Pertussis Is a Frequent Cause of Prolonged Cough Illness in Adults and Adolescents

Linda D. Senzilet,1 Scott A. Halperin,2 John S. Spika,2 Merrilyn Alagaratnam,1 Annette Morris,2 Bruce Smith,3 and the Sentinel Health Unit Surveillance System Pertussis Working Group1

1Bureau of Surveillance and Field Epidemiology, Laboratory Centre for Disease Control, Health Canada, and 2Bureau of Infectious Diseases, Laboratory Centre for Disease Control, Health Canada, Ottawa, Ontario; 3Clinical Trials Research Center, Dalhousie University/IWK Health Centre, Halifax, Nova Scotia, Canada

(See the editorial commentary by Edwards on pages 1698–9)

Although pertussis is increasingly recognized as a cause of prolonged cough illness in adolescents and adults, its prevalence is not well established. We evaluated pertussis infection in 442 adolescents and adults ≥12 years old (mean age, 41.3 years) who had a cough-related illness of 7–56 days’ duration. For 4 patients (0.9%), results of nasopharyngeal culture or PCR were positive for Bordetella pertussis; for 10 patients (2.3%), either results of culture or PCR were positive or pertussis antibody titers increased 4-fold. Eighty-eight patients (19.9%) had either laboratory-confirmed pertussis or laboratory evidence of pertussis. These patients had significantly longer duration of cough than did patients without laboratory evidence of pertussis (56 days vs. 46 days), and more of them had vomiting with cough (45.5% vs. 28.5%, respectively). Pertussis is a common cause of prolonged cough illness in adolescents and adults and is frequently associated with other symptoms of whooping cough.

Pertussis is a highly communicable, vaccine-preventable respiratory disease. In Canada, the incidence of reported pertussis has increased dramatically, from 5.4 cases per 100,000 population (1350 cases) in 1984 to 30.2 cases per 100,000 population (8030 cases) in 1990 and to 34.7 cases per 100,000 population (10,151 cases) in 1994 [1]. In both Canada and the United States, the highest incidence of reported cases of pertussis is among infants; however, the most rapid increase in incidence has been among adolescents and adults [2]. In 1999, ~10% of reported cases of pertussis in the United States were in people ≥15 years old, and outbreaks of pertussis among adolescents and adults have been reported elsewhere [3–5]. The epidemiology of pertussis in adolescents and adults is not well defined because of the broad spectrum of clinical manifestations. In children, pertussis is characterized by occasional mild fever, paroxysmal cough, whooping cough, and posttussive vomiting. Although classic pertussis occurs in adolescents and adults [6, 7], the disease often is atypical, sometimes manifested only by a protracted, nondistinctive cough [8, 9].

Pertussis has been shown to be an important cause of cough illness in college students, military recruits, referrals to a pulmonary specialist, and visitors to hospital emergency departments [10–13]. The objectives of this study were to determine the prevalence of laboratory-confirmed infection with Bordetella pertussis in
study subjects ≥12 years old who had a cough illness of 1–8 weeks’ duration and to describe the clinical manifestations of pertussis in this age group.

PATIENTS AND METHODS

Network. The Sentinel Health Unit Surveillance System (SHUSS) was a network of 9 health units located in 8 Canadian provinces. The 9 health units had an aggregate 1996 population of 2,853,985, comprising 9.9% of the population of Canada. Four of the sites were in urban centers (population range, 193,670–663,195), whereas the remaining 5 sites were in both urban and rural communities (population range, 134,545–278,500). SHUSS was funded and coordinated by the Laboratory Centre for Disease Control, Health Canada, and was mandated to conduct targeted research and surveillance to address selected public health issues. The network was operational from 1993 to 1998.

Recruitment. Participants were recruited for 15 months, from October 1996 through December 1997. Participants were referred to the study either by their family physicians or referred themselves (the study was advertised in physicians’ offices, pharmacies, and through the media). Participants were eligible for the study if they were ≥12 years old and had a cough of 1–8 weeks’ duration. Patients were excluded if they were immunocompromised (if they had HIV infection, AIDS, a history of transplantation, or if they were currently undergoing chemotherapy or radiotherapy); if they were receiving long-term orally administered steroid therapy; if they had pulmonary tuberculosis, asthma, chronic bronchitis, or other known chronic cough illness with a cough that had not changed in character in the past month; or if they were receiving angiotensin converting enzyme inhibitors or other medications known to cause cough.

