An accurate system of identifying and classifying suspected measles cases is critical for the measles surveillance system in the United States. To examine the performance of the clinical case definition in predicting laboratory confirmation of suspected cases of measles, we reviewed 4 studies conducted between 1981 and 1994. A clinical case definition was examined that included a generalized maculopapular rash, fever (≥38.3°C, if measured), and either a cough, coryza, or conjunctivitis. Serological confirmation of measles was done either by hemagglutination inhibition assay, complement fixation assay, or enzyme immunoassays. The positive predictive value of the clinical case definition decreased from 74% to 1% as incidence decreased from 171 cases/100,000 population to 1.3 cases/100,000 population. Sensitivity was high, and for the larger studies with the most precise estimates, sensitivity was 76%–88%. The low positive predictive value of the clinical case definition in settings of low incidence demonstrates that serological confirmation is essential to ensure an accurate diagnosis of measles when measles is rare.

Measles surveillance is an essential component of the strategy to eliminate the disease in the United States. The surveillance of measles is based on a case classification system that identifies suspected, probable, and confirmed cases [1]. Any person with a generalized maculopapular rash and fever is considered to have a suspected case. Cases are classified as probable measles if they meet the clinical case definition adopted in 1979 by the Council of State and Territorial Epidemiologists [2]. The clinical case definition for measles is a generalized maculopapular rash lasting for ≥3 days, temperature of ≥38.3°C, and 1 of the following: cough, coryza, or conjunctivitis [2, 3]. When measles incidence is high, the clinical case definition performs reasonably well in identifying measles cases. However, the accuracy (validity and reliability) of the clinical case definition in correctly detecting measles cases is affected as measles elimination progresses.

Until 1996, besides laboratory-confirmed cases, a clinical case of measles, with epidemiological linkage to at least 1 other clinical case, was also accepted as confirmatory for measles during outbreaks in the United States [2, 3]. Since 1997, confirmation of measles in the United States requires not only that the case meet the clinical criteria for measles but that there is also laboratory evidence of measles virus infection or epidemiological linkage to a laboratory-confirmed case [4].

For a number of years, other countries in the Western Hemisphere have targeted measles for elimination. In 1994, ministers of health of these countries in North and South America established the goal of measles eradication from the Western Hemisphere by 2000. To achieve this goal, the Pan American Health Organization (PAHO) developed an enhanced 3-component measles vaccination strategy (“catch-up,” “keep-up,” and “follow-up”) with enhanced measles surveillance [5, 6]. The clinical case definition for measles used in the United States also has been used by other countries in the PAHO region [6].

Many countries with endemic measles still rely only on the clinical case definition to detect measles through their surveillance system. However, as the incidence of measles decreases, the positive predictive value (predictive value positive [PVP]) of any clinical case definition decreases [7].
To document the impact of decreased measles incidence on the accuracy of the measles clinical case definition, we used data from 4 studies conducted in the Western Hemisphere during a period of declining incidence of the disease. We estimate the performance of the measles clinical case definition in detecting a serologically confirmed case of measles, demonstrating that performance of the case definition declines with declining disease incidence.

METHODS

In all 4 studies, persons were eligible for enrollment if they had a rash and fever. Information obtained on each participant included demographics (e.g., age and sex), clinical manifestations of illness, timing of serum specimen collection, and laboratory results. Clinical manifestations primarily included signs and symptoms found in the clinical case definition. The studies were either a prospective or a retrospective cohort design.

A clinical case of measles was defined as a generalized maculopapular rash of ≥3 days' duration, temperature of ≥38.3°C (if measured; if not recorded, if the patient "felt hot"), and at least one of the “3 Cs” (cough, coryza, or conjunctivitis). A clinical case was confirmed by means of serological tests. The 4 studies varied by location, study period, setting of study, study population, and serological test for measuring antibody to measles (table 1).

