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Immune status of health care workers to measles virus: evaluation of protective titers in four measles IgG EIAs

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ABSTRACT

Background: Following the recognition of a measles case in a hospital in The Netherlands, health care workers (HCW) from the premises were screened by a commercial enzyme immunoassay (EIA) for measles IgG to identify persons at risk for measles. At least 10% of the HCW were tested measles IgG-negative. As this was considered an unusually high proportion, we hypothesized suboptimal sensitivity of EIAs, especially in medical personnel that had vaccine-induced immunity rather than antibodies resulting from natural infection.
Objectives: To determine (vaccine-induced) measles immunity in HCW, using different EIAs compared to the plaque reduction neutralization (PRN) test, the best surrogate marker for vaccine efficacy and immune protection.
Study design: Sera from HCW were tested for measles IgG antibodies in three commercial EIAs, in a bead-based multiplex immunoassay (MIA) and in the PRN test, and evaluated against age and vaccination history of the HCW.
Results: Of the 154 HCW, born between 1960 and 1995, 153 (99.4%) had protective levels of measles antibodies (PRN > 120 mI U/ml). The three EIAs failed to detect any measles IgG antibodies in approximately 10% of the HCW, while this percentage was approximately 3% for the MIA. Negative IgG results rose to 19% for individuals born between 1975 and 1985, pointing to an age group largely representing vaccinated persons from the first measles vaccination period in The Netherlands.
Conclusion: The results show limitations in the usefulness of current EIA assays for determining protective measles antibodies in persons with a vaccination history.

1. Background

Delayed recognition of measles in a hospital poses a threat for hospitalized patients and a challenge for the infection control department. Measles is the most transmissible human disease known and medical settings constitute a highly significant site of measles transmission [1–4]. Health care workers (HCW) are at substantially higher risk than the general population for becoming infected with measles. This is due to their professional duties and the re-emergence of measles in several developed countries causing an increasing number of hospital admissions for measles [1–6]. When infected, HCW constitute a risk of transmission to non-immune or immune-compromised patients. Therefore, documentation of their measles immune status and vaccination has recently been emphasized [2,3,7]. In the US, for example, HCW who were born in 1957 or later are considered immune only if they have laboratory confirmation of immunity or documentation of having received two appropriate doses of vaccine [7]. Nowadays, in many countries, depending on the start of national vaccination campaigns for measles, there are increasing numbers of HCW

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with vaccination-acquired immunity instead of immunity acquired after measles infection. Immunity in this group relies both on complete (2-dose) and adequate vaccination and the ability to sustain immune protection. Waning immunity in these HCW will increase the risk of nosocomial infections [8].

Although documentation of appropriate vaccination is not a guarantee for 100% protection [6,9–13], laboratory confirmation of immunity is also hampered by drawbacks. While the plaque reduction neutralization (PRN) test is regarded as gold standard method for measles immunity [14–20], the assay is technically demanding, labor-intensive and difficult to standardize between laboratories [19,21]. Clinical laboratories therefore mostly use commercially available enzyme immunoassays (EIAs) for the detection of measles virus IgG antibodies. However, these EIAs have been described to be less sensitive than the PRN test [16,17,21], and thus may underestimate measles immunity in HCW. The increasing number of HCW with vaccination-acquired immunity warrants the re-evaluation of commercial measles IgG EIAs for assessing measles immunity in vaccinated persons.

2. Background to present study

In February 2013, a 13 month old child was admitted to the hospital with a pneumonia. The child was diagnosed with measles on day 2 (positive measles PCR on throat swab), after it became clear that the mother of the child had a proven measles infection. Subsequently, strict infection control measures were taken. Two secondary cases of measles among healthcare workers occurred. A 30 year old nurse and a 32 year old laboratory technician, both working at the emergency department of the hospital, became ill with rash, fever and malaise. Their clinical course was relatively mild and short. They were both fully (2×) vaccinated against measles during childhood, and were diagnosed based on positive IgM serology and detection of wildtype measles virus in oropharyngeal specimens, which was genotypically identical to the virus that was detected in the index child (genotype D8, data not shown).

