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Clinical, laboratorial diagnosis and prophylaxis of measles in Brazil

Diagnóstico clínico, laboratorial e profilático do sarampo no Brasil

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ABSTRACT

Measles is an acute febrile exanthematic disease of viral etiology, highly contagious, being the cause of morbidity and mortality of children in developing countries, whereas it has become rarer in developed countries due to vaccination. Its differential diagnosis should be made with other childhood viral respiratory diseases such as influenza, rhinovirus and adenovirus, and exanthematic febrile diseases such as rubella, roseola and varicella. In tropical regions, it should be performed with dengue, zika and chikungunya. Its clinical picture presents the following phases: incubation, usually asymptomatic; a prodrome, in which fever, malaise, coryza can occur, besides Koplik's signs; exanthematic, with presence of maculopapular exanthema after the fever condition that progresses to a craniocaudal evolution, with clinical improvement in uncomplicated cases. Common complications are pneumonia, otitis media, keratitis; the rarest are acute disseminated encephalomyelitis and subacute sclerosing panencephalitis. Nonspecific laboratory alterations are seen in the blood count. The specific laboratory diagnosis is based on the detection of viral ribonucleic acid (RNA) [polymerase chain reaction (PCR) of nasal swab samples, oral mucosa or urine]. Immunoglobulin class M (IgM) can be detected during the exanthematous period by enzyme-linked immunosorbent assay (ELISA), and immunoglobulin class G (IgG) throughout the convalescence period, and the detection of specific IgG by the plaque reduction neutralization test may also be performed. The prophylaxis of the disease is based on vaccination in children from 15 months in order to reach about 85% to 95% of the population, what confers herd immunity. Thus, vaccination is the most effective measure in combating measles, since the treatment consists only of clinical and symptomatic support.

Key words: measles; exanthema; polymerase chain reaction; enzyme-linked immunosorbent assay; *Morbillivirus*.

RESUMO

O sarampo é uma doença exantemática febril aguda de etiologia viral altamente contagiosa. É causa de morbidade e mortalidade de crianças em países em desenvolvimento, ao passo que se tornou mais rara em países desenvolvidos devido à vacinação. O diagnóstico diferencial deve ser realizado em relação a outras doenças da infância, como influenza, rinovírus, adenoviroses, rubéola, roséola e varicela. Já em regiões tropicais, inclui dengue, vírus da zika e chikungunya. Seu quadro clínico apresenta as seguintes fases: a de incubação – em geral assintomática; a prodrômica – na qual podem ocorrer febre, mal-estar e coriza, além de sinais de Koplik; e a exantemática – com presença de exantema maculopapular após o quadro febril, que progride de forma craniocaudal, com melhora clínica em casos não complicados. Complicações comuns são pneumonia, otite média e ceratoconjuntivite; as mais raras, encefalomielite disseminada aguda e panencefalite esclerosante subaguda. Alterações laboratoriais inespecíficas são vistas no hemograma. O diagnóstico laboratorial específico baseia-se na detecção do ácido ribonucleico (RNA) viral [reação em cadeia da polimerase (PCR) de amostras de swab *nasal, mucosa oral ou urina]. Imunoglobulina da classe M (IgM) pode ser detectada durante o período exantemático por ensaio de imunoadsorção enzimática (ELISA) e imunoglobulina da classe G (IgG), ao longo do período de convalescença, podendo também ser realizada a detecção de IgG específica pelo teste de neutralização por redução de placas. A profilaxia da doença é baseada na vacinação em crianças a partir dos 15 meses de*

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idade, visando atingir cerca de 85% a 95% da população, o que confere imunidade de rebanho. A vacinação é a medida mais eficaz no combate ao sarampo, visto que o tratamento consiste apenas em suporte clínico.

Unitermos: *sarampo; exantema; reação em cadeia da polimerase; ensaio de imunoadsorção enzimática;* Morbillivirus.