Data and specimen collection. At the time of the initial telephone contact, participants were administered an acute illness questionnaire that elicited information concerning the symptoms of the present illness and treatment to date, vaccination history, and past history of pertussis. Two visits were made to the home 5–9 weeks apart for the collection of biological specimens. Nasopharyngeal aspirate specimens were obtained at the first visit by passing a fine flexible catheter (5 French), attached to a 5-mL syringe, through a naris into the posterior nasopharynx [14]. Gentle suction was applied and held while withdrawing the syringe. The catheter tubing containing secretions (still attached to the syringe) was placed in a sterile urine container, and the top was closed over the catheter, with the syringe outside. The entire apparatus was placed in a plastic bag with a zipper seal and was transported to the laboratory. At the second home visit, participants were administered a convalescent illness questionnaire that elicited information about the status of their symptoms since the previous visit. Serum was collected by venipuncture at both home visits. Halfway through the study, several questions about symptoms were modified to capture start and stop dates of symptoms, to more accurately calculate the total symptom duration.

Laboratory methods. Nasopharyngeal aspirate catheters were rinsed with 1% casamino acids in PBS and were inoculated onto pertussis selective media (Bordet-Gengou or charcoal-blood agar with and without antibiotics) at each participating site [15]. Serum and residual catheter secretions were stored frozen and were shipped in batches to the Clinical Trials Research Center in Halifax. Residual secretions were assayed by PCR [16], and serum samples were tested for IgG and IgA antibodies to pertussis toxin (PT), filamentous hemagglutinin (FHA), pertactin (PRN), and fimbriae (FIM) by use of EIA [17].

Case definitions. Five definitions were used for laboratory confirmation of pertussis cases. A case was considered to be
confirmed pertussis if (1) culture or (2) PCR of nasopharyngeal aspirate specimens was positive for *B. pertussis* and/or (3) if there was a 4-fold increase between acute-phase and convalescent-phase titers of antibody to PT and/or antibodies to 2 of the other pertussis antigens (FHA, PRN, or FIM). A case was considered to have laboratory evidence suggestive of pertussis if (4) titers of antibody to PT and/or antibodies to 2 of the pertussis antigens FHA, PRN, or FIM were higher than the 99.99th percentile for 575 healthy Canadian adults (who included blood donors, pregnant women, and Canadian Forces recruits); and/or if (5) titers of PT antibody and/or antibodies to 2 of the pertussis antigens FHA, PRN, or FIM were >3 SDs greater than the geometric mean titer for healthy adult control subjects (∼98th percentile). Serologic definitions for a particular antigen were met if either the IgG or IgA antibody for that antigen met the set criteria.

**Statistics.** At each of the 9 sites, to detect a prevalence rate of 0.15 ± 0.06 with 95% confidence, we required 136 enrollees (index patients) per site. On the basis of our estimate of rates of refusal and drop-out, the planned recruitment was 151 index patients per site. Data were analyzed by Epi Info version 6.04 (Centers for Disease Control and Prevention). We calculated differences between subjects with and subjects without pertussis who had various clinical attributes using 151 index patients per site. Data were analyzed by Epi Info version 6.04 (Centers for Disease Control and Prevention). We calculated differences between subjects with and subjects without pertussis with respect to median days of cough, median days with violent cough, and median days of whooping cough using either the Student’s *t* test or Kruskal-Wallis test. We calculated differences in the proportion of subjects with and subjects without pertussis who had various clinical attributes using either Fisher’s exact test or the χ² test.

