Measles surveillance in Victoria, Australia
Yung-Hsuan J Wang,a Ross M Andrews,ab & Stephen B Lamberta

Objective Many countries are implementing measles elimination strategies. In Australia, the State of Victoria has conducted enhanced measles surveillance since 1997 using case interviews and home-based specimen collection for laboratory confirmation. We attempted to identify features of notified cases that would better target surveillance resources.

Methods We retrospectively classified notifications received from 1998 to 2003 as having been received in an epidemic (one or more laboratory-confirmed cases) or an interepidemic period (no laboratory-confirmed cases). We labelled the first case notified in any epidemic period that was not laboratory-confirmed at the time of notification as a “sentinel case”. To maximize detection of sentinel cases while minimizing the follow-up of eventually discarded notifications, we generated algorithms using sentinel cases and interepidemic notifications.

Findings We identified 10 sentinel cases with 422 interepidemic notifications from 1281 Victorian notifications. Sentinel cases were more likely to report fever at rash onset (odds ratio (OR) 15.7, 95% confidence interval (CI) 2.1–688.9), cough (OR 10.4, 95% CI: 1.4–456.7), conjunctivitis (OR 7.9, 95% CI: 1.8–39.1), or year of birth between 1968 and 1981 (OR 31.8, 95% CI: 6.7–162.3). Prospective application of an algorithm consisting of fever at rash onset or born between 1968 and 1981 in the review period would have detected all sentinel cases and avoided the need for enhanced follow-up of 162 of the 422 eventually discarded notifications.

Conclusion Elimination strategies should be refined to suit regional and local priorities. The prospective application of an algorithm in Victoria is likely to reduce enhanced measles surveillance resource use in interepidemic periods, while still detecting early cases during measles outbreaks.

Keywords Measles/epidemiology; Epidemiologic methods; Disease notification; Sentinel surveillance; Australia (source: MeSH, NLM). Mots clés Rougeole/épidémiologie; Méthode épidémiologique; Notification maladie; Surveillance par système sentinelle; Australie (source: MeSH, INSERM). Palabras clave Rubéola/epidemiología; Métodos epidemiológicos; Notificación de enfermedad; Vigilancia de guardia; Australia (fuente: DeCS, BIREME).

Introduction
Due to the success of measles vaccination, measles elimination strategies are currently being implemented or considered by many countries.1 2 In times of good measles control, infections are rare and enhancing routine surveillance with laboratory testing will show most notifications are not due to measles.3 4

In Victoria, local measles control has been very effective: current coverage of measles–mumps–rubella (MMR) vaccine is high, at 94% for receipt of the first dose (due at 12 months) by two years of age.5 Current Victorian measles epidemiology consists of long periods with few notifications and no reported laboratory-confirmed cases (interepidemic periods) punctuated by importations with usually limited local spread, and rarely larger outbreaks.6 7 This disease epidemiology is confirmed by the molecular epidemiology which shows an increasingly rapid turnover of virus genotypes over time.8 All of these findings combine to suggest measles has been eliminated from Victoria.

Surveillance of notifiable infectious diseases and their control is the core business of the Communicable Diseases Section at the Victorian Department of Human Services (DHS). Infectious diseases surveillance programmes are managed centrally in the state capital, Melbourne, and response measures are organized in conjunction with local health officers. Currently, 63 infectious diseases are notifiable under Schedule 3 of the Health (Infectious Diseases) Regulations 2001 in Victoria by doctors and laboratories.9 In 2003, DHS received 24 745 notifications from within the state.10

In 1997 Victoria established an enhanced measles surveillance system with the aim of following up and obtaining laboratory confirmation from every notification.11 Enhanced measles surveillance is resource intensive, both in terms of staff and the time it takes to maintain the system. It is also expensive in terms of testing costs. Previous analysis of the Victorian enhanced measles surveillance data showed only 6% of notified cases

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that had serological testing during an interepidemic period were laboratory-confirmed as measles. Public health resources may be more effectively directed to other programmes, particularly during interepidemic periods. Our aim was to determine whether enhanced surveillance was required for every notification by examining the notification data over the last six years (1998 to 2003).