RESUMEN

El sarampión es una enfermedad exantemática febril aguda de etiología viral altamente contagiosa. Causa morbilidad y mortalidad de niños en países en desarrollo, mientras que se hizo más raro en países desarrollados gracias a la vacunación. El diagnóstico diferencial se hace con otras enfermedades infantiles, como influenza, rinovirus, adenovirus, rubéola, roséola y varicela. En regiones tropicales, incluye dengue, zika y chikungunya. Su cuadro clínico presenta las siguientes fases: incubación – en general asintomática; pródromo – en la cual pueden ocurrir fiebre, malestar y coriza, además de manchas de Koplik; y la exantemática – con presencia de exantema máculo-papular después del cuadro febril, que se disemina desde la cara a tronco y extremidades, con mejora clínica en casos no complicados. Complicaciones comunes son neumonía, otitis media y queratoconjuntivitis; las más raras, encefalomielitis aguda diseminada y panencefalitis esclerosante subaguda. Alteraciones inespecíficas de laboratorio son vistas en el hemograma. El diagnóstico específico de laboratorio se basa en el aislamiento del ácido ribonucleico (ARN) viral (PCR de muestras nasales, mucosa oral u orina). La inmunoglobulina M (IgM) pude ser detectada durante el período exantemático por ensayo por inmunoadsorción ligado a enzimas (ELISA); la inmunoglobulina G (IgG), a lo largo del período de convalecencia, y la detección de IgG específica por la prueba de neutralización por reducción de placa. La profilaxis de la enfermedad se basa en vacunación en niños desde los 15 meses de edad, buscando alcanzar 85%-95% de la población, lo que confiere inmunidad de grupo. La vacunación es la medida más eficaz en el combate al sarampión, puesto que el tratamiento consiste sólo en soporte clínico.

Palabras clave: *sarampión; exantema; reacción en cadena de la polimerasa; ensayo de inmunoadsorción enzimática;* Morbillivirus.

INTRODUCTION AND DEFINITION

Measles is an acute exanthematic febrile disease of high transmissibility, caused by Paramyxoviridae virus of the genus *Morbillivirus*. It is one of the classic affections of childhood, of global distribution, with no predilection for race or gender. The measles virus has eight classes (A-H), which can be subdivided into 24 genotypes. The distribution of each genotype is continuous and geographically modeled[1, 2].

Transmission occurs from person to person, through nasopharyngeal secretions expelled by coughing, sneezing, speaking, or breathing. The virus can be transmitted four to six days before or four days after the rash onset. Although it may occur in newborns of susceptible mothers, measles is relatively rare in the first six months due to the transplacental transfer of maternal antibodies[3, 4].

Measles represents an important cause of hospitalization, morbidity and mortality in childhood; the lethal outcome is closely related to the degree of socioeconomic development of affected individuals, hygiene standards, nutrition and proper health care. A major worldwide problem in eliminating this disease is the inability to immunize the entire population. Therefore, individuals who are susceptible to the virus may transmit the disease and cause a regional outbreak[3].

Since the advent of vaccination, the disease has become rare in North America and in many developed countries. Overall, the number of reported cases of measles decreased from 146 cases per million in 2000 to 36 cases per million in 2015. In the USA, the annual incidence of measles was 2.06 and 0.08 per million inhabitants in 2001 and 2015, respectively. Currently, measles in developed countries is mainly the result of cases imported from places where the disease is endemic and almost exclusively in individuals who are not vaccinated or who have an incomplete vaccination schedule. For example, there was a measles outbreak in Okinawa, Japan, in March 2018. The virus is believed to have entered Japanese territory through Thai immigrants[4, 5].

In Brazil, measles has been a notifiable disease since 1968. Until 1991, the country faced nine epidemics, one every two years, on average. The highest number of reported cases was recorded in 1986 (129,942), representing an incidence rate of 97.7 per

100,000 inhabitants. Until the early 1990s, the most affected age group was children under 15 years. In the 1980s, there was a gradual decline in the number of deaths, with 15,638 records. This reduction was attributed to the increase in vaccination coverage and the improvement of medical care offered to children with post-measles complications. In 1992, Brazil adopted the goal of eliminating measles for the year 2000, with the implementation of the National Measles Elimination Plan, which was the first national vaccination campaign[4] against the disease.