Performance of clinical case definition. The performance (sensitivity, specificity, and predictive values [positive and negative]) of the measles clinical case definition was evaluated in detecting serologically confirmed cases by examining the clinical case definition against a reference standard of serological confirmation of the rash illness as either positive or negative for measles (figure 1) [7]. Sensitivity and specificity measure the validity of the clinical case definition. Serological confirmation is the usual laboratory method for measles confirmation, although isolation of the measles virus is more sensitive, but virus isolation is not as widely available as are serological tests. Sensitivity was defined as the proportion of all serologically confirmed cases of measles (positive by serological tests) that met the clinical case definition (i.e., the true-positive rate). Sensitivity was computed by dividing the number of serologically confirmed cases classified as a clinical case (a) by all serologically confirmed cases (a + c) (figure 1).

Specificity was the proportion of all rash illnesses not serologically confirmed (negative results of serological testing) that were not clinical cases (i.e., true-negative rate). Specificity was computed by dividing the number of persons with a negative serological test result for measles whose illness did not meet the case definition (b) by all of the serologically negative cases (b + d) (figure 1).

PVP was the proportion of rash illnesses that met the clinical case definition and had a positive serological result (i.e., the probability). It was computed by dividing the number of people who met the case definition and were serologically confirmed as having clinical cases (a) by the total number of persons meeting the clinical case definition (a + b) (figure 1). Negative predictive value (predictive value negative [PVN]) was the proportion of all rash illnesses that did not meet the clinical case definition that were not serologically confirmed. PVN was computed by dividing the number of rash illnesses that were not classified as a clinical case and were not serologically confirmed (d) by all persons who did not have a clinical case (c + d) (figure 1).

Relationship of incidence and prediction of measles. The relationship of PVP and incidence of measles was examined because PVP varies with incidence, unlike sensitivity, which theoretically remains constant regardless of incidence. Although Bayes’ theorem is a formula of conditional probabilities that relates prevalence (incidence) with PVP, PVN, sensitivity, and specificity, the computed PVP from Bayes’ theorem may not be similar to the observed PVP if prevalence (incidence) of disease is statistically rare (<1%) [13]. To assess the observed relationship for the 4 studies of measles incidence and PVP of the clinical case definition in detecting measles when incidence is very low, the observed PVP was plotted against the incidence.

Statistical analysis. Because the number of participants was small for computing some of the indicators of performance of the clinical case definition, statistical methods that assumed a normal distribution and computed approximate 95% confidence intervals (CIs; i.e., parametric methods) were not used. Instead, an exact (nonparametric) statistical method was used for computing 95% CIs for sensitivity, specificity, PVP, and PVN assuming a binomial distribution (Clopper-Pearson method), using StatXact computer software [14]. The relationship between measles incidence and PVP was displayed by means of a logarithmic scale for measles incidence and an arithmetic scale for the PVP.

RESULTS

Florida, California, and New York City, 1981–1983. Information and serum specimens were obtained from 233 patients with rash illness and fever, ranging in age from 2 months to 73 years. Of these, 51 were excluded from further analysis because they had inadequate or inappropriately timed sera. Of 182 participants with complete results, 54 had indeterminate serological evaluation. Of the remaining 128 participants, 77 (60%) had illnesses confirmed as measles by serological evaluation and 51 (40%) had illnesses that were negative for measles.