Methods

Under the Health (Infectious Diseases) Regulations, physicians and laboratories are required to notify DHS upon an initial diagnosis of presumptive measles. The enhanced measles surveillance system ensures a public health nurse at DHS follows up all measles notifications with a standard telephone interview, including their measles immunization history. Notifications are classified as having had documented measles vaccination if they had received at least one dose of live-attenuated measles vaccine and the patient or the immunization provider can state the date of vaccine administration. If not already performed as part of making the diagnosis, home-based serological testing by a paediatric phlebotomist is offered. Other specimens are collected at this time as clinically indicated. Sera are tested for measles-specific immunoglobulin (IgM) and IgG, and other specimens, such as a combined nose-throat swab, may be tested for measles ribonucleic acid (RNA) by polymerase chain reaction (PCR) method, at the Victorian Infectious Diseases Reference Laboratory (VIDRL). Serum specimens negative for measles-specific IgM are further tested for rubella and parvovirus B19.

We examined all measles notifications in Victoria between 1998 (by which time enhanced surveillance was fully functional), and 2003. For the purposes of this analysis we classified notifications in two ways — by confirmation status, and by being received in an epidemic or an interepidemic period. A measles notification was classified as confirmed if there was:

- laboratory-definitive evidence of measles infection defined by isolation of the measles virus, detection of the virus antigen, detection of measles RNA by nucleic acid testing, measles IgG seroconversion or significant titre rise in paired sera, or detection of measles specific IgM;
- clinical illness compatible with the national case definition (rash, fever at rash onset, and at least one of cough, coryza, conjunctivitis, or Koplik’s spots) and the case was epidemiologically linked to a laboratory confirmed case.

Notifications that did not fulfil the above criteria were classified as discarded notifications.

We defined an epidemic period as beginning from the date a confirmed case of measles was reported to DHS and ending at 28 days (two measles incubation periods to appearance of rash) from rash onset of the last confirmed case. We defined an interepidemic period as beginning the day after an epidemic period concluded and ending the day prior to the date of notification of the next confirmed measles case, that is, when the next epidemic period commenced.

We attempted to identify features of notified cases that could be used during interepidemic periods to target enhanced surveillance by focusing our analysis on sentinel cases. Sentinel cases were confirmed measles cases notified on the first day of epidemic periods that were laboratory confirmed after the day of notification. Cases that were laboratory confirmed at notification were excluded from the analysis, as such cases, being already confirmed, would routinely trigger enhanced follow-up in any modified system. We compared sentinel cases with interepidemic, discarded notifications by calculating odds ratios for the presence of features routinely collected as part of enhanced follow-up. The variables included in our analysis were sex, year of birth, measles vaccination history, recent travel out of Victoria, the presence of fever at rash onset, rash, rash for more than three days, cough, conjunctivitis, coryza, and Koplik’s spots. The years of birth between 1968 and 1981 were particularly examined as they have previously been identified as high-risk birth years and contain a higher proportion of people who are seronegative for measles being both unvaccinated against measles and not having had exposure to endemically circulating wild measles virus.

We used the features found more commonly in sentinel cases than interepidemic notifications to generate algorithms in an attempt to accurately differentiate between these two types of notifications. The algorithms contained each feature alone or in combination with other features using either AND or OR operators. The aim in generating these algorithms was to identify the algorithm that could most reduce enhanced surveillance requirements during interepidemic periods, while maintaining maximum sensitivity for sentinel cases. We calculated test-specific values for each algorithm (sensitivity, specificity, positive predictive value, and negative predictive value) by applying them retrospectively to the notification data received in the period under review. We used the best

Fig. 1. Measles notifications by confirmation status and year of birth, Victoria, Australia, 1998–2003 (n = 1281)
performing algorithm to propose a new protocol for managing measles notifications in Victoria during interepidemic periods.