The Brazilian Ministry of Health (MH) created in 1999 a task force against measles with the appointment of at least one surveillance technician for each state. In the year 2015, among 3,207 cases 214 were confirmed: in Ceará (211 cases, genotype D8), Roraima (one case, genotype D8) and São Paulo (two cases, without genotype identification). In 2016, Brazil received the certificate of elimination of measles virus circulation by the World Health Organization (WHO), declaring the Americas a Region free of measles. Despite widespread vaccine coverage, outbreaks of the disease have been observed when there are 3% to 7% susceptible people in the population[3, 6].

Since July 2017, Venezuela has had an outbreak of measles. The sociopolitical and economic situation caused an intense migratory movement that contributed to the spread of the virus to other geographical areas. Due to the immigration of Venezuelans, on April 2018, the Roraima State reported a suspected case of measles, in the municipality of Boa Vista, Roraima, Brazil. It was a 1-year-old Venezuelan, unvaccinated child, who presented fever, rash, accompanied by cough, coryza and conjunctivitis. The case was confirmed by laboratory criteria. After this case, more than 279 suspected cases were reported, 79 confirmed cases, with two deaths and 16 discarded. In the Amazonas state, from February to April 2018, 251 cases were reported, 16 confirmed, 29 discarded and 206 remain under investigation[3, 6, 7].

CLINICAL MANIFESTATIONS

Measles typically has distinct phases: incubation, prodromal and exanthematic. Its transmission is possible about five days before and four days after the onset of the rash, and more than 90% of people exposed will develop the disease. The incubation phase lasts 10-14 days and it is usually asymptomatic, when there is viremia after respiratory transmission, followed by viral replication. The prodromal phase lasts 2-8 days, with the presence of nonspecific symptoms, as fever, malaise, cough, coryza and conjunctivitis. In some patients, Koplik's signs appear 24-48 hours before the onset of the rash[8].

Maculopapular rash emerges in the exanthematic phase, initially in the face and spreading to the trunk and extremities 3-4 days after of beginning of fever, lasting around three days. Clinical improvement occurs in around one week in uncomplicated cases. Children with cellular immunodeficiencies, as carriers of human immunodeficiency virus (HIV), might not develop the characteristic rash or it might be delayed[8, 9].

Measles can present common complications, mainly primary or secondary pneumonia, especially in young, immunocompromised, malnourished individuals and in children with vitamin A deficiency. Other complications are otitis media, keratoconjunctivitis and diarrhea[8].

As rarer and more serious form of complications we have the acute disseminated encephalomyelitis, in which the patient may present with fever, headache, ataxia and seizures, with evidence in magnetic resonance images (MRI), showing lesions in the white matter, sometimes thalamus, basal ganglia and cephalic trunk. Another form is the subacute sclerosing panencephalitis, which may occur months or years after the initial measles picture, with progressive worsening of cognitive and motor functions, convulsions and even death. In immunocompromised individuals, a rare complication that may occur is measles inclusion body encephalitis, in which the patient may present with altered mental status, seizures, focal epilepsy, hearing loss, momentary blindness, and can progress to coma and death[10].

The clinical definition of measles (maculopapular rash, fever, associated with coryza, conjunctivitis or cough) has a high sensitivity (between 75% and 90%), but has a low positive predictive value when measles incidence is low, indicating the importance of methods to confirm a case when there are not many new cases[8].

Measles is an important cause of morbidity and mortality in pregnant women, who are more likely to be hospitalized, have complications of pneumonia and die in relation to non-infected pregnant women. It is also related to higher fetal morbidity and mortality, leading to higher risk of miscarriage, low birth weight, prematurity, need for neonatal intensive care unit (ICU) hospitalization in relation to fetuses of non-infected pregnant women[11].

