182	0.264±0.064	40	204	0.196±0.054	16	795	0.020±0.010

Ex.: Exanthema; S/S: Signs and symptoms; SE: Standard error
*As there was only one case of rubella in the age group <15 years, both groups were analyzed together.

tained with other combinations of signs and symptoms studied (Table 1). In rubella epidemic years (1994–1997) the PPV was also low (Table 2), although substantially higher than those obtained in periods of lower incidence of the disease (1998–2002). In addition, no combinations of signs and symptoms assessed were able to detect all rubella cases that occurred in both periods.

DISCUSSION

In a scenario of high incidence, the sensitivity of suspect case definition may not be relevant for control purposes, which are not much affected if a proportion of cases are not detected. On the other hand, in very low incidence settings, a sensitive definition is emphasized to ensure that all possible cases are captured, even if many false positive are included. The latter scenario seems to apply to the current situation in most parts of Brazil, in which the reduction in the number of confirmed cases of rubella shown in Table 2 has also followed the consolidation of the immunization activities against rubella.

Since rash was a selection criterion for investigation of suspect cases referred for serology, the suspect case definition for surveillance is analogous to a serial combination of "tests" (criteria), namely, rash and other signs/symptoms in multiple associations. The sensitivity of serial combinations is the product of the sensitivity of its components.[6] Data did not allow the estimation of the sensitivity of rash. Assuming that approximately half of those individuals infected with rubella have symptoms,[3] a 50% sensitivity of rash would be a plausible estimate. Therefore, the serial combination of rash with other signs and symptoms could only result in very low levels of sensitivity and reduced negative predictive values. Although rash in itself is thought to define a group with higher probability of rubella, the results of the present study pointed out that there was no optimum combination of signs and symptoms with satisfactory predictive value in subjects presenting with rash, even in periods of higher incidence of rubella. Considering an 8.8% (104/1,186) prevalence of rubella in the study rash cases, PPVs obtained in this study indicated low sensitivity and specificity. These results are consistent with the recommendation that all suspect rubella cases, particularly those isolated cases that do not occur as part of an outbreak, should be confirmed by laboratory testing.[2] This issue of case definition become more complicated by the fact that partially immune persons may have mild illnesses, which make detection of a suspected case still more difficult.[11] Inaccurate diagnosis of rash illness may result in disease spread, as well as inefficient use of limited resources.

Considering the results obtained by the combinations of signs and symptoms studied, it did not seem that serial combinations could enhance case detection. Also, because a sizable proportion of infections may not present rash, major signs and symptoms such as fever and arthropathy or lymphadenopathy without rash might be added to the case definition in small areas of suboptimal vaccine coverage, or in the field investigation of a confirmed case. Low levels of specificity of those criteria could be overcome with additional epidemiological data, such as contact with another rash disease confirmed by laboratory, written documentation of prior rubella vaccine or laboratory evidence of rubella immunity, used to help the investigation of a suspected case.[2] In any event, the role of the rubella suspect case definition is to ensure surveillance based on laboratory diagnosis and to monitor the occurrence of other suspected cases in the same region. The selection of individuals with higher probability of rubella ensures that the high accuracy of the serologic test maximizes the predictive value of positive IgM sera.

The sensitivity and specificity of the EIA are generally considered very high and the results of serology are taken as the ultimate diagnostic criterion. However, as in many laboratory tests which measure antibody response, accuracy of the EIA for rubella is expected to vary as the disease progresses, being lower in the early course of infection. The study group was still heterogeneous in terms of timing of clinical and laboratory assessment, and of disease severity, despite the fact that asymptomatic infections and cases without rash were not eligible. Timing of blood collection did not seem to justify the observed proportion of inconclusive serological test results. Several other causes of rash, such as, mononucleosis, enterovirus, echovirus, coxsackievirus and streptococcal infections might have accounted for the large proportion of "inconclusive" cases.

Another limitation of this study was the consideration of the clinical picture based on just one contact between patient and physician, as new signs and symptoms developing later were not available. Also, data on vaccination status was lacking documentation, thus, limiting reliability. Nevertheless, those considerations probably enhance the usefulness of the results presented, as they were obtained under average conditions of public health care units wherein disease surveillance often gets started.

The results of the present study suggest that current suspect case definitions, which include signs and symptoms other than rash such as that of the Brazilian Ministry of Health may limit case finding and delay detection of outbreaks. Because of the syndromic character of surveillance, rash, regardless of additional signs and symptoms, should continue to prompt laboratory tests in the approach to patients suspected of infections. Rash diseases should be investigated as a whole for surveillance purposes and collection of clinical specimens for laboratory diagnosis, except for epidemic periods, in which the disease causing the epidemic should prevail. Although this strategy may result in high costs, the benefits of interrupting the widespread circulation of rubella virus and preventing the occurrence of CRS should pay off.

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