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Negative impact of clinical misdiagnosis of measles on health workers' confidence in measles vaccine

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SUMMARY

We conducted a survey to determine the accuracy of the clinical diagnosis of measles in Zimbabwe. Between December 1996 and February 1997, we collected blood samples and clinical and demographic information from a sample of 105 children with a clinical diagnosis of measles. A clinical case of measles was defined as a person with a history of fever, rash for three or more days, and either cough, coryza, or conjunctivitis. A laboratory-confirmed case of measles or rubella had IgM antibodies against measles virus or rubella virus respectively. A total of 91% of children met the clinical case definition. Among those who met the clinical case definition for measles, 72% were IgM-positive for measles virus only, 23% were IgM-positive for rubella virus only, 3% were IgM-positive for both measles and rubella viruses, and 2% were IgM-negative for both viruses. This study demonstrates the importance of considering selective laboratory confirmation of measles in periods of high disease incidence when the effectiveness of the vaccine is questioned.

INTRODUCTION

Measles causes almost half a million deaths each year in Africa despite the availability of a vaccine with an estimated effectiveness of 85% when given at 9 months of age [1]. Most measles cases are diagnosed on clinical grounds in Africa. In low-incidence settings, laboratory confirmation becomes necessary because of the reduction in the positive predictive value of the clinical case definition and because the clinical acumen of clinicians also declines. By contrast, in high-incidence settings, in which the goal is to identify outbreaks and not isolated cases, most practitioners rely on a clinical case definition to diagnose persons with measles.

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In Zimbabwe, like the rest of Africa, monovalent measles vaccine is recommended for children at 9 months of age. Measles vaccination coverage in Zimbabwe ranged from 79 to 83% between 1990 and 1995 (Zimbabwe National Health Information System). Rubella vaccine is not routinely available, except in the private sector. In the mid-1990s, there was a growing impression among health-care workers that the protective value of the measles vaccine was lower than the 85% effectiveness commonly cited [2]. This loss of confidence in the vaccine was based upon what initially appeared to be a higher proportion of reported measles cases being due to vaccine failures than would be expected using Orenstein's rough guide for calculation of vaccine efficacy [3]. As a result, Mudzamiri [2] conducted a study, which showed that the efficacy of the measles vaccine in Zimbabwe was in the lower end of the expected range (78%; 95% CI

of 54–90). Mudzamiri's study relied upon the clinical diagnosis of measles, which may underestimate the true vaccine efficacy if some clinically diagnosed cases of measles are due to other pathogens [4]. To respond to this problem, we conducted a study in 1997 to compare the accuracy of the clinical case definition for measles with laboratory diagnosis in Matabeleland South Province, Zimbabwe.

METHODS

As part of the measles case investigation of persons with suspected measles infection in four rural districts in Matebeleland South Province and Bulawayo City, Zimbabwe, a community health nurse and a local investigator collected demographic information, symptom histories, and history of vaccination and previous measles infection. In addition, between 11 December 1996 and 12 February 1997 we collected clotted blood samples from a sample of 105 children diagnosed with clinical measles to perform laboratory confirmation of the clinical diagnosis. All cases investigated had an onset of rash illness between 3 and 28 days prior to sample collection, to maximize the likelihood of detecting measles virus-specific IgM in persons with suspected measles [5].

Serum samples were tested for the presence of measles virus-specific IgM and IgG by using a previously described monoclonal antibody-based capture EIA and an indirect EIA respectively [6]. Samples were also tested for rubella virus IgM and IgG antibodies by using commercially available indirect EIAs [Wampole Laboratories (Cranberry, NJ, USA) and Biowhittaker (Walkersville, MD, USA) respectively]. Both the measles and rubella virus IgM assays contain steps to remove IgG, which should reduce the risk of cross-reaction with rheumatoid factor.

A clinical case of measles was defined as a person with a history of fever, rash for 3 or more days, and either cough, coryza, or conjunctivitis. A laboratory-confirmed case of measles was defined as a person with measles virus-specific IgM who had not been vaccinated in the previous 60 days, and a laboratory-confirmed case of rubella was defined as a person with rubella virus-specific IgM.

RESULTS

Ninety-six (91%) of the 105 children met the measles clinical case definition. Of the 105 children with suspected measles, 71% were IgM positive for measles virus. The median age of the children was 8 years (range 1–17 years). Among those who met the measles clinical case definition, 72% were IgM positive for measles virus only, 23% were IgM positive for rubella virus only, 3% were IgM positive for both measles virus and rubella virus, and 2% were IgM negative for both measles and rubella viruses. For the nine children who did not meet the measles clinical case definition, two had laboratory-confirmed measles, four had laboratory-confirmed rubella, and three were IgM negative for both measles and rubella viruses.