DIFFERENTIAL DIAGNOSIS

Before the exanthematic phase, the differential diagnosis should be made with other viral respiratory diseases of childhood, such as influenza, rhinovirus, adenovirus. Differential diagnosis should also be made with other acute exanthematous fever

diseases, such as dengue, rubella, Kawasaki disease, varicella, roseola (exanthema subitum), enteroviruses[12].

LABORATORY DIAGNOSIS

Non-specific exams

Complete blood cell count may reveal leukopenia, lymphopenia with, sometimes, relative lymphocytosis, thrombocytopenia and absolute neutropenia[13]. Liver function test results may reveal elevated transaminase levels in patients with measles hepatitis[14].

Specific exams

Specific laboratory diagnosis of measles can be performed serologically, in which the enzyme-linked immunosorbent assay (ELISA) method is used to detect the presence of virus-specific immunoglobulin class M (IgM) in the plasma, having a greater sensitivity around four days after the onset of the rash. In the acute phase, the detection of antibodies of the IgM class can be performed by other techniques different from ELISA, as indirect immunofluorescence and hemagglutination inhibition. The IgM levels decay during the convalescence period, which lasts 1-2 months, and the virus-specific immunoglobulin class G (IgG) rises, with increase of about four times its titration after the acute phase and can be used as laboratory diagnosis or for seroconversion verification[8, 15].

The gold standard immunoassay in laboratory diagnosis of measles is the plaque reduction neutralization test (PRNT) for specific IgG detection. In relation to ELISA, it has greater sensitivity and the same specificity (100%), but it is costlier[16].

The use of a clinical laboratory in the diagnosis of measles infection can be performed by analysis of urine, oropharyngeal and nasopharyngeal secretions, blood, cerebrospinal fluid, and tissues by the polymerase chain reaction (PCR) technique, preferably on the first three days of the onset of symptoms, before IgM antibodies are detectable[6, 15, 17]. The current national standard recommends viral isolation and/or reverse transcription (RT)-PCR in the biological samples collected in swabs. Collect three swabs (two nostrils and one oropharynx) with rayon swab and add them to 15 ml sterile polypropylene conical tube, screw cap, dry. Cut the swab rods to properly close the tube with respiratory secretion. Place the tube in a styrofoam box with recyclable ice and send to the reference laboratory within six hours[18].

The material to be collected for serological analysis is venous blood, in the amount of 5 to 10 ml. Blood should be drawn aseptically, in vacuum system, in a 10 ml-dry tube without anticoagulant. For urine analysis, samples should be collected in a new sterile bottle, from 15 ml to 100 ml, preferably the first morning midstream clean-catch specimen; if it was not possible to get the first urine of the day, collect it at another time. After collection, place the specimen in a styrofoam box with recyclable ice and send it as soon as possible (within six hours) to the laboratory. Urine should not be frozen in the unit[18].

The clinical and laboratory evolution of measles is summarized in **Figure 1**.

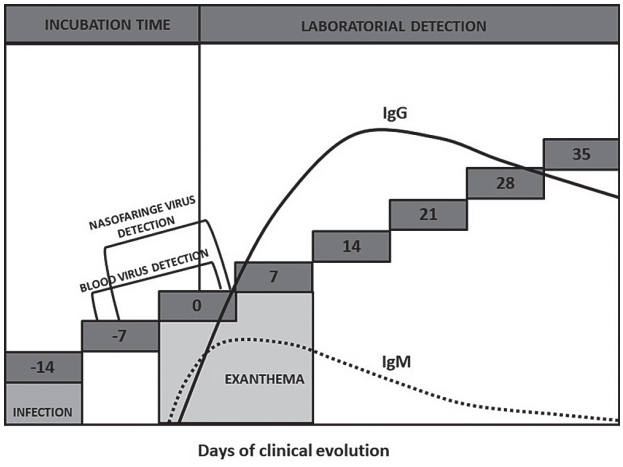

FIGURE 1 – *Clinical and laboratory evolution of measles*
IgM and IgG: immunoglobulin class M and G.
Source: Adapted from WHO, 2007.

