Diagnosis of measles by clinical case definition in dengue-endemic areas: implications for measles surveillance and control

V.J. Dietz, P. Nieburg, D.J. Gubler, & I. Gomez

In many countries, measles surveillance relies heavily on the use of a standard clinical case definition; however, the clinical signs and symptoms of measles are similar to those of dengue. For example, during 1985, in Puerto Rico, 22 (23%) of 94 cases of illnesses with rashes that met the measles clinical case definition were serologically confirmed as measles, but 32 (34%) others were serologically confirmed as dengue. Retrospective analysis at the San Juan Laboratories of the Centers for Disease Control showed also that at least 28% of all laboratory-confirmed cases of dengue in Puerto Rico in 1985 met the measles clinical case definition. If the true measles vaccine efficacy (VE) is assumed to be 90%, the occurrence of laboratory-confirmed dengue cases that meet the measles clinical case definition results in a reduction of the apparent measles VE to only 64% (a 29% relative reduction from the true VE). The results of the study demonstrate the importance of a laboratory-based surveillance system in measles control or elimination efforts in dengue-endemic areas.

Introduction

Measles is a leading cause of morbidity and mortality among children worldwide and is responsible for 1.5 million deaths annually in developing countries (1). Measles control should therefore be a high priority for national ministries of health. This has prompted some regions, such as the English-speaking Caribbean, to adopt measles elimination as a goal (2).

At its 1990 meeting, the Global Advisory Group of the WHO Expanded Programme on Immunization set guidelines and recommendations to aid country-specific efforts in both measles control and elimination. A emphasized were the need for improved surveillance using a standard clinical case definition, achievement of a high level of vaccine coverage, and rapid initiation of aggressive outbreak control efforts for reported measles cases. Because many developing countries do not have the laboratory capability to diagnose measles, a clinical case definition for use in measles control or elimination programmes must be both highly sensitive and specific. The identification of potential measles cases, followed by the initiation of immediate and often extensive outbreak control measures, should be standardized. Uniformity in case identification, notification, and management is imperative, because clinical impressions may vary geographically. For example, confusion can occur in differentiating between dengue and measles. In Puerto Rico, cases of clinically diagnosed measles have been laboratory-confirmed as dengue and vice versa for a number of years (3); and in Mexico, clinically diagnosed dengue cases have been laboratory-confirmed as measles (4).

The following measles case definition is currently recommended by both WHO and the Centers for Disease Control (CDC): an illness lasting at least 3 days beginning with an acute febrile illness with rash and cough, with Koplik's spots in the oral mucosa. Additionally, in areas where dengue is endemic, the presence of hemorrhagic fever or sudden death in young children should prompt further investigation.

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days, with maculopapular rash, fever (≥38.3 °C), and one or more of a cough, coryza, or conjunctivitis (5).
No data exist on the reliability or validity of this case definition in dengue-endemic areas. Dengue is the commonest human arboviral infection and is also a febrile illness with a rash. Its geographical distribution is widespread, including the Caribbean, Latin America and south-east Asia (6, 7, 18). Although dengue is an illness usually associated with headache and body aches, respiratory symptoms occur frequently. For example, in Puerto Rico 43% of persons with laboratory-confirmed dengue in 1985 had a cough (CDC, unpublished data, 1986). Such observations have led to the recommendation that dengue surveillance be laboratory-based (8).

As disease eradication programmes become commoner, several important issues have emerged relating to the use of case definitions in such programmes (9). For elimination efforts, case definitions must be sensitive enough to permit the detection of nearly all potential cases and subsequent initiation of standardized control activities; as a result, however, the specificity may suffer, leading to unwarranted outbreak control measures (PAHO, unpublished data, 1990) and, for vaccine-preventable diseases, to false impressions of low vaccine efficacy (VE).

In this investigation, we used recent surveillance data from Puerto Rico to quantify the potential misclassification that could occur through the use of the measles case definition in areas where both measles and dengue occur, such as the Caribbean. We also quantified the impact of this misclassification on measles VE when the standard measles clinical case definition was used to identify measles cases in the presence of endemic dengue.

Materials and methods

Data collection and analysis of clinical specimens

As part of an ongoing dengue surveillance system, CDC's San Juan Laboratories (SJL) is notified about clinically diagnosed cases of dengue in Puerto Rico and receives the accompanying serum specimens for laboratory confirmation. SJL also receives serum specimens for laboratory confirmation of many clinically diagnosed cases of measles. To quantify potential misclassification, we included for evaluation all clinically diagnosed dengue and measles cases in Puerto Rico for 1985 for which there were serum samples. Because at that time SJL was the only facility in Puerto Rico performing laboratory testing for either of these two diseases, we are confident that all laboratory-confirmed cases of measles and dengue on the island were included in this study.

Serum samples were submitted for testing, together with a completed standard clinical questionnaire. Dengue was confirmed by virus isolation (10), haemagglutination inhibition (HI) (11), or by use of the dengue IgM-capture (MAC)-enzyme-linked immunosorbent assay test (G.E. Sather et al., CDC unpublished data). Measles was confirmed by a 24-fold rise in measles-specific IgG HI titres between two specimens taken 2–3 weeks apart (12).

Statistical analyses were performed using Epic-Info software, and the relative risk, with 95% confidence intervals, Mantel-Haenszel $\chi^2$, and $\chi^2$ tests for trend were calculated (13). $P$-values of <0.05 were considered to be significant.

Measles clinical case definition

To investigate potential misclassification, we used the above-described measles and dengue data to determine the total number of illnesses with rashes that were reported to SJL for laboratory confirmation that met the measles clinical case definition. We then determined the following proportions: those that were laboratory-confirmed as measles (true positives); those that were laboratory-positive for dengue (false positives); and those that were positive for neither.

Inadvertent inclusion of dengue cases as measles

Measles VE is normally determined by calculating the difference in measles attack rates (AR) between vaccinated and non-vaccinated populations (14). In areas with surveillance systems that are serologically based, only laboratory-confirmed cases of measles would be included in calculations of measles VE. However, in areas that rely on clinical case definitions for case ascertainment, all illnesses with rashes that met the measles case definition (including true dengue cases) would be mistakenly included. To illustrate the impact of such misclassification, we used the 1985 Puerto Rico surveillance data (all cases notified to SJL as dengue or measles and for which sera were available) and calculated the measles VE with and without the inclusion of laboratory-confirmed dengue cases.

Results

Evaluation of clinical case definitions

In 1985, SJL received notification of 296 febrile illnesses with rashes for laboratory confirmation of either dengue or measles. Of these, 226 were clinically diagnosed and reported as dengue, of which 133 (59%) were confirmed in the laboratory.
The other 70 illnesses with rashes were clinically diagnosed and reported as measles, and 33 (47%) of these were confirmed in the laboratory to be measles. Of the 296 illnesses with rashes that were notified, 94 met the clinical case definition for measles; 23% of these 94 cases were serologically confirmed to be measles, whereas 34% were confirmed to be dengue (Table 1). The proportion of cases that both met the measles case definition and were confirmed serologically was independent of age. This was not the case with reported dengue, for which the proportion of confirmed cases increased with age ($P < 0.05$, $\chi^2$ test for trend).

At least 28% of all laboratory-confirmed Puerto Rican dengue cases met the measles clinical case definition (Table 2). The proportion of confirmed dengue cases that met the measles case definition was highest among children aged <5 years (56% versus 24% for those aged $\geq 5$ years; relative risk (RR) = 3.3, 95% confidence interval (CI) = 1.3, 8.0; $P = 0.008$, Mantel-Haenszel $\chi^2$ test). Such true dengue cases would have warranted immediate measles outbreak control measures, had the notification of clinically identified measles cases been taken at face value.

### Table 1: Serological results, by age, for the reported illnesses with rashes that met the measles clinical case definition, Puerto Rico, 1985

<table>
<thead>
<tr>
<th>Age of reported cases (years)</th>
<th>&lt;5</th>
<th>5–14</th>
<th>$\geq 15$</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. that met definition</td>
<td>55</td>
<td>13</td>
<td>26</td>
<td>94</td>
</tr>
<tr>
<td>Serological results:</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Measles</td>
<td>13 (24)</td>
<td>4 (31)</td>
<td>5 (19)</td>
<td>22 (23)</td>
</tr>
<tr>
<td>Dengue $^b$</td>
<td>9 (16)</td>
<td>7 (54)</td>
<td>16 (62)</td>
<td>32 (34)</td>
</tr>
</tbody>
</table>

$^a$ Figures in parentheses are percentages.  
$^b$ $P < 0.05$, $\chi^2$ test for trend.

### Table 2: Proportion of laboratory-confirmed dengue cases that met the measles case definition, Puerto Rico, 1985

<table>
<thead>
<tr>
<th>Age (years)</th>
<th>&lt;5</th>
<th>5–14</th>
<th>$\geq 15$</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of cases</td>
<td>16</td>
<td>33</td>
<td>64</td>
<td>113</td>
</tr>
<tr>
<td>No. that met definition</td>
<td>9 (56)</td>
<td>7 (21)</td>
<td>16 (25)</td>
<td>32 (28)</td>
</tr>
</tbody>
</table>

$^a$ Figures in parentheses are percentages.  
$^b$ $P = 0.008$, Mantel-Haenszel $\chi^2$ test.

### Inadvertent inclusion of dengue cases as measles

VE is normally determined using the following relationship:

$$VE = ((ARU - ARV)/ARU) \times 100\%$$

where $ARU$ and $ARV$ are the attack rates in the unvaccinated and vaccinated populations, respectively (14).

We assumed that the Puerto Rico surveillance data were collected during a suspected measles outbreak in a population of 1000 persons. The 94 persons who met the measles case definition were considered to be clinical measles cases; actually, only 22 had measles, 32 had dengue, and the remaining 40 had other viral illnesses. We assumed also a true VE of 90% and a measles vaccine coverage level of 80% (800 persons). The proportion of measles patients who had been vaccinated (PCV) can be determined using the relationship:

$$PCV = (PPV - (PPV \times VE))/(1 - (PPV \times VE)) = (0.80 - 0.72)/(1 - 0.72) = 29\%$$

where $PPV = $ proportion of the total population vaccinated (14).

Thus, six (29%) of the 22 true cases of measles would have been vaccinated. These six cases occurred among 800 vaccinated persons (attack rate, 0.8%) and the other 16 among 200 unvaccinated persons (attack rate, 8%). However, during endemic or epidemic dengue transmission, dengue cases that fit the measles clinical case definition would also be considered to be measles and, as such, would be included in the VE calculations. Because dengue would be expected to occur with equal frequency throughout the entire population, regardless of their measles vaccine history, we can assume that 26 (80%) of the 32 dengue cases were among the 800 vaccinated, and six (20%) were among the 200 non-vaccinated persons. Thus, in the calculation of the measles VE, 32 cases (6 of which were true cases) would appear as measles among the vaccinated, and 22 cases (16 of which are true cases) among the unvaccinated, i.e.,

$$VE = ((22/200) - (32/800))/(22/200) = 64\%$$

Although the true VE would be 90%, field calculations of VE, since they include dengue cases that were incorrectly identified as measles under the
clinical case definition, would give an apparent VE of 64%, an absolute VE reduction of 26%, and a relative reduction of 29% (26/90).

**Discussion**

The measles case definition has been used extensively and successfully in the USA and in Europe, both of which are free of endemic dengue. Nevertheless, our results illustrate the potential confusion that can occur in distinguishing measles from dengue if the measles clinical case definition is used in a dengue-endemic area. The reliance on the use of the case definition to identify measles for the subsequent initiation of control or elimination measures can result in epidemiologically unnecessary efforts. The magnitude and frequency of such efforts would depend on the dengue incidence at any particular time. However, endemic and epidemic activity for both dengue and measles often tend to overlap temporally. For example, the 1977 dengue outbreak in Puerto Rico coincided with both a measles and a rubella outbreak (15), and investigators reported difficulty in differentiating these three diseases on a clinical basis.

This potential misclassification carries serious implications for dengue and measles control measures. Identification of measles cases should lead to a review of vaccine coverage levels, evaluation of VE, and, if necessary, immediate introduction of immunization activities. Identification of dengue cases, on the other hand, warrants vector control measures which, to be effective, must be initiated rapidly and on a wide scale. The misclassification of true dengue infections as measles could result in a delay in initiating such control activities. As we have shown, inadvertent inclusion of true dengue cases as measles in surveys of measles VE in areas where both diseases occur will underestimate the true measles VE. Also, in Mozambique, Cutts et al. showed that reliance solely on cases of measles diagnosed by clinical recall gave VE estimates almost 50% lower than those obtained by serological confirmation (16). Such underestimation can result in an inappropriate focus on vaccine production or delivery (cold chain) systems.

One limitation of our retrospective analysis is that, because the questionnaires used to obtain data on clinical symptoms were designed for dengue, information on conjunctivitis (part of the measles case definition) was not collected. However, this omission reduced the possibility of misclassification, since the inclusion of additional symptoms may increase the number of dengue and other cases that incorrectly met the measles case definition. In addition, while conjunctivitis has not been associated with dengue, recent investigations in Mexico have reported that, of 115 confirmed measles cases in several outbreaks, nearly 100% had conjunctivitis (Secretariat of Health, Mexico, unpublished data, 1990). Therefore, the absence of conjunctivitis data probably does not adversely affect our analysis.

A further limitation is the lack of certainty that our data were representative of all cases of measles or dengue in Puerto Rico. We have no information to support or refute the hypothesis that physicians routinely draw blood samples from doubtful or more clinically difficult cases; if this were the case, however, it might explain some misclassification.

However, even with these limitations our analysis illustrates the potential for misclassification. The impact on VE is independent of population size; however, the VE is not independent of the PPV, as the PPV decreases, the VE decreases. A PPV of 80% was chosen because it approximates the official measles vaccine coverage levels (17).

In areas not involved in formal measles elimination programmes, the clinical impression is often used for notification and subsequent control activities. For example, cases diagnosed clinically as dengue, but which meet the measles case definition, may be reported only as dengue. Our analysis focused on the potential for misclassification when an illness meets a standardized clinical case definition that then acts as a trigger for outbreak control measures. However, during a simultaneous outbreak of measles and dengue, clinical misclassification should ideally be addressed by testing serologically for both diseases.

Current surveillance methods for dengue can be applied to measles, and both systems could be combined. The monitoring of all illnesses with rashes, using random testing, at sentinel sites is highly effective for detecting increased or new dengue activity (6). Serological and virological surveillance, therefore, are currently the most sensitive surveillance methods for dengue (6). Febrile illnesses that are clinically diagnosed as measles but have negative measles serology should automatically be tested for dengue, and cases of reported dengue with negative dengue serology/virology should be tested for measles antibodies.

With increased emphasis on measles control activities, greater attention must be paid to serological surveillance for the disease. Failure to consider clinical misclassification of measles and dengue in dengue-endemic areas may result in inappropriate diagnostic conclusions and misdirected control efforts for both diseases. Also, failure to identify correctly true measles cases, especially during endemic dengue activity, may result in the loss of confidence by the community in the use of measles vaccine.
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Résumé
Diagnostic de rougeole selon la définition clinique du cas dans les zones d’endémie de la dengue: conséquences sur la surveillance de la rougeole et la lutte antirougeoleuse
La lutte contre la rougeole est une activité hautement prioritaria, ayant conduit certains pays à adopter comme objectif l’élimination de cette maladie. L’OMS a établi des directives afin d’aider les pays dans leurs activités de lutte antirougeoleuse. Ces recommandations insistent sur la nécessité d’améliorer la surveillance au moyen d’une définition type du cas fondée sur les observations cliniques. De nombreux pays ne disposent pas des moyens de laboratoire nécessaires pour le diagnostic de la rougeole. Il est donc extrêmement important de pouvoir utiliser une définition du cas sensible et spécifique. Il n’existe toutefois aucune donnée sur l’emploi de la définition du cas de rougeole dans les zones où la dengue est endémique. La dengue, la plus fréquente des arboviroses humaines, possède une vaste répartition géographique et frappe notamment les Caraïbes, l’Amérique latine et l’Asie du Sud-Est.

Nous avons utilisé des données de surveillance en provenance de Porto Rico pour évaluer la proportion des erreurs de classification des cas qui peuvent survenir au cours des activités d’élimination de la rougeole, lorsqu’on utilise la définition du cas de rougeole dans des régions où seviennent à la fois la rougeole et la dengue. Nous avons également calculé l’impact des erreurs de classification sur l’estimation de l’efficacité de la vaccination antirougeoleuse.

En 1985, 296 cas de fièvre éruptive ont été rapportés à Porto Rico en vue de leur confirmation au laboratoire comme dengue ou comme rougeole; parmi ces cas, 94 satisfaisaient à la définition clinique du cas de rougeole. Bien que 23% de ces derniers cas aient été sérologiquement confirmés comme cas de rougeole, 34% ont été confirmés comme cas de dengue. De plus, au moins 28% de l’ensemble des cas de dengue confirmés au laboratoire à Porto Rico remplaçaient les critères de la définition clinique du cas de rougeole.

En supposant que les données aient été collectées au cours d’une épidémie de rougeole, nous avons déterminé l’impact des erreurs de classification des cas sur le calcul de l’efficacité de la vaccination antirougeoleuse. Pour cela, nous avons supposé une efficacité de la vaccination antirougeoleuse de 90%, avec une couverture vaccinale de 80% dans une population de 1000 personnes. Le calcul sur le terrain de l’efficacité de la vaccination, en incluant les cas de dengue classés par erreur comme rougeole selon la définition clinique du cas, a donné une efficacité vaccinale apparente de 64%, soit une baisse absolue de l’efficacité vaccinale de 26% et une baisse relative de 29%.

Les résultats de cette étude illustrent la confusion qui risque de résulter de la difficulté de distinguer la rougeole de la dengue lorsqu’on utilise la définition clinique du cas de rougeole dans une zone d’endémie de la dengue. En se fiant à une telle définition pour identifier les cas de rougeole en vue de la mise en œuvre de mesures de lutte antirougeoleuse ou d’élimination de la rougeole, on risque d’aboutir à des activités de lutte qui ne se justifient pas sur le plan épidémiologique. Ces travaux montrent donc l’importance d’un système de surveillance fondé sur les examens de laboratoire dans le cadre des efforts de lutte antirougeoleuse ou d’élimination de la rougeole dans les zones où la dengue est endémique.

References
8. Dietz, V.J. et al. Epidemic dengue 1 in Brazil, 1986:


