Laboratory confirmation of measles in elimination settings: experience from the Republic of the Marshall Islands, 2003

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Objective To highlight the complications involved in interpreting laboratory tests of measles immunoglobulin M (IgM) for confirmation of infection during a measles outbreak in a highly vaccinated population after conducting a mass immunization campaign as a control measure.

Methods This case study was undertaken in the Republic of the Marshall Islands during a measles outbreak in 2003, when response immunization was conducted. A measles case was defined as fever and rash and one or more of cough, coryza or conjunctivitis. Between 13 July and 7 November 2003, serum samples were obtained from suspected measles cases for serologic testing and nasopharyngeal swabs were taken for viral isolation by reverse transcriptase polymerase chain reaction (RT–PCR).

Findings Specimens were collected from 201 suspected measles cases (19% of total): of the ones that satisfied the clinical case definition, 45% were IgM positive (IgM+) and, of these, 24% had received measles vaccination within the previous 45 days (up to 45 days after vaccination an IgM+ result could be due to either vaccination or wild-type measles infection). The proportion of IgM+ results varied with clinical presentation, the timing of specimen collection and vaccination status. Positive results on RT–PCR occurred in specimens from eight IgM-negative and four IgM+ individuals who had recently been vaccinated.

Conclusion During measles outbreaks, limiting IgM testing to individuals who meet the clinical case definition and have not been recently vaccinated allows for measles to be confirmed while conserving resources.

Une traduction en français de ce résumé figure à la fin de l'article. *Al final del artículo se facilita una traducción al español.* **الترجمة العربية لهذه الخلاصة في نهاية النص الكامل لهذه المقالة.**

Introduction

To measure the success of a measles control programme, laboratory confirmation of suspected measles cases is essential. Current recommendations for laboratory confirmation of measles vary according to the phase of measles control in a region or country and to laboratory capacity.[1] In the early phase, cases are diagnosed clinically almost exclusively; the role of the laboratory is to confirm initial cases and to isolate and analyse wild-type virus strains from selected cases to characterize the genotype of circulating measles viruses (MVs).

As countries progress from measles control to elimination, case-based surveillance is recommended. This involves detailed case investigation and collection of key variables such as age, vaccination status and outcome of illness. At this phase, the role of the laboratory is to confirm measles cases, to monitor circulating MV genotypes and – in collaboration with epidemiologists – to monitor measles immunity levels in the population. WHO recommends that both case-based investigation and specimen collection should be discontinued when outbreaks occur in settings targeted for measles elimination. Instead, 5–10 clinical specimens for serologic and molecular epidemiologic testing should be collected at the beginning of the outbreak to confirm MV as the etiologic agent and genetically characterize the virus. Clinical specimens should also be collected at 2–3-week intervals from each new chain of transmission until the outbreak is controlled.

Many countries in resource-poor settings are rapidly advancing towards measles elimination and are collecting specimens from all cases for investigation in the laboratory. In spite of the recommendations, there is still an emphasis on investigating and obtaining laboratory samples from all cases in an outbreak.[2,3] This approach can drain existing funds and human resources and divert attention away from effective outbreak control measures.

Labnet International, Inc. (Labnet) – a WHO global measles/rubella laboratory network comprising about 700 laboratories – has been established to support measles surveillance. For confirmation of measles, Labnet has adopted the immunoglobulin M (IgM) enzyme immunoassay (EIA) performed on serum collected at first contact.[4,5] The assay is reliable, sensitive and specific; however, IgM production and detection are affected by the vaccination status of suspected cases, the length of time since vaccination and the timing of specimen collection.[5] Confirmation of measles is also complicated by the use of outbreak response immunization (ORI) because, up to 45 days' post-vaccination, an IgM positive (IgM+) result could be due to either the vaccine or wild-type measles infection.[6]

In 2003, the Republic of the Marshall Islands (RMI) (population 51 000) experienced a large measles outbreak. A total of 1122 reported rash illnesses were investigated, of which 1082 were from Majuro, the RMI capital. The RMI has used

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the measles–mumps–rubella (MMR) vaccine in its routine childhood vaccination schedule since the early 1970s. Several supplementary immunization activities were implemented for various age groups, and a two-dose MMR vaccination schedule was introduced in 1998. The estimated national measles vaccine coverage for children aged 12–23 months in the RMI varied from 52% to 94% during 1990–2002 and, until 2003, no measles cases had been reported in the country since an outbreak in 1988.[7] A study conducted in the course of investigating the 2003 outbreak demonstrated an efficacy of 92% for one dose of measles vaccine; the outbreak was therefore attributed to suboptimal routine vaccination coverage.[8]

The RMI public health department initiated nationwide ORI activities and increased efforts to raise public awareness. At the same time, the department promoted active case finding and investigation of suspected measles cases by health-care providers and ensured that cases were managed appropriately. Based on the age distribution of reported cases, MMR vaccine was administered to persons aged 6 months to 40 years. Through the ORI, approximately 33 000 individuals (about 93% of the target population) were vaccinated.

The 2003 outbreak offered the opportunity to examine the performance of laboratory confirmation of IgM against MV during an outbreak in a highly vaccinated population where a mass immunization campaign was conducted as a control measure.

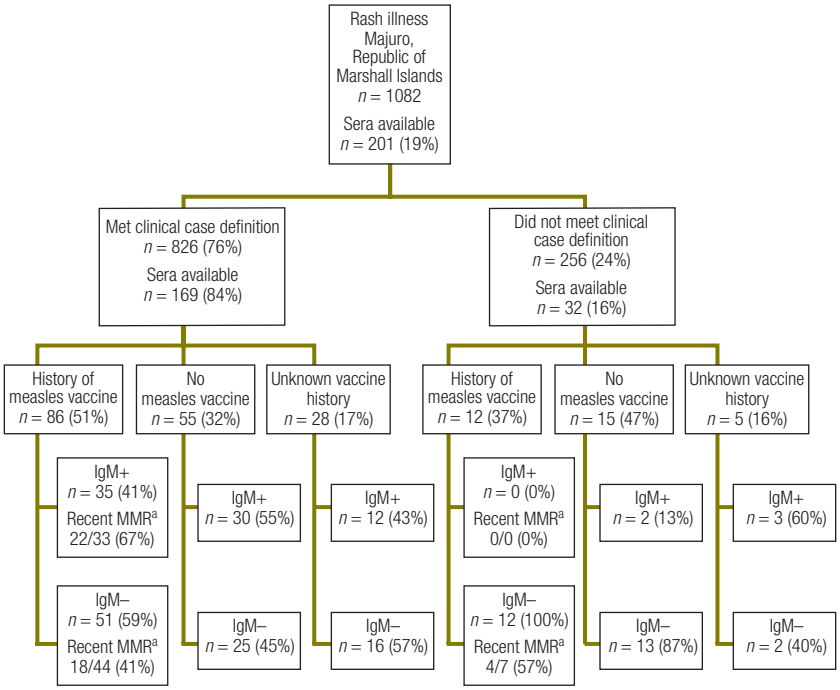
Methods

We used the WHO measles clinical case definition – fever and rash and one or more of cough, coryza or conjunctivitis – and applied this to residents of Majuro, RMI's most populous atoll (coral-reef island), between 13 July and 7 November 2003. A laboratory-confirmed case was defined as a patient with serologic or virologic evidence of acute measles infection. Cases were investigated using a standardized data-collection form with demographic information, clinical features, vaccination history and outcome of illness. Vaccination history was obtained through parental or patient recall, personal and medical records, and immunization logs maintained by the local health department. Patients were classified as "vaccinated" if the recall or documentation provided the number or dates of their vaccinations; "no history of vaccine" if they reported receiving no measles vaccine and had no documentation of vaccination; and "unknown vaccination status" if such status was not known by patient history and there was no documentation of vaccination.

We collected serum for serologic testing and nasopharyngeal swabs for virus isolation and genetic characterization from a subset of suspected measles cases; however, the selection was not systematic and went beyond cases meeting the clinical case definition (Fig. 1). Commonly, specimens were collected during the first medical contact and tested at the United States Centers for Disease Control and Prevention (CDC) for anti-measles virus IgM using established assays.[9] An IgM+ cut-off value was defined as a P–N > 0.09 and a P/N of > 3.0, with P representing the measured optical density values for MV antigen-containing wells, and N the optical density values for wells containing tissue culture control antigen. Indeterminate results fulfilled one of the criteria but not the other and were included as IgM+ for the analysis. Reverse transcriptase polymerase chain reaction (RT–PCR) assays for MV ribonucleic acid (RNA) were performed as previously described.[10]

Data were entered into Microsoft Excel and analysed using SAS, version 8.02 (SAS Institute, Cary, NC, United States of America). The Mantel-Haenszel χ^2 test or Fisher's exact test (when cell size < 5) was used to calculate *P*-values, with statistical significance set at $P < 0.05$.

Fig. 1. **Flowchart of laboratory results in individuals tested during a measles outbreak, by clinical case definition and vaccination status, Republic of the Marshall Islands, 2003**



IgM, immunoglobulin M; MMR, measles–mumps–rubella.

[a] Recent MMR was defined as vaccination less than 45 days before blood collection. In the fractions, the numerator represents the number with a history of recent MMR, and the denominator represents the number (out of the IgM+ or IgM– total) whose vaccination date was known. The dates are missing for 14 individuals: 2 who met the clinical case definition (CCD)+, had been vaccinated (vax+), and were IgM+; 7 who were CCD+, vax+ and IgM–; 5 who did not meet the CCD (CCD–) and were vax+ and IgM–.

Results

Of 1082 suspected measles cases investigated, 826 (76%) met the measles clinical-case definition, and of 840 cases with information on vaccination status, 573 (68%) had received at least one dose of MMR vaccine. Blood samples were collected from 201 (19% of total) suspected measles cases. Initially, 10 samples were collected to confirm the outbreak; most subsequent samples

were collected after the peak of the outbreak and after the ORI had begun. Of the 201 cases with specimens, 169 (84%) met the clinical-case definition (Fig. 1) and 31 of the 169 had documented receipt of two MMR doses. Overall, 77 (46%) of the 169 cases meeting the clinical case definition were IgM+; 35 of these had a known history of MMR vaccination, 22 of them within the previous 45 days. For cases with unknown vaccination status, 43% (12 out of 28) were IgM+. After excluding those vaccinated less than 45 days before blood collection, only 28% (13/46) of those with a history of MMR vaccination were IgM+, compared with 55% (30/55) of those with no history of vaccination ($P = 0.008$).

Among laboratory-tested cases that met the clinical-case definition, IgM results varied by timing of specimen collection, history of measles vaccination and time since MMR vaccination. Only 34% of sera were collected during the ideal collection period of 4–28 days after rash onset, while 50% were collected within 3 days of rash onset (Table 1). Overall, regardless of vaccination history, the proportion of IgM+ results was highest when blood was collected 4–28 days after rash onset (60%) and lowest when it was collected within 3 days of rash onset (36%) ($P = 0.007$). When blood was collected 4–28 days after rash onset, 73% of individuals with no history of vaccination were IgM+, compared with only 39% (5/13) of individuals who had received at least one dose of vaccine. When specimens were obtained within 3 days of rash onset, only 40% (12/30) of individuals with no previous history of vaccination were IgM+. Of individuals who received one dose of measles vaccine, 71% (5/7) were IgM+ within 3 days of rash onset compared with 25% (1/4) of those sampled 4–28 days after rash onset. Among those who received at least two doses of vaccine, 44% (4/9) of those whose samples were collected in the 4–28-day period after rash onset were IgM+, compared with 8% (1/13) of those whose samples were obtained within 3 days ($P = 0.048$).

RT–PCR results were available for 38 suspected cases, of which 13 (34%) were positive for genotype H1 wild-type MV; no MV vaccine sequences were identified. Both RT–PCR and the results of serum tests were available for 27 suspected cases whose specimens had been collected mostly within 3 days of rash onset. IgM test and RT–PCR results were positive in four individuals that were thus confirmed as measles cases. Eight had positive results on RT–PCR but were IgM negative (IgM–). Thus, it was possible to confirm infection with wild-type measles virus in the laboratory despite a negative IgM test result (6 out of 8 cases had a positive vaccination history). Four specimens from individuals who received ORI showed amplified products bearing genotype H1 nucleotide sequences. Without these RT–PCR results, these individuals could not have been confirmed as cases.