New approaches are in development to increase the sensitivity of measles diagnosis. The possibility of using rod-shaped Au-Pt core/shell nanoparticles (Au@Pt NRs) in the detection of measles-specific antibodies could significantly increase the sensitivity of serological diagnosis. Currently, the commercially available ELISA uses horseradish peroxidase (HRP) and can detect measles-specific IgM on a concentration of 10×10^4 ng/ml, while Au@Pt NR-antigen conjugate-based ELISA was able to detect the specific immunoglobulin at concentrations of 10 ng/ml, which is three orders of magnitude higher than the currently commercial available HRP-based ELISA. The use of the nanoparticle-enzyme conjugate could greatly increase the sensitivity of ELISA and help the establishment of a specific measles diagnosis[19].

VACCINATION

Measles prophylaxis is done by vaccination. In Brazil, the vaccine offered by the public health system is made up of attenuated

virus for measles, rubella, mumps and varicella, for children from 15 months to up to 4 years. Two doses are recommended: the second, three months after the first. Only those who had a record of two doses applied after the 12 months of age are considered adequately treated[7].

The priority of the National Immunization Program is the vaccination of children, adolescents and adults up to 49 years of age; therefore, the MH provides two doses of the vaccine for all younger than 30 years (up to 29 years of age) and a single dose for those 30 to 49 years. Health professionals, when not vaccinated, should receive two doses of triple viral vaccine (MMR vaccine), with a minimum interval of 30 days between them, regardless of age[7, 20]. The objective of the vaccination is to block new cases and confer herd immunity to unvaccinated individuals to reach 85%-95% vaccination levels[8, 21].

Pain, heat and redness at the place where the vaccine was applied after approximately 2 hours are considered side effects of vaccination. Sometimes, fever above 39°C is observed for two days, about 5-12 days after the application, as well as transient rash and, more rarely, febrile seizures. Allergic reactions to vaccine components, such as hypersensitivity reactions and, more rarely, anaphylactic shock, are also described. Serious and life-threatening complications, as septicemia and toxic shock syndrome, are related to failure in the vaccination procedure. Vaccination is contraindicated in cases of immunosuppression, infants younger than 6 months of age, gestation and in known history of hypersensitivity reactions[8, 9].

POST-EXPOSURE PROPHYLAXIS

In case of contact, vaccination should be carried out within three days, in order to reduce the chance of developing the disease and/or its gravity. In cases when it is not possible to use the vaccine immediately because of a contraindication, immunoglobulin should be administered intramuscularly within up to six days. In outbreak situations or contact with a person with suspected measles, infants from 6 months of age should be vaccinated. However, this dose should not be considered valid, and therefore, they will need to receive habitual doses afterwards[7-9].

FINAL CONSIDERATIONS

Measles is a highly contagious disease that can lead to potentially fatal consequences among individuals who have not been vaccinated. It is necessary that the immunization of children and of all the other individuals is universal to eliminate transmission. Measles outbreaks may occur because of immunity gaps and vaccine refusal is a big problem in developed countries. The proportion of fatal cases ranges from less than 0.1% to 5%, depending on factors such as the age of measles acquisition, nutritional status, vaccine coverage and conditions of the patient and of its accessibility to health care. The leading causes of death in developing countries are complications of measles, as diarrhea and pneumonia[22, 23].

Laboratory analyses are fundamental to the definitive diagnosis, since other febrile exanthematic diseases can simulate symptoms.

For the purposes of epidemiological surveillance, it is necessary to collect clinical specimens for viral identification by genotyping, and thus to differentiate an autochthonous case from an imported case or even related to the (rarer) vaccine virus. Notification of suspected cases should be made within 24 hours to the local Health Department for the purpose of blocking outbreaks, mainly in non-vaccinated individuals. The most important clinical measure remains prophylaxis for disease control, especially vaccination, since the treatment is limited to clinical and symptomatic support, and there is no specific approach against the virus[16, 21, 24]. Finally, the initial approach of individuals suspected of measles and the notification moment are detailed in **Figure 2**.