Of the 128 participants, 39% were from Florida, 35% were from New York City, and 26% were from California. The approximate median age was 15 years in Florida, 11 years in California, and 5 years in New York City.
<table>
<thead>
<tr>
<th>Location [reference]</th>
<th>Study period</th>
<th>Setting</th>
<th>Study population</th>
<th>Serological test (site performed)</th>
<th>Serological specimen</th>
<th>Measles confirmation</th>
</tr>
</thead>
<tbody>
<tr>
<td>FL, CA, and NY</td>
<td>Sep 1981–Sep 1983</td>
<td>School-based outbreak</td>
<td>128 HI (CDC) or CF (FDRS)</td>
<td>Acute specimen (drawn &lt;5 days after rash onset); convalescent specimen (drawn &gt;10 days after rash onset)</td>
<td>&gt;4-fold rise in total measles HI or CF antibody or positive for measles IgM antibody in acute serum specimen&lt;sup&gt;a&lt;/sup&gt;</td>
<td></td>
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<tr>
<td>Lee County, FL [8]</td>
<td>Sep–Nov 1981</td>
<td>School-based outbreak</td>
<td>82</td>
<td>EIA (CDC) [10, 11]</td>
<td>Any specimen positive for measles-specific IgM antibody&lt;sup&gt;b&lt;/sup&gt;</td>
<td></td>
</tr>
<tr>
<td>San Diego, CA</td>
<td>Apr–June 1982</td>
<td>School-based outbreak</td>
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<tr>
<td>New York, NY</td>
<td>Jan–Sep 1983</td>
<td>Passive surveillance: children aged &lt;5 years</td>
<td>82</td>
<td>EIA (CDC) [10, 11]</td>
<td>Any specimen positive for measles-specific IgM antibody&lt;sup&gt;b&lt;/sup&gt;</td>
<td></td>
</tr>
<tr>
<td>Brooklyn, NY [9]</td>
<td>Jan 1994–Jan 1995</td>
<td>Children seen in the Children’s Medical Center of Brooklyn after informed consent obtained from parents</td>
<td>82</td>
<td>EIA (CDC) [10, 11]</td>
<td>Any specimen positive for measles-specific IgM antibody&lt;sup&gt;b&lt;/sup&gt;</td>
<td></td>
</tr>
<tr>
<td>18 countries in English-speaking Caribbean and Suriname</td>
<td>Sep 1991–July 1992</td>
<td>Active surveillance system for measles [5, 6]</td>
<td>121</td>
<td>EIA (CAREC)</td>
<td>Specimen positive for measles-specific IgM antibody&lt;sup&gt;c&lt;/sup&gt;</td>
<td></td>
</tr>
<tr>
<td>Venezuela</td>
<td>1993–1995</td>
<td>Children aged 6 months—14 years attending 1 of 3 maternal and child health hospital outpatient departments in urban areas during a measles outbreak [12]</td>
<td>379</td>
<td>EIA (CDC) [10, 11]</td>
<td>Any specimen positive for measles-specific IgM antibody&lt;sup&gt;c&lt;/sup&gt;</td>
<td></td>
</tr>
</tbody>
</table>

**NOTE.** CAREC, Caribbean Epidemiology Research Center; CDC, Centers for Disease Control and Prevention; CF, complement fixation assay; EIA, enzyme immunoassay; FDRS, Florida Department of Rehabilitative Services; HI, hemagglutinin inhibition assay.

<sup>a</sup> Indeterminate or negative serological results were considered negative for measles antibody.

<sup>b</sup> $P/N > 0.10$ and $P/N > 3.00$, where $P$ is optical density in duplicate antigen-positive wells and $N$ is optical density in duplicate negative wells.

<sup>c</sup> ISR > 1.10, where ISR (immune status ratio) is defined as mean absorbance of triplicate patient serum wells divided by a calibrator value (mean absorbance of 2 positive calibrators multiplied by the master lot specific factor).
Figure 1. Performance of measles clinical case definition, United States, 1981–1983 and 1994–1995. Serological tests included complement fixation and hemagglutination inhibition. Incidence is the number of cases per population. Sensitivity, specificity, PVPs, and PVNs are shown with 95% confidence intervals (New York City, 1994–1995).

The sensitivity and specificity of the clinical case definition for measles were 88% and 48%, respectively (figure 1). The PVP of the clinical case definition was 74% and the PVN was 70%. Ninety-five percent confidence intervals were not reported for sensitivity, specificity, PVP, or PVN. The incidence of measles was available only for the Lee County, Florida, outbreak (171 cases/100,000 population) [8].

**New York City, January 1994–1995.** Of 133 eligible patients with rash and fever, 99 agreed to participate in the study and had sufficient clinical information to evaluate the clinical case definition. Of the 99, there were 85 (33 female, 52 male) who also had adequate serum specimens and were included in the study. Ages ranged from 1 month to 14 years (median, 47 months).