**RESULTS**

**Enrollment and demographics.** Enrollment in the study was much lower than expected. Six hundred twenty-seven patients were deemed eligible for the study; 604 agreed to be contacted and were referred to the study coordinator. Of these, 162 declined to participate; the age of nonparticipants was known for all but 2 patients and ranged from 12.5 to 90.9 years (mean age, 37.2 years; 58.4% female). A total of 442 (70.5%) of the 627 eligible patients agreed to be enrolled (mean age, 41.3 years; range, 12.3–88.4 years; 69.5% female). The largest proportion of participants were 20–39 years old (31.8%), those 12–19 years old (19.2%) had cases that met this single-serum serologic definition. Eighty-four participants (19.1%) had laboratory evidence suggestive of pertussis according to case definition 5 (titers >3 SDs greater than the geometric mean titers for the control subjects); 78 of the 84 had cases that met this single serum serologic definition. Combining cases that met definitions 1–4, 44 participants (10.0%) had either laboratory confirmation or laboratory evidence of pertussis. Combining cases that met definitions 1, 2, 3 and 5, 88 adults and adolescents had either laboratory confirmation or laboratory evidence of pertussis (prevalence, 19.9% [95% CI, 16.3–24.0]). If only presence of antibody to PT and/or positive results for culture and PCR were used in the case definition (that is, excluding measurement of antibody against FHA, PRN, and FIM), 86% of cases would have been confirmed using definitions 1–3, 92% using definitions 1–4, and 86% using definitions 1, 2, 3 and 5.

Female participants comprised 71.6% of adolescents and adults with pertussis. The largest proportion of adolescents and adults with pertussis were 20–39 years old (40.9%), followed (in order of decreasing age-group size) by those 40–59 years old (31.8%), those 20–39 years old (14.8%), and those 12–19 years old (9.2%). Of the adolescent participants, 51.3% were girls; however, in the older age groups, the ratio of females to males ranged from 2:1 to 3:1. The median duration of cough at the time of enrollment was 20 days (range, 7–56 days).

**Laboratory confirmation of pertussis.** All but 2 participants (440; 99.5%) provided specimens of nasopharyngeal secretions; 393 (88.9%) participants provided 2 serum samples, and 440 (99.5%) provided ≥1 serum sample. Three hundred ninety-two of the enrollees (88.7%) completed the clinical questionnaires and provided all the biological specimens requested. Only PCR results for only 314 participants were included in the analysis; PCR specimens from 2 health units were contaminated during the process of preparing them for shipment and were excluded from the analysis.

Ten participants (2.3%) had laboratory-confirmed pertussis according to case definitions 1–3 (a nasopharyngeal aspirate culture and/or PCR positive for *B. pertussis* and/or a 4-fold increase between the acute-phase and convalescent-phase titers of PT antibody and/or antibodies to 2 of the other pertussis antigens [FHA, FIM, or PRN]; table 1). One of the patients had a case that was positive by culture and by PCR; the other culture-positive patients did not have PCR done on their specimens. Of the 4 patients culture-positive or PCR-positive cases, 1 had a ≥4-fold increase in the titer of antibody to PT or antibody to 2 of the other pertussis antigens; 6 of the 10 patients had cases confirmed by seroconversion only.

Thirty-six participants (8.3%) had laboratory evidence suggestive of pertussis according to case definition 4 (titers of PT antibody and/or antibodies to 2 of the other pertussis antigens [FHA, FIM, or PRN] that were higher than the 99.99th percentile of the control subjects). Of these 36 patients, all but 2 (1 who had a case confirmed by PCR and 1 with a case that showed a 4-fold increase in antibody titer) had cases that met this single-titer serologic definition only. Eighty-four participants (19.1%) had laboratory evidence suggestive of pertussis according to case definition 5 (titers >3 SDs greater than the geometric mean titers for the control subjects); 78 of the 84 had cases that met this single serum serologic definition.

Combining cases that met definitions 1–4, 44 participants (10.0%) had either laboratory confirmation or laboratory evidence of pertussis. Combining cases that met definitions 1, 2, 3 and 5, 88 adults and adolescents had either laboratory confirmation or laboratory evidence of pertussis (prevalence, 19.9% [95% CI, 16.3–24.0]). If only presence of antibody to PT and/or positive results for culture and PCR were used in the case definition (that is, excluding measurement of antibody against FHA, PRN, and FIM), 86% of cases would have been confirmed using definitions 1–3, 92% using definitions 1–4, and 86% using definitions 1, 2, 3 and 5.
Clinical characteristics. The proportion of participants who reported prior immunization with pertussis vaccine was similar in the group with and the group without laboratory evidence of pertussis; this held true for the subset of participants who had written immunization histories (table 2). Less than 10% of both groups reported a previous pertussis infection. Although the proportion who reported cough or violent cough was similar, participants with laboratory confirmation or evidence had a significantly longer duration of cough illness (56 vs. 46 days; \( P = .0006 \)), had a significantly longer duration of violent cough (43 vs. 31 days; \( P = .0008 \)), and were more likely to have experienced vomiting after coughing episodes (45.5% vs. 28.5%; \( P = .002 \)). There was no significant difference between the 2 groups in either the prevalence or duration of whooping cough.