We took a conservative approach in managing missing or “unknown” fields in the notification data. In calculating the likely presence of a notification feature, we applied the value “not present” if the feature was not reported for the notification. For example, if the presence of rash was not documented for a notification, this feature was given the value of “not present”. The effect of this would be to only identify notifications in which the presence of rash was truly reported. Conversely, in calculating the number of notifications that do not require enhanced follow-up using the ideal algorithm, we applied the value “present” if the feature was not reported for the notification. For example, if the presence of rash was not documented for a notification, this feature was given the value of “present”. The effect of this would be to remove the need for enhanced follow-up only in notifications that truly denied the presence of rash.

We made statistical comparisons of the notifications by calculating the odds ratio (OR), Fisher’s exact P-value, and exact 95% confidence interval (CI) for the presence of the specific features. The enhanced measles surveillance data were stored on the Notifiable Infectious Diseases Surveillance system (WHO 05.150) and on Microsoft Access 2000 (Microsoft Corporation, US). Data were analysed using Stata 8.0.17

Results

Between 1998 and 2003 DHS received 1281 measles notifications with 251 (20%) of these being confirmed cases (Fig. 1). The year of birth for 69% (173/251) of the confirmed cases was between 1968 and 1981, consistent with previously identified high-risk birth years for measles in Victoria (Fig. 2).7,14

There were 21 epidemic and 21 interepidemic periods in the six study years. The median duration for interepidemic periods was 45 days (range: 1–157 days) and 32 days (range: 2–146 days) for epidemic periods. In total there were 1073 discarded measles notifications, with 422 (41%) received in interepidemic periods and 608 (59%) in epidemic periods. In the 21 epidemic periods, 24 measles cases were notified on the first day of the epidemic periods: three epidemic periods had two measles cases notified on the first day. Of these first-day notifications, 14 were already laboratory-confirmed at the time of notification. The remaining 10 cases had not been laboratory-confirmed at the time of notification and were sentinel cases.

The data fields of some notifications were incomplete in the database. A confirmed history of documented measles vaccination was unavailable in 30% (3/10) of sentinel cases and in 81% (343/422) of interepidemic notifications. Three sentinel cases had acquired their infection overseas; however, recent travel status was not recorded in 10% (1/10) of sentinel cases and 81% (343/422) of interepidemic notifications. Similarly, presence of Koplik’s spots was unknown in 80% (8/10) of sentinel cases and 71% (298/422) of interepidemic notifications. We excluded these fields from the analysis due to their being incomplete. In line with the Australian clinical case definition of measles, the notification database consistently recorded the presence of “fever at rash onset” rather than “fever”;13 thus, we were also able to compare the presence of fever alone between sentinel cases and interepidemic notifications.

We compared the available features of the 10 sentinel cases with that of the 422 discarded interepidemic notifications. Sentinel cases were more likely than interepidemic notifications to report fever at rash onset (or 15.7, 95% CI: 2.1–688.9), cough (or 10.4, 95% CI: 1.4–456.7), conjunctivitis (or 7.9, 95% CI: 1.8–39.1), or being born between 1968 and 1981 (or 31.8, 95% CI: 6.7–162.3) (Table 1). Sex of the patient, the presence of rash, rash for more than three days at the time of follow-up, or coryza did not distinguish between the two notification types.

We generated 48 algorithms using combinations of the four features — fever at rash onset, cough, conjunctivitis, or born between 1968 and 1981 — more commonly reported by sentinel cases. Six algorithms achieved a sensitivity of 100% for detecting sentinel cases when applied retrospectively to sentinel cases and interepidemic notifications (Table 2). The algorithms consisting of fever at rash onset or being born between 1968 and 1981 had the maximum sensitivity of 100% for sentinel cases, and a maximum positive predictive value of identifying eventually confirmed cases of 6%. Applying this algorithm in interepidemic periods as the decision-making tool for whether a notification would receive enhanced surveillance would have prevented the need for enhanced follow-up of 38% (162/422) of the interepidemic notifications received between 1998 and 2003. This algorithm would only be used in the measles surveillance protocol at DHS during interepidemic periods to guide whether enhanced surveillance would be performed. During epidemic periods, enhanced surveillance follow-up, including home-based serological testing, would be undertaken for all notifications (Fig. 3).