As part of the preventive measures taken in response to these 2 measles cases, measles immunity status was assessed in HCW working at the departments of the two measles-infected HCW, including the department where the index-patient had been admitted. Blood samples of HCW were drawn and data on age, sex and vaccination status or past infection were collected. HCW born in 1960 and before were considered protected by natural infection [22] and excluded from the survey.

The EIA available in the hospital setting was the Vidas measles IgG (VIDAS® Measles IgG bioMerieux, Marcy l'Etoile, France). This EIA revealed a relatively high number of negative and equivocal results. The National Institute of Public Health (RIVM) was consulted for comparing the results of this EIA with the standard PRN test. Two other commercial EIAs, and a bead-based multiplex immunoassay (MIA) [23] for detection of measles IgG antibodies were included in the survey.

3. Objective

The present study describes the assessment of measles virus immunity in hospital personnel according to their age and vaccination history, using 4 different measles IgG assays in comparison with the PRN test.

4. Study design

4.1. Routine screening for measles IgG

The first EIA used for screening was the Vidas measles IgG (VIDAS® Measles IgG bioMerieux, Marcy l'Etoile, France). The test is a sandwich immunoassay to detect final fluorescence (ELFA) on the fully automated robot VIDAS30, and uses an antigen derived from an Edmonston virus strain. Results are expressed as negative (<0.50), equivocal (≥0.5–<0.7) and positive (≥0.7) test values (TV).

4.2. PRN test

The PRN test was based on the original method developed by Albrecht et al. and standardized according to the recent 24-well plate culture protocol established for WHO [21,24]. We followed this PRN protocol and used a 2nd generation culture stock of virus that was derived from the 6th passage of the original Edmonston B strain that was kindly provided by Dr. Paul Albrecht [25]. The WHO 3rd International Standard for measles antibody containing 3000 mI U/ml was used (NIBSC code 97/648), which enabled the 50% neutralizing antibody end-point dose (titer, ND50) of test samples to be transformed to antibody concentrations expressed in mI U/ml. The cut-off value is ≥120 mI U/ml, which is the antibody concentration considered to be protective [14,15,18]. All PRN tests included triplicate serial dilutions of the standard serum, generating an average unitage for each PRN test. Serum from each HCW was tested in triplicate in three independent assays. The average unitage value from 3 test results per serum was used as final PRN result, using the Kärber formula to calculate individual ND50 test results.

4.3. Enzygnost measles IgG EIA

Elisa using the 'Enzygnost' anti-measles IgG test kit (Siemens Healthcare Diagnostics Products GmbH, Marburg, Germany) was performed following kit instructions for fully automatic processing and evaluation of the test on a BEP® 2000 system. Optical densities were measured at 450 nm and results were calculated as corrected ΔOD, with cut-off values of <0.1(negative), 0.1–0.2 (equivocal), >0.2 (positive). According to the manufacturer, an OD value of 0.198 (equivocal result) corresponds to 187.5 mI U/ml of the WHO 3rd International Standard for measles.

4.4. Liaison measles IgG EIA

Measles IgG was measured using an indirect sandwich chemiluminescence immunoassay (CLIA, Liaison, DiaSorin, Saluggia, Italy), which uses recombinant measles nucleoprotein expressed in baculovirus coated on paramagnetic microparticles as solid phase. The assay was performed on a fully automated LIAISON analyzer according to the manufacturer's instructions. Measles IgG concentrations were automatically generated and expressed as arbitrary units (AU/ml). Cut-off values were <13.5 A U/ml (negative), 13.5–16.5 A U/ml (equivocal), and => 16.5 A U/ml (positive), with an assay range claimed by the manufacturer of 5–300 A U/ml. According to the manufacturer, a cut-off value just below 16.5 A U/ml (equivocal result) corresponds to 175 mI U/ml of the WHO 3rd International Standard for measles.

4.5. MIA measles IgG test

A bead-based multiplex immunoassay (MIA) was used for the quantitative detection of antibodies against measles and was recently implemented at the National Institute of Public Health (RIVM) for large cross-sectional serosurveys [22,23]. In brief, serum samples from the HCW were diluted 1/200 and 1/4000, and antibody concentrations were obtained by interpolation of the mean fluorescent intensity in the standard curve that was calibrated against the WHO 3rd international standard serum for measles and expressed in mI U/ml, as recently described [23]. Antibody concentrations of ≥120 mI U/ml were considered protective. The lower