Overall, 89 (85%) of the 105 children had histories of previous measles vaccination (61 of these confirmed by vaccination card), three reported no history of vaccination, and 13 were unsure of their vaccination histories. Sixty-one (82%) of the 74 children with laboratory-confirmed measles gave histories of previous measles vaccination, while 28 (90%) of 31 of children without measles had a history of previous measles vaccination.

We identified laboratory evidence of co-circulation of measles and rubella in 7 of the 9 towns in which at least six children were enrolled in the study. Measles was the predominant agent identified in 6 of the towns, and rubella was the predominant virus detected in 3 of the towns.

DISCUSSION

In this sample of 105 children, the diagnosis of measles was confirmed in 71%. Three per cent of children had laboratory evidence of both measles and rubella infections. The three cases with dual IgM-positive results represent either false positive results or recent infections with both viruses. We cannot determine which of these hypotheses is accurate due to unavailability of either specimens for virus isolation or paired serum samples for detection of a fourfold rise in neutralizing antibodies. However, the second hypothesis cannot be ruled out; rubella virus IgM may persist for several months and there was evidence of co-circulation of both viruses in the towns where these three children lived.

The problem in accurately identifying measles disease was not related to the ability of the health workers to utilize the clinical case definition; 91% of the cases met the clinical case definition. The clinical case definition is extremely sensitive but less specific; many other infections can present with similar clinical symptoms, including rubella, roseola, parvovirus B19, enteroviruses, streptococci, and

adenoviruses [7–13]. The positive predictive value of the clinical case definition will vary with the incidence of measles disease. During outbreaks of measles, the positive predictive value will be high, and will fall dramatically as the incidence of disease decreases. For this reason, laboratory confirmation is recommended from all suspected cases when the incidence of measles is low. In this study, using laboratory confirmation as the gold standard for the diagnosis of measles, the clinical case definition had an overall positive predictive value of 75%. While this positive predictive value is fairly high compared to other studies, it also confirms the impression of the field epidemiologists that some reported cases are not measles.

The methodological approach of the present investigation did not allow us to calculate the vaccine efficacy. Specifically, the vaccination status of 13% of children was unknown and the sample size of children without measles was sufficiently small, that calculations of vaccine efficacy included huge confidence bounds which included negative values. However, the data from this paper support the concept that the true vaccine efficacy may be higher than previously recognized. Dietz and colleagues [4] demonstrated that the calculation of measles vaccine efficacy based upon a clinical case definition may markedly underestimate the true vaccine efficacy when other illnesses are responsible for many of the clinically diagnosed measles cases. Specifically, in a study conducted in Puerto Rico, they found that only 23 and 34% of clinically diagnosed measles cases were serologically confirmed as measles and dengue, respectively. They estimated that the use of a clinical case definition only (without laboratory confirmation) would result in a reduction in calculated vaccine efficacy from 90 to 64%. Similarly, Cutts and colleagues estimated that the use of a maternal history of measles to calculate vaccine efficacy in Mozambique resulted in a reduction of the vaccine efficacy from 66 to 37% [14].

Using the same analogy for the situation in Zimbabwe, given that 25% of the cases were misdiagnosed as measles, it is likely that the vaccine efficacy is higher than the estimate of vaccine efficacy that was previously reported by Mudzamiri and colleagues [2]. Similarly, a recent study conducted in Malawi to calculate the vaccine efficacy using a clinical case definition probably underestimated the true vaccine efficacy [15]. In that study, Yamaguchi and colleagues reported a measles vaccine efficacy of 67% among children 9–11 months of age and 69% among children 12–23 months of age, but could not identify any programmatic reason, such as cold chain failure, that might otherwise explain the apparent low vaccine efficacy. The hypothesis that the true vaccine efficacy in Malawi was higher than detected in Yamaguchi's study is supported by the absence of reported laboratory-confirmed measles cases and deaths in Malawi in 2000–2001, despite improvement in rash and fever surveillance established following implementation in 1998 of a WHO-recommended measles elimination strategy in Malawi [16].

Our study highlights the fact that the level of clinical diagnostic accuracy of measles was not as high as formerly believed in this developing country setting with a high incidence of measles. It also highlights the potential negative impact of misdiagnosis on professional and public perceptions of the effectiveness of measles vaccine. Even in settings of high incidence of measles, health workers should consider laboratory confirmation of measles disease rather than clinical confirmation before concluding that measles vaccine is not effective.

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