Twenty-six patients met the clinical case definition of measles. Measles IgM antibodies were initially detected in 5 patients. Of these, 3 were excluded from further analysis because of recent measles vaccination. Of the remaining 2 patients with positive results for measles IgM, 1 met the clinical case definition of measles. The case patient who did not meet the clinical case definition had generalized maculopapular rash and fever but did not have cough, coryza, or conjunctivitis. The sensitivity of the clinical case definition for measles was 50%, the specificity was 69%, the PVP was 4%, and the PVN was 98% (figure 1). During the study period, the incidence of measles in the county (Kings County) was 1.3 cases/100,000 population among persons <18 years of age.

**English-speaking Caribbean and Suriname, September 1991–July 1992.** Two hundred ninety-eight eligible persons (with rash and fever) were reported to the active surveillance system. Of these, 121 (41%) had complete clinical information and serological results for assessing whether the clinical case definition
was met. More than one-half (52%) of cases were in children <5 years of age. Infants <12 months accounted for 23% of cases. Children 5–14 years of age accounted for 34% of cases, and persons ≥15 years of age accounted for 15% of cases.

Ninety-three patients met the clinical case definition, including the patient with serologically confirmed measles. This case was serologically confirmed by the EIA at the Caribbean Epidemiology Research Center (CAREC) and validated at the Centers for Disease Control and Prevention. Thus, the sensitivity was 100% (figure 2). Specificity was 23% and the PVP was only 1%. Reported measles incidence was 0.03 cases/100,000 population at that time.

**Venezuela, 1993–1995.** Four hundred forty-eight children were eligible (had rash and fever) and were enrolled in the study; 420 (94%) responded to the follow-up questionnaire. Complete clinical information and measles antibody results were available for 404 persons. Twenty-five persons were excluded from the study because they were vaccinated within 8 weeks (60 days) of acute or convalescent serum specimens.

Of the 379 children in study population, about one-half (51%) were male. Of the participants, 28% (106) were <1 year of age, 40% (152) were 1–4 years of age, and 32% (121) were 5–14 years of age.

Overall, 26% (98) were serologically diagnosed as having measles. The sensitivity was 76% and specificity was 51% (figure 2). The PVP of this clinical case definition was 35% and the PVN was 86%. During the study period, measles incidence in Venezuela was 64 cases/100,000 population.

**Relationship of incidence and prediction of measles.** As the incidence of measles decreased to <171 cases/100,000 population, the PVP also decreased. At incidences of >100 cases/100,000 population, a 50% decrease in incidence was linked to a 30% decrease in the PVP (figure 3). For example, as incidence decreased from 100 cases per 100,000 population to 50 cases per 100,000 population, the PVP decreased from 0.50 to 0.20 (χ² for trend, 110; P < .0001).

The sensitivity of the clinical case definition decreased from 88% (95% CI, 79%–95%) when incidence was 171 cases/100,000
population to 76% (95% CI, 66%–83%) when incidence was 64 cases/100,000 population, but this difference may not be statistically significant. In the 2 studies with very low incidence, there were too few laboratory-confirmed cases to accurately assess sensitivity.

**DISCUSSION**

The PVP of the measles clinical case definition in all studies was directly related to measles incidence. In studies in which the incidence of measles was relatively high, most or many of the cases that met the case definition had positive results of serological testing. In studies with a lower incidence, only a small percentage of the cases that met the clinical case definition were serologically confirmed. In the United States, since 1997, measles incidence has been <1 case per 1 million population, and the prediction of measles using the clinical case definition is likely to be even closer to 0.

The sensitivity of the clinical case definition did not vary much with incidence of measles. Sensitivity was high (76%–88%) and may be statistically similar in the 2 largest studies that estimated sensitivity. The 95% CIs for these studies may overlap. The earliest study, conducted in the United States from 1981 through 1983, did not report a 95% confidence interval. A reliable estimate of sensitivity was not possible in 2 studies with very low incidence (New York City, 1994–1995, and the CAREC study, 1991–1992). The low incidence resulted in only 1 or 2 serologically confirmed cases and very wide 95% CIs.