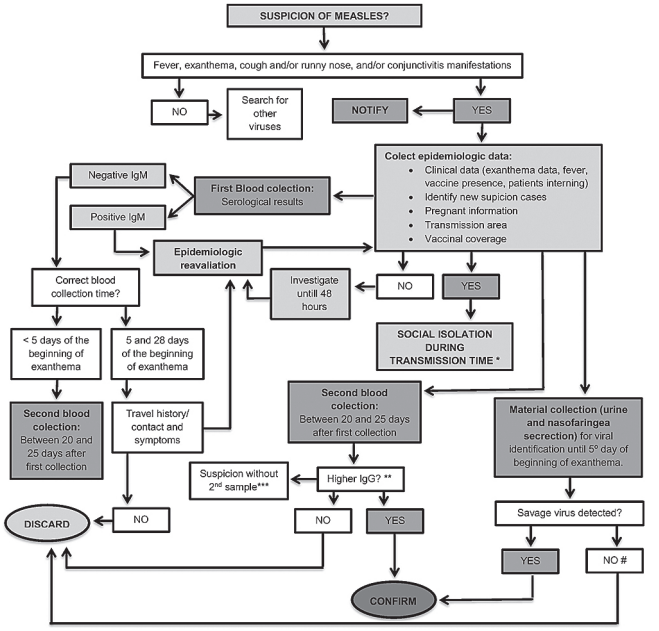

FIGURE 2 – *Initial approach of individuals suspected of measles*

*IgM and IgG: immunoglobulin classes M and G; PCR: polymerase chain reaction; *incubation time: seven to 18 days; transmission period: five days before and five days after exanthema onset/selected vaccination in susceptible contacts; **confirmed with the presence of characteristic symptoms; ***IgM positive patients may be very well analyzed if there is not a second sample; #analyze PCR result veracity before discarding a suspicion case.*

Source: Adapted from Guia de Vigilância em Saúde, 2017.

REFERENCES

1. Organização Pan-Americana de Saúde (OPAS). Folha informativa – Sarampo. Updated on 2019, Jan. Available at: https://www.paho.org/bra/index.php?option=com_content&view=article&id=5633:folha-informativa-sarampo&Itemid=1060. [Accessed on: 2019, Jan 24].

2. Sarampo. Available at: http://ftp.medicina.ufmg.br/observaped/artigos_infecciosas/SARAMPO_22_8_2014.pdf. [Accessed on: 2018, Nov 12].

3. Brasil. Ministério da Saúde. Secretaria de Vigilância em Saúde. Departamento de Vigilância Epidemiológica. Coordenação-geral de Desenvolvimento da Epidemiologia em Serviços. Guia de Vigilância Epidemiológica. 2ª ed. Brasília; 2017. p. 113-128.

4. Brasil. Ministério da Saúde. Secretaria de Vigilância em Saúde. Departamento de Vigilância das Doenças Transmissíveis. Manual dos Centros de Referência para Imunobiológicos Especiais. 4ª ed. Brasília; 2014. 160p.: il.

5. Li LM, Oza S, Hogan D, et al. Global, regional, and national causes of under-5 mortality in 2000-15: an updated systematic analysis with implications for the Sustainable Development Goals. Lancet. 2016; 388(10063): 3027-35. DOI: 10.1016/S0140-6736(16)31593-8

6. Brasil. Ministério da Saúde. Sistema Único de Saúde. Informe no. 17 (2017/2018). Situação do sarampo no Brasil – 2018. Brasília; 2018. p. 1-10.

7. Ballalai I, Michelin L, Kfouri R. Nota técnica conjunta das sociedades brasileiras de imunizações, infectologia e pediatria de 16/07/18. Available at: https://sbim.org.br/images/files/nota-tecnica-conjunta-sarampo-sbimsbisbp20180716.pdf. [Accessed on: 2018, Nov 21].

8. Moss WJ. Measles. Lancet. 2017; 390: 2490-502.

9. World Health Organization. Weekly epidemiological record. Measles vaccines: WHO position paper – April 2017. 28 April 2017, 92nd year no. 17, 2017, 92, 205-28. Available at: http://www.who.int/wer. [Accessed on: 2019, Jan 24].

10. Griffin DE. Measles virus and the nervous system. Handbook Clin Neurol. 123(2014): 577-90. DOI: 10.1016/B978-0-444-53488-0.00027-4.

11. Rasmussen SA, Jamieson DJ. What obstetric health care providers need to know about measles and pregnancy. Obstet Gynecol. 2015; 126(1): 163-70. DOI: 10.1097/AOG.0000000000000903.

12. Bellini WJ, Helfand RF. The challenges and strategies for laboratory diagnosis of measles in an international setting. J Infect Dis. 2003; 187 Suppl 1: S283-90. DOI: 10.1086/368040.

13. Sociedade de Pediatria do Estado do Rio de Janeiro (SOPERJ). Sarampo. Available at: www.soperj.org.br/imagebank/sarampo.pdf. [Accessed on: 2018, Nov 9].

14. MSD Manual Professional Version. Tensini BL. Measles. Available at: https://www.msdmanuals.com/professional/pediatrics/miscellaneous-viral-infections-in-infants-and-children/measles. [Accessed on: 2019, Mar 13].

15. Freire LMS, Menezes FR. Sarampo. In: Tonelli E, Freire LMS, editors. Doenças infecciosas na infância e adolescência. 2ª ed. Rio de Janeiro: MEDSI; 2000. p. 851-83.

16. Cohen BJ, Doblas D, Andrews N. Comparison of plaque reduction neutralisation test (PRNT) and measles virus-specific IgG ELISA for assessing immunogenicity of measles vaccination. Vaccine. 2008; 26(50): 6392-7. DOI: 10.1016/j.vaccine.2008.08.074.

17. World Health Organization (WHO). Manual for the laboratory-based surveillance of measles, rubella, and congenital rubella syndrome. Chapter 1, 1.3. Available at: www.who.int/immunization/monitoring_surveillance/burden/laboratory/manual_section1.7/en/. [Accessed on: 2019, Jan 24].

18. Sáfadi, MAP. Nota técnica da Sociedade Brasileira de Pediatria de 16/07/18. Available at: http://www.spsp.org.br/2018/07/16/spsp-nota-informativa-julho-de-2018-atualizacao-sobre-sarampo. [Accessed on: 2019, Mar 12].

19. Long L, Liu J, Lu K, et al. Highly sensitive and robust peroxidase-like activity of Au-Pt core/shell nanorod-antigen conjugates for measles virus diagnosis. J Nanobiotechnol. 2018; 16(1): 46.

20. Rio Saúde. Prefeitura da cidade do Rio de Janeiro. Secretaria Municipal de Saúde. Coordenação-geral da Divisão de Vigilância em Saúde. Orientação para notificação/investigação de casos suspeitos de sarampo (CID10: B05), junho 2018. Available at: http://old.cremerj.org.br/downloads/801.PDF. [Accessed on: 2019, Jan 24].

21. Katz SL, Hinman AR. Summary and conclusions: measles elimination meeting, 16-17 March 2000. J Infect Dis. 2004; 189 Suppl 1: S43-7. DOI: 10.1086/377696.

22. Leung AK, Hon KL, Leong KF, Sergi CM. Measles: a disease often forgotten but not gone. Hong Kong Med J. 2018; 24(5): 512-20. DOI: 10.12809/hkmj187470.

23. Hussain A, Ali S, Ahmed M, Hussain S. The anti-vaccination movement: a regression in modern medicine. Cureus. 2018; 10(7): e2919. DOI: 10.7759/cureus.2919.

24. Ballalai I, Kfouri R. Nota técnica conjunta das sociedades brasileiras de imunizações e pediatria de 28/11/18. Available at: https://sbim.org.br/images/files/notas-tecnicas/nt-conjunta-sbimsbp-sarampo-regiao-norte-281118-v2.pdf. [Accessed on: 2019, Jan 24].

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