Fig. 2. Measles notification by confirmation status and date of notification, Victoria, Australia, 1998–2003 (n = 1281)
Table 1. Odds ratio of sentinel cases and interepidemic notifications by feature category, Victoria, Australia, 1998–2003

<table>
<thead>
<tr>
<th>Feature category</th>
<th>Sentinel cases n = 10</th>
<th>Interepidemic notifications n = 422</th>
<th>Odds ratio (95% confidence interval)</th>
<th>Number of missing or unknown entries (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male</td>
<td>6 (60)</td>
<td>199 (47)</td>
<td>1.7 (0.4–8.2)</td>
<td>0</td>
</tr>
<tr>
<td>Fever at rash onset</td>
<td>9 (90)</td>
<td>154 (36)</td>
<td>15.7 (2.1–688.9)</td>
<td>1 (10)</td>
</tr>
<tr>
<td>Rash</td>
<td>10 (100)</td>
<td>422 (100)</td>
<td>N/A*</td>
<td>0</td>
</tr>
<tr>
<td>Rash &gt;3 days</td>
<td>10 (100)</td>
<td>375 (89)</td>
<td>N/A*</td>
<td>0</td>
</tr>
<tr>
<td>Cough</td>
<td>9 (90)</td>
<td>196 (46)</td>
<td>10.4 (1.4–456.7)</td>
<td>1 (10)</td>
</tr>
<tr>
<td>Conjunctivitis</td>
<td>6 (60)</td>
<td>67 (16)</td>
<td>7.9 (1.8–39.1)</td>
<td>2 (20)</td>
</tr>
<tr>
<td>Coryza</td>
<td>8 (80)</td>
<td>208 (49)</td>
<td>4.1 (0.8–40.1)</td>
<td>1 (10)</td>
</tr>
<tr>
<td>Born 1968–81</td>
<td>6 (60)</td>
<td>19 (5)</td>
<td>31.8 (6.7–162.3)</td>
<td>0</td>
</tr>
</tbody>
</table>

* No data available.

Conclusion

Results from our study show that, in a region with good disease control, the universal application of enhanced follow-up of measles notifications is not always necessary and may be wasteful of scarce resources. Many viruses can present as a febrile-rash illness mimicking measles, particularly in children, and in an elimination setting, such as in Victoria, when coverage of the MMR vaccine is high, the majority of such cases will not be due to measles.3,4

Data obtained from the enhanced surveillance system since 1998 allowed us to determine that sentinel cases notified to DHS were more likely than interepidemic notifications to report fever at rash onset, cough, conjunctivitis, or being born between 1968 and 1981. Combinations of these features were used to generate a potentially resource-saving algorithm. If we had been able to apply this response algorithm in the interepidemic periods between 1998 and 2003, we would have been able to identify the first reported case(s) in all epidemic periods, where the first case was not notified as a laboratory-confirmed case, and been able to avoid enhanced follow-up with laboratory testing on a substantial proportion (38%) of eventually discarded notifications. Reduced resource use as a result of application of the algorithm may be reallocated to strengthen surveillance in other areas of need, such as clarification of the epidemiology of mumps and rubella in Victoria.18

Caution should be used in interpreting results from retrospective observational studies based on notification data, such as this, and limitations and generalizability must be considered before wider application. Some of the issues in this study were the small number of sentinel cases identified, incomplete fields in the routinely collected enhanced surveillance data, the risk of missing early cases in outbreaks with the implementation of such a system, and the applicability of the findings to other jurisdictions and in Victoria in the future.

As measles does not appear to be circulating endemically in Victoria and there are other causes of an illness where the patient presents with rash, some clinicians may be more inclined to obtain laboratory confirmation prior to notifying measles cases to DHS. Consequently, we were able to compare only 10 sentinel cases with interepidemic notifications in the review period to generate the resource-saving algorithm. Many clinical fields, including recent travel history and measles immunization status, were incomplete in the Victorian data. The calculated resource savings of the recommended protocol may be underestimated since we took a conservative approach in managing unknown data in the analysis. There may be better fields to use in the algorithm, such as history of overseas travel or immunization status for measles-containing vaccines (reported by 30% and 90% of sentinel cases, respectively) that we were unable to assess due to their incompleteness. However, the features — fever at rash onset or born between 1968 and 1981 — were well

Table 2. Test values of algorithms with 100% sensitivity for sentinel cases, Victoria, Australia, 1998–2003

<table>
<thead>
<tr>
<th>Algorithms</th>
<th>Sensitivity</th>
<th>Specificity</th>
<th>PPV*</th>
<th>NPV*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fever at rash onset or birth cohort*</td>
<td>100</td>
<td>60</td>
<td>6</td>
<td>100</td>
</tr>
<tr>
<td>At least one of: fever at rash onset or conjunctivitis or birth cohort*</td>
<td>100</td>
<td>54</td>
<td>5</td>
<td>100</td>
</tr>
<tr>
<td>Cough or birth cohort*</td>
<td>100</td>
<td>51</td>
<td>5</td>
<td>100</td>
</tr>
<tr>
<td>At least one of: cough or conjunctivitis or birth cohort*</td>
<td>100</td>
<td>47</td>
<td>4</td>
<td>100</td>
</tr>
<tr>
<td>At least one of: fever at rash onset or cough or birth cohort*</td>
<td>100</td>
<td>38</td>
<td>4</td>
<td>100</td>
</tr>
<tr>
<td>At least one of: fever at rash onset or cough or conjunctivitis or birth cohort*</td>
<td>100</td>
<td>36</td>
<td>4</td>
<td>100</td>
</tr>
</tbody>
</table>

* Positive predictive value.

b Negative predictive value.

* Born between 1968 and 1981.
completed, and their use in interepidemic periods during the review period would have achieved 100% sensitivity for detecting sentinel cases.

It is possible that the first case of measles in the event of an outbreak may be missed if enhanced surveillance follow-up is reduced in interepidemic periods, although analysis of the data over the last six years showed this would not have occurred using the algorithm during this time. In Victoria, it is unlikely that measles cases remain undetected by the surveillance system for an extended period due to the typically explosive nature of previous outbreaks, mainly involving young adults.\textsuperscript{6, 7, 19}

Enhanced surveillance may appear an inefficient use of limited resources during interepidemic periods, but balanced with this are the ability to detect and intervene in measles outbreaks early, and the ability to definitively classify nearly all notified cases according to a set of standardised laboratory criteria. Use of the preferred algorithm to guide follow-up during interepidemic periods should not impact on outbreak detection, but may mean more than one-third of notifications during interepidemic periods do not have a final laboratory classification. As such, this strategy is not suitable in settings where measles is well controlled, but the prospect of global eradication is some way off. Jurisdictions that have adopted enhanced measles surveillance may consider modifying the system using features of locally-notified cases that predict individuals who warrant enhanced follow-up and serological testing in interepidemic periods to increase surveillance efficiency. Similar to the approach used for the global eradication of smallpox and poliomyelitis, follow-up of every measles notification will again be necessary as that goal nears. \textsuperscript{6}

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Competing interests: none declared.

Résumé
Surveillance de la rougeole dans l’État de Victoria, en Australie

Objectif De nombreux pays appliquent des stratégies d’élimination de la rougeole. En Australie, l’État de Victoria mène une surveillance renforcée de la rougeole depuis 1997, à partir d’interrogatoires des cas et de prélèvements à domicile pour confirmation en laboratoire. L’article s’efforce d’identifier les caractéristiques des cas notifiés en vue d’une meilleure affectation des moyens alloués à la surveillance.

Méthodes On a procédé à une classification rétrospective des notifications reçues entre 1998 et 2003 pendant une période d’épidémie (un ou plusieurs cas confirmés en laboratoire) ou une période interépidémique (absence de cas confirmé en laboratoire). Le premier cas notifié au départ de toute période épidémique et non confirmé en laboratoire au moment de sa notification a été appelé « cas sentinelle ». Dans le but de maximiser le nombre de « cas sentinelles » détectés, tout en minimisant le suivi des notifications finalement écartées, des algorithmes d’optimisation utilisant les cas sentinelles et les notifications interépidémiques ont été mis au point.

Résultats Dix cas sentinelles et 422 notifications interépidémiques ont été identifiés à partir de 1281 notifications de cas dans l’État de Victoria. L’étude a relevé qu’il était plus probable que la notification des cas sentinelles signale la présence de fièvre lors de l’apparition des boutons [odds ratio (OR) = 15,7, intervalle de confiance à 95 % (IC) : 2,1 - 688,9], de toux (OR = 10,4 ; IC à 95 % : 1,4 - 456,7) ou d’une conjonctivite (OR = 7,9 ; CI à 95 % : 1,8 - 39,1), ou encore une année de naissance comprise entre 1968 et 1981 (OR = 31,8 ; CI à 95 % : 6,7 - 162,3). L’application de manière prospective à la période analysée d’un algorithme utilisant la présence de fièvre lors de l’apparition des boutons ou le fait d’être né entre 1968 et 1981 aurait permis de
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Objetivo Muchos países están aplicando estrategias de eliminación del sarampión. En Australia, el Estado de Victoria viene llevando a cabo desde 1997 actividades reforzadas de vigilancia de esta enfermedad, basadas en entrevistas de casos y recogida de muestras domiciliarias para confirmación en laboratorio. Decidimos identificar las características de los casos notificados que nos permitiesen orientar mejor los recursos de vigilancia.

Métodos Clasificamos de forma retrospectiva las notificaciones recibidas entre 1998 y 2003 como correspondientes a un periodo epidémico (uno o más casos confirmados en laboratorio) o interepidémico (ningún caso confirmado en laboratorio). Consideramos «caso centinela» el primer caso notificado en un periodo epidémico que no se hubiera confirmado en laboratorio en el momento de la notificación. A fin de maximizar la detección de casos centinela y reducir al mínimo el seguimiento de notificaciones finalmente descartadas, generamos algoritmos basados en los casos centinela y las notificaciones interepidémicas.

Resultados Identificamos 10 casos centinela y 422 notificaciones interepidémicas a partir de 1281 notificaciones en el Estado de Victoria. Los casos centinela tenían más probabilidades de presentar fiebre en el momento de aparición de la erupción cutánea (razón de posibilidades (OR): 15,7, intervalo de confianza (IC) del 95%: 2,1-688,9), tos (OR:10,4, IC95%: 1,4-456,7), conjuntivitis (OR: 7,9, IC95%: 1,8-39,1), o año de nacimiento comprendido entre 1968 y 1981 (OR: 31,8, IC95%: 6,7-162,3). La aplicación prospectiva de un algoritmo consistente en la presencia de fiebre en el momento de aparición de la erupción o una fecha de nacimiento comprendida entre 1968 y 1981 en el periodo analizado habría permitido detectar todos los casos centinela, y evitado la necesidad de un seguimiento reforzado de 162 de las 422 notificaciones finalmente descartadas.

Conclusión Las estrategias de eliminación del sarampión deberían perfeccionarse en función de las prioridades regionales y locales. La aplicación prospectiva del algoritmo desarrollado en Victoria permitirá probablemente reducir la necesidad de mejorar los recursos de vigilancia del sarampión en los periodos interepidémicos, sin menoscabo de la detección de los casos tempranos en los brotes de la enfermedad.
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References