Table 1. **Ratio of IgM+ confirmed cases to cases meeting the measles clinical case definition, by timing of specimen collection and vaccination status, the Republic of the Marshall Islands, 2003**

Vaccination history[a]	Time of specimen collection (days after rash onset)		
	≤ 3 Ratio (%)	4–28 Ratio (%)	> 28 Ratio (%)
Unknown	3/10 (30)	4/7 (57)	5/11 (45)
No measles vaccination	12/30 (40)	11/15 (73)	5/7 (71)
Measles vaccination (most recent dose ≥ 45 days before blood collection)			
1 dose	5/7 (71)	1/4 (25)	0/1 (0)
2 or more doses	1/13 (8)	4/9 (44)	0/3 (0)
Measles vaccination[b] (most recent dose < 45 days before blood collection)			
1 dose	7/15 (47)	9/14 (64)	1/2 (50)
2 or more doses	0/2 (0)	3/4 (75)	0/0 (0)
Total samples	77 (50)	53 (34)	24 (16)
Total IgM+ samples	28 (36)	32 (60)	11 (46)

[a] The clinical case definition was met by 169 individuals for whom serum was available; 154 of them are included in this table, and 15 were missing the dates needed to determine either the timing of blood collection or of vaccination.

[b] IgM against the measles virus due to recent receipt of the measles vaccine cannot be differentiated from that due to recent measles infection.

Discussion

Our results confirm that the interpretation of serologic tests for the detection of IgM against the MV can be compromised in measles elimination settings with moderate to high levels of vaccine coverage, particularly where ORI activities are being conducted in response to a measles outbreak. We confirmed that the MV was the etiologic agent of the 2003 outbreak in the RMI by detecting IgM against the MV and MV RNA.[7] We also used limited testing (IgM EIA) to rule out other infectious agents (for rubella, dengue and parvovirus B-19) as the cause of the outbreak. However, most of the cases tested that met the clinical case definition and had a history of measles vaccination were IgM–. Individuals who did not meet the clinical case definition had extremely low rates of laboratory confirmation, irrespective of vaccination history, suggesting that efforts to confirm such cases through laboratory tests are not warranted.

Among cases that fit the clinical case definition, only 46% tested positive for IgM against the MV. Several factors could account for the high proportion of IgM– results. Blood collection outside the recommended time period may result in an IgM– test result because the individual may not have mounted a detectable IgM response.[11,12] Also, although the numbers are small, the data imply that vaccine recipients may mount a more rapid IgM response than unvaccinated individuals. In the latter, the IgM response may be either short-lived or absent; therefore, it may be missed even if serum is drawn during the optimal 4–28-day period after the onset of the rash.[6] The identification of eight vaccinated IgM– individuals in whom clinical evidence of measles infection was confirmed by RT–PCR and RNA sequencing supports these points. Finally, awareness of the measles

outbreak may have led to a more liberal interpretation of the measles case definition, so that non-measles rash illnesses were reported as measles and serum specimens were then sent for laboratory testing.

Due to ORI activities, 24% of IgM+ cases had received the MMR vaccine in the month before their illness. Measles cannot be confirmed by testing for IgM in cases vaccinated 45 days or less prior to blood collection because the antibody response to the vaccine mimics the response to wild-type virus infection.[13] MMR vaccination can lead to rash and fever but seldom causes cough, coryza and conjunctivitis. These individuals met the clinical case definition, which suggests they had measles rather than a vaccine reaction. The only way to clearly differentiate natural disease from a vaccine response in ORI recipients is to genetically characterize the MV involved through RNA detection and sequencing. During this outbreak, RT–PCR testing identified only wild-type measles virus, and not vaccine virus, as a cause of illness.

This study had limitations. Patients were selected for serum testing by convenience rather than by representative sampling of the outbreak population. Anecdotal reports from co-investigators suggested that many cases with mild symptoms were disproportionately selected for serum testing. When vaccination could not be documented, patient recall was accepted, although as a result the vaccinations actually received may have been under or overestimated.[14,15] Various studies show that parental recall of vaccination is less accurate than medical records[16,17] and does not correlate well with protective antibodies measured in serum;[18] however, these studies were not conducted within 2 months of ORI activity in the midst of a measles outbreak.

Measles IgM testing in recently vaccinated individuals is inconclusive because a positive result could be due to either infection with the wild-type virus or to vaccination. The interpretation of IgM– results in distantly vaccinated cases is also challenging. Our findings that some of these cases were positive for MV RNA on RT–PCR suggest that in vaccinated individuals it may not be appropriate to rule out measles on the basis of an IgM– test result, especially if specimens were collected outside the optimal time window. Alternative laboratory diagnostic tools are needed for confirmation of measles in settings with high vaccination coverage; however, such tests would currently be beyond the scope of most Labnet facilities.

Our findings suggest that serologic IgM testing – although effective as a tool for confirming the etiologic agent causing outbreaks – has limited use in highly vaccinated populations, particularly in outbreak settings where ORI is being conducted. The situation seen in the RMI in 2003 will be encountered more frequently in the future as countries move towards measles elimination and ORI is more often used to control outbreaks.[19]

In measles-elimination settings, every suspected measles case must be fully investigated to understand whether actual cases are due to importation or to re-introduction of circulating virus in an under-immunized population. This information can then be used to manage immunization programmes. However, in practice it is not clear when to change from case-based investigation to outbreak investigation during an outbreak in such settings. In recent published accounts of measles outbreaks, case-based and laboratory investigations were conducted for more than 5–10 outbreak-related cases (laboratory-confirmed cases: Italy 26[20], United States of America 34[2], Brazil 112[3] and Switzerland 693[21]).

Guidelines should clearly state when to discontinue case-based investigation and pursue control measures (with attention focused on collecting appropriate epidemiological information and laboratory specimens). Case investigation should be thorough, with a focus on clinical disease features and vaccination histories, to facilitate the interpretation of laboratory results. Viral specimens should be collected from cases that meet a stringent clinical-case definition and may also be obtained from individuals receiving ORI to provide additional information on circulating genotypes and possible transmission pathways (such samples currently provide the only way to confirm measles in an ORI recipient). IgM testing should be limited to individuals who meet a stringent case definition and have not received ORI. Limiting IgM testing and specimen collection in this manner will allow confirmation of wild-type measles during an outbreak while conserving personnel and laboratory resources. This study confirms the need to explore alternative laboratory approaches and protocols for laboratory confirmation of measles in measles-elimination settings with high vaccination coverage. ■

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Competing interests: None declared.

Résumé

Confirmation en laboratoire des cas de rougeole dans des pays où cette maladie est en cours d'élimination : expérience obtenue en 2003 par la République des îles Marshall

Objectif Mettre en lumière la complexité de l'interprétation des dosages en laboratoire de l'immunoglobuline M (IgM), en vue de confirmer les cas d'infection rougeoleuse, dans le cadre d'une flambée de rougeole touchant une population hautement vaccinée, qui a été soumise à une campagne de vaccination de masse en tant que mesure de lutte contre cette maladie.

Méthodes L'étude a été menée dans la République des Iles Marshall pendant une flambée de rougeole survenue en 2003, lors de l'organisation d'une campagne de vaccination de riposte. Un cas de rougeole était défini comme la présence de fièvre et d'une éruption cutanée, plus un ou plusieurs des symptômes suivants : toux, coryza et conjonctivite. Entre le 13 juillet et le 7 novembre 2003, des échantillons de sérum ont été prélevés chez des cas suspects de rougeole afin de pratiquer des tests sérologiques et des écouvillonnages nasopharyngés ont été effectués en vue d'isoler le virus par rétro-transcription PCR.

Résultats On a recueilli des échantillons chez 201 cas suspects de rougeole (19 % au total) : sur l'ensemble de ceux correspondant à la définition de cas clinique, 45 % étaient positifs pour les IgM (IgM+) et, parmi ces derniers cas, 24 % avaient été vaccinés contre la rougeole au cours des 45 derniers jours (jusqu'à 45 jours après la vaccination, un résultat IgM+ peut être dû soit à la vaccination, soit à une infection par une souche rougeoleuse de type sauvage). La proportion de résultats IgM+ variait en fonction du tableau clinique, du moment où avait été prélevé l'échantillon et du statut vaccinal. La RT-PCR a donné des résultats positifs sur les échantillons provenant de huit individus négatifs pour les IgM et de quatre individus IgM+ récemment vaccinés.
Conclusion Pendant les flambées de rougeole, le fait de restreindre le dosage des IgM aux individus satisfaisant la définition clinique de cas et n'ayant pas été vaccinés récemment permet de confirmer les cas de rougeole tout en préservant les ressources.