Specificity did vary by incidence of measles. Although sensitivity is not affected by incidence of disease, specificity may vary depending on the incidence of other rash exanthems (e.g., rubella) in the population. For example, if rubella cases or other exanthems meet the clinical case definition, the specificity will decrease as the incidence of these exanthems increases in the population. In contrast, if rubella or other exanthems do not meet the clinical case definition, the specificity will increase with increasing incidence of these exanthems in the population.

As elimination of measles is approached, accurate identification of each case of measles becomes more important and more difficult. It is more important to accurately identify each case because one case may be the only evidence of measles transmission in an area. One misidentified case may signal measles transmission in a setting in which there is none. The public health system responds vigorously to measles cases and initiates outbreak control in the community, which may include vaccination of a large population exposed to measles, such as in schools. Misidentification of measles cases results in misdirection of the outbreak response, which may be initiated when not needed or not initiated when needed. The high PVP in all studies demonstrates, in general, that resources were conserved because rash illnesses not meeting the measles clinical case definition were other illnesses (i.e., high PVP). Accurate identification of a measles case is more difficult as elimination is approached, because when measles is rare, most of the illnesses that clinically resemble measles are not measles (i.e., the PVP of clinical case definition is low) and an increased proportion of the actual measles cases may have a mild presentation that does not meet the clinical case definition (i.e., the clinical case definition is less sensitive for vaccinated persons than unvaccinated persons because of vaccine-modified disease) [15].

In the United States, the measles case classification used for surveillance has evolved into a system that is more complex than a single clinical case definition and more accurate at the currently very low incidence of disease. To maximize the ability of the system to detect all measles cases, we use a sensitive definition of suspected cases to screen cases for investigation. To maximize the likelihood that a confirmed case is truly measles, we use a highly sensitive and specific serological test for
confirmation, particularly the recommended EIA [16, 17]. As the need for higher certainty in the diagnosis increases in the United States, so has the percentage of laboratory-confirmed measles cases reported to the National Notifiable Disease Surveillance System. By 1999, 82% of the reported cases were laboratory-confirmed [18].

The clinical case definition, once the primary basis of measles case confirmation in practice, now has a limited role in the case classification system. Now it is used to define probable cases, which is really an intermediary definition in practice, pending laboratory results. If laboratory specimens are not available, the clinical case definition can be used to confirm cases, but this requires an epidemiological link to a laboratory-confirmed case. If there is no laboratory specimen and no epidemiological link to a laboratory-confirmed case, the probable case is discarded. As shown in this analysis, the likelihood that a probable case (i.e., a case meeting the clinical case definition) is actually measles is extremely low in the absence of other supporting evidence. Nevertheless, probable cases that are discarded represent a failure of the surveillance system to obtain laboratory specimens from a patient who might have had measles.

This review of 4 studies has a number of potential limitations. These limitations include different study populations and different laboratory tests to detect an acute illness of measles; a small number of serologically confirmed cases in some studies; and in some studies, a lack of recent vaccination of patients to examine the effect of vaccine-modified measles. A limitation of examining the clinical case definition among vaccinated case patients may become an increasing problem as measles vaccination programs achieve higher vaccine coverage.

Despite the potential limitations, these studies demonstrate the relationship of the PVP of the measles clinical case definition and the incidence of measles in settings in which measles incidence is statistically rare (<1%). To ensure that measles elimination continues to progress when incidence is near zero, all suspected cases of measles that are truly measles cases need to be detected. Clinical diagnosis of measles alone without serological confirmation is not accurate enough for measles elimination. In addition, detection of virus may need to play more of a role in laboratory confirmation as elimination progresses among vaccine-modified measles cases in which disease is milder [19]. A surveillance system that includes a sensitive definition for suspected cases to be investigated and laboratory testing of suspected cases for confirmation is critical to identify true cases and guide public health action.

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