DISCUSSION

In this multicenter study that geographically spanned Canada, 1 in 5 adolescents or adults with prolonged cough had laboratory evidence of pertussis, with a mean duration of cough of 8 weeks and a mean duration of violent cough of 6 weeks. Because not all participants were followed until their symptoms abated, these durations may be underestimates. Forty-five percent of the subjects with laboratory-confirmed pertussis experienced vomiting after their coughing episodes. The greatest number of cases was confirmed in participants 20–39 years old; however, the highest proportion of cough illnesses caused by \( B. \) pertussis occurred in adolescents 12–19 years old.

Although pertussis has long been known to be a cause of prolonged cough illness in adults [18], there has been a renewed interest recently because of the increase in reported cases among adolescents and adults [2, 4]. Seroepidemiological studies suggest that pertussis is a common and frequently unrecognized infection in adults [19–22]. Studies of household contacts of patients with pertussis have demonstrated that adults can have both symptomatic and asymptomatic pertussis and can be either the initial source or recipient of pertussis in the household [8, 23–26]. There is a range of estimates for the proportion of cough illnesses caused by \( B. \) pertussis, in part because of different study designs and variable serologic definitions of pertussis (table 3). The prevalence of nearly 20% that we found in our adult and adolescent study population is similar to the prevalences found in other studies: 21% in a study of adults who presented at the emergency department of a university hospital with the chief complaint of cough that had lasted \( \geq 14 \) days [29] and 26% of adolescents or adults who presented with cough during a pertussis epidemic [27]. Similarly, in a German study of family members of vaccine recipients with cough illness that lasted \( > 1 \) week, adults had a prevalence of pertussis of 26% [24]. A US study of adults with cough illness of \( \geq 2 \) weeks’ duration found a prevalence of 12.4%; however, only a single

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Table 2. Clinical characteristics of participants with or without laboratory confirmation or evidence of pertussis.

<table>
<thead>
<tr>
<th>Symptom or clinical characteristic</th>
<th>Laboratory-confirmed pertussis (n = 88)</th>
<th>Laboratory evidence of pertussis (n = 354)</th>
<th>( P )</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean age, years</td>
<td>38.3</td>
<td>42.0</td>
<td>.06(^a)</td>
</tr>
<tr>
<td>Vaccinated</td>
<td>49 (55.7)</td>
<td>172 (48.6)</td>
<td>.23(^b)</td>
</tr>
<tr>
<td>Vaccination status confirmed(^c)</td>
<td>6 (61.5)</td>
<td>31 (72.1)</td>
<td>.47(^d)</td>
</tr>
<tr>
<td>Ever received diagnosis of pertussis</td>
<td>5 (5.7)</td>
<td>29 (8.2)</td>
<td>.43(^e)</td>
</tr>
<tr>
<td>Days with cough, median(^e)</td>
<td>56</td>
<td>46</td>
<td>.0006(^f)</td>
</tr>
<tr>
<td>Days missed of work or school, median(^e)</td>
<td>4.5</td>
<td>4.0</td>
<td>.20(^f)</td>
</tr>
<tr>
<td>Whooping cough</td>
<td>25 (28.4)</td>
<td>96 (27.1)</td>
<td>.81(^b)</td>
</tr>
<tr>
<td>Days with whooping cough, median(^e)</td>
<td>33</td>
<td>23</td>
<td>.08(^f)</td>
</tr>
<tr>
<td>Violent cough</td>
<td>82 (93.2)</td>
<td>318 (89.8)</td>
<td>.34(^b)</td>
</tr>
<tr>
<td>Days with violent cough, median(^e)</td>
<td>43</td>
<td>31</td>
<td>.0008(^f)</td>
</tr>
<tr>
<td>Vomiting</td>
<td>40 (45.5)</td>
<td>101 (28.5)</td>
<td>.002(^b)</td>
</tr>
<tr>
<td>Night cough</td>
<td>74 (84.1)</td>
<td>276 (78.0)</td>
<td>.21(^b)</td>
</tr>
<tr>
<td>Apnea for 30 s after cough</td>
<td>12 (13.6)</td>
<td>55 (15.5)</td>
<td>.66(^b)</td>
</tr>
</tbody>
</table>