Resumen

Confirmación de laboratorio del sarampión en un contexto de eliminación: experiencia de la República de las Islas Marshall, 2003

Objetivo Poner de relieve la complejidad de la interpretación de las pruebas de laboratorio de determinación de la inmunoglobulina M (IgM) del sarampión como confirmación de la infección en el contexto de un brote de esa enfermedad en una población altamente vacunada tras llevar a cabo una campaña de inmunización masiva como medida de control.
Métodos El estudio se llevó a cabo en la República de las Islas Marshall durante un brote de sarampión registrado en 2003, año en que se emprendieron actividades de inmunización de respuesta. Se consideró definitorio de los casos de sarampión la presencia de fiebre, exantema y uno o más de los tres signos siguientes: tos, catarro o conjuntivitis. Entre el 13 julio y el 7 de noviembre de 2003 se obtuvieron muestras de suero de casos sospechosos de sarampión para realizar pruebas serológicas y se practicaron frotis nasofaríngeos para aislar el virus mediante la reacción en cadena de la polimerasa con transcriptasa inversa (RT–PCR).
Resultados Se obtuvieron muestras de 201 casos sospechosos de sarampión (19% del total): entre los que satisfacían la definición de caso clínico, el 45% fueron IgM-positivos (IgM+), y de éstos el 24% habían recibido vacunación antisarampionosa en los últimos 45 días (hasta 45 días después de la vacunación la IgM puede ser positiva como consecuencia ya sea de la vacunación o de una infección por el virus salvaje del sarampión). La proporción de resultados IgM+ varió según las manifestaciones clínicas iniciales, el momento de obtención de la muestra y el estado de vacunación. La RT–PCR dio resultados positivos en las muestras de ocho personas IgM-negativas y cuatro IgM-positivas que habían sido vacunadas recientemente.
Conclusión Durante los brotes de sarampión es posible confirmar los casos de la enfermedad y ahorrar recursos si las pruebas de IgM se restringen a las personas que cumplen la definición de caso clínico y no han sido vacunadas recientemente.

ملخص

التأكيد المختبري للحصبة في المناطق التي أمكن التخلص من الحصبة فيها: تجربة من جمهورية جزر مارشال، 2003

الغرض: تسليط الضوء على التعقيدات التي تنشأ عن تفسير الفحوص المختبرية للغلوبولين المناعي للحصبة لتأكيد الإصابة بالعدوى أثناء حدوث فاشية في مجتمع تلقى جرعات التلقيح المقررة، بعد حملة تمنيع شاملة تمت كتدبير لمكافحة هذا المرض.
الطريقة: أجريت الدراسة في جمهورية جزر مارشال إبَّان فاشية للحصبة وقعت عام 2003 حيث جرى التمنيع لمواجهة هذه الفاشية. وعُرِّفت حالة الحصبة بأنها حمى، وطفح، وواحد أو أكثر من أعراض السعال، أو الزكام، أو التهاب الملتحمة. وأخذت خلال الفترة ما بين 13 تموز/يوليو و7 تشرين الثاني/نوفمبر 2003، عينات مصلية من حالات يشتبه في إصابتها بالحصبة، وذلك لإجراء اختبارات مصلية عليها، كما أخذت مسحات بلعومية أنفية لاستفراد الفيروسات بأسلوب المنتسخة العكسية لسلسلة تفاعل أنزيم البوليميريز.
الموجودات: جمعت العينات من 201 حالة يشتبه في إصابتها بالحصبة (19% من الإجمالي)، من تلك التي توافقت مع التعريف السريري (الإكلينيكي) للحالة، وتبين إيجابية الغلوبولين المناعي في 45% من هذه الحالات، 24% كانت قد تلقت لقاحاً ضد الحصبة خلال الـ 45 يوماً السابقة (إيجابية الغلوبولين المناعي بعد مرور فترة تصل إلى 45 يوماً على تلقي اللقاح يمكن أن تكون راجعة إما إلى تلقي اللقاح ضد المرض أو إلى العدوى بالنمط البري للحصبة). وقد تفاوتت نتائج إيجابية الغلوبولين المناعي وفقاً للاستعلان السريري (الإكلينيكي)، وتوقيت جمع العينة، والوضع الخاص بالتلقيح. وجاءت نتائج اختبار المنتسخة العكسية لسلسلة تفاعل إنزيم البوليميريز إيجابية في عينات من ثمانية أشخاص سلبيي الغلوبولين المناعي، ومن أربعة أشخاص إيجابيي الغلوبولين المناعي، كانوا قد تلقوا اللقاح ضد الحصبة قبل وقت قصير.
الاستنتاج: إن قَصْر إجراء اختبار الغلوبولين المناعي عند وقوع فاشيات الحصبة على الأشخاص الذين تتوافق حالاتهم مع التعريف السريري (الإكلينيكي) للحالة، ولم يتلقوا لقاحاً ضد المرض في وقت قريب، يتيح تأكيد العدوى، ويحافظ في نفس الوقت على الموارد.

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