NOTE. Data are no. (%) of participants, except where noted.

\(^{a}\) Student’s \( t \) test.

\(^{b}\) \( \chi^2 \) test.

\(^{c}\) Index cases with written records \((n = 56)\).

\(^{d}\) Fisher’s exact test.

\(^{e}\) Patients for whom start and stop dates are known \((n = 402 \text{ for cough}, n = 206 \text{ for days missed}, n = 106 \text{ for whooping cough}, \text{ and } n = 350 \text{ for violent cough})\).

\(^{f}\) Kruskal-Wallis test.
Table 3. Summary of studies that estimated the proportion of prolonged cough illness caused by Bordetella pertussis in adolescent and adults.

<table>
<thead>
<tr>
<th>Reference</th>
<th>Population studied</th>
<th>Enrollment criterion</th>
<th>Pertussis confirmed by results of culture or PCR (% of cases so confirmed)</th>
<th>Serological definition used</th>
<th>Cases confirmed as B. pertussis infection, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>[9]</td>
<td>Adult patients in an emergency department</td>
<td>14 Days' cough</td>
<td>No</td>
<td>—</td>
<td>21</td>
</tr>
<tr>
<td>[27]</td>
<td>Patients at an ambulatory clinic during an outbreak</td>
<td>Cough</td>
<td>No</td>
<td>—</td>
<td>26</td>
</tr>
<tr>
<td>[24]</td>
<td>Household contacts of patients with pertussis</td>
<td>7 Days' cough</td>
<td>No</td>
<td>—</td>
<td>26</td>
</tr>
<tr>
<td>[28]</td>
<td>Patients at an ambulatory clinic (population-based)</td>
<td>14 Days' cough</td>
<td>No</td>
<td>Single serum sample; presence of IgG antibody to PT</td>
<td>12.4</td>
</tr>
<tr>
<td>[10]</td>
<td>University students</td>
<td>6 Days' cough</td>
<td>No</td>
<td>—</td>
<td>26</td>
</tr>
<tr>
<td>PR</td>
<td>Ambulatory and self-referred patients</td>
<td>7 Days' cough</td>
<td>Culture (0.5); PCR (1.0)</td>
<td>—</td>
<td>10–19.9</td>
</tr>
<tr>
<td>[13]</td>
<td>Pulmonary clinic</td>
<td>Persistent cough</td>
<td>—</td>
<td>—</td>
<td>25.7</td>
</tr>
</tbody>
</table>

NOTE. PR, present report; PT, pertussis toxin.

serum sample was tested, only IgG antibodies to PT were measured, and no nasopharyngeal specimen was obtained for culture [28]. A study of US Marine Corps trainees 18–29 years old with cough illness of >1 week’s duration found a prevalence of pertussis of 17%; this study used case definitions based on results of paired serologic tests, similar to those used in our study [11]. In a study of cough illness of ≥6 days’ duration in patients at a university student health service, 26% of patients had serologic evidence of pertussis [10].

Although the present study is one of the largest to date of adult cough illness, it was not possible to calculate regional variations in prevalence because of the lower-than-anticipated enrollment. Typically, pertussis epidemics occur in 3–5–year cycles. The numbers of reported cases and rates of pertussis in Canada during the period that this study was conducted (1996–1997) were the lowest since 1993 (figure 1). A survey of SHUSS health units showed that the number of routinely reported pertussis in patients of all ages for the period September–December 1996 (n = 276) were much lower than during the same time period for the previous 2 years (597 cases and 1052 cases, respectively). Furthermore, nearly 30% of eligible referred patients refused to participate in this study, perhaps because of the invasive nature of the specimen procurement.

The characteristics of clinical illness in participants in our study who had laboratory-confirmed or laboratory evidence of pertussis was similar to other published descriptions of symptomatic pertussis in adults [7, 8, 10, 24, 27, 29]. Our data suggest that, when prolonged cough is present, it is frequently associated with other classic pertussis symptoms, such as whooping cough and vomiting with cough. Our findings lend further support to those of a recent Canadian study which demonstrated that pertussis in adolescents and adults is associated with substantial morbidity [30].

As with most other community-based studies, our study defined laboratory evidence of pertussis primarily on the basis of serologic criteria; few cases were confirmed by culture or PCR results. [10, 11]. Increases in antibody titer were also difficult to demonstrate, perhaps because the “acute-phase” specimen was obtained well into the clinical course of illness. Although our serologic criteria, which compared antibody levels to those of a control population, were stringent (titers >3 SDs greater

Figure 1. Reported pertussis cases and rates of infection in Canada, 1990–1997. Arrows indicate the start and end of this study.
than the geometric mean titer or above the 99.99th percentile of a population of control subjects), but as arbitrary thresholds, they could either overestimate the true number of cases (because of the presence of antibody from a previous illnesses) or underestimate it.

There are several other limitations to this study that might limit the generalizability of the results. The sentinel health units were self-selected; therefore, these results may not be generalizable to Canada as a whole. The prevalence rates were calculated for a convenience sample, rather than a random sample of adults and adolescents with cough illness. It is likely that referrals reflected the more severe end of the spectrum of cough illness of ≥7 days’ duration. Symptom data were based on self-reports to the study coordinator, and the status of symptoms was not followed beyond the date of the convalescent interview, so we do not know the complete duration of symptoms for patients who were still coughing at the time of that interview. Our study is also unable to address the prevalence of asymptomatic pertussis. Studies that prospectively follow adolescents and adults for cough illness and obtain specimens early in the course of illness may better define the epidemiology of pertussis in this age group.

For physicians who treat adults and adolescents with prolonged cough illness, this study suggests that pertussis should be an important part of the differential diagnosis. However, we found that pertussis could not be confirmed by laboratory tests for >80% of participants. Although other possible etiologies were not sought in this study, careful clinical evaluation of patients with prolonged cough illness is necessary, and other cultures (bacterial and viral), serologic tests, or diagnostic imaging (chest radiograph) may be indicated. Empiric therapy with antibiotics active against B. pertussis (erythromycin, azithromycin, or clarithromycin) could be considered; however, the late presentation of these patients means that it is unlikely that treatment would affect either the clinical course of the illness or the transmission of the organism to others (in light of the infrequency of cultures positive for B. pertussis). This study does highlight the need for readily available, well-standardized serologic tests for the diagnosis of pertussis.

Despite its limitations, this study provides additional data that pertussis is not only a childhood disease. Adolescents, young and middle-aged adults, and even the elderly are susceptible to this illness. Cough illnesses of well over 1 month in duration, especially in the presence of violent cough and cough with vomiting, are important signs that may distinguish adolescents and adults with pertussis from those with other cough illnesses. Early identification of infected people in these age groups also would permit the consideration of chemoprophylaxis for patient contacts who may be susceptible and at high risk. The recent demonstration that acellular pertussis vaccines are safe and immunogenic in adolescents and adults [31–33] and the licensing of one product for use in adolescents and adults in Canada may provide the opportunity to control pertussis in adolescents and adults. Further epidemiological evaluation is essential, to assess the cost benefit of such a program [34].

MEMBERS OF THE SENTINEL HEALTH UNIT SURVEILLANCE SYSTEM WORKING GROUP
Jan Appleton and Heather Allen (Okanagan Similkameen Health Region, Kelowna, British Columbia), Darlene Girard (City of Winnipeg Community Services, Winnipeg, Manitoba), Cathy Anderson and Laura Sharp (Saskatoon District Health–Public Health Services, Saskatoon, Saskatchewan), Arleen Latorraca-Walsh (Prince Edward Island Health and Social Services, Charlottetown, Prince Edward Island), Suzanne Ménard and Marie-France Fournier (Régie régionale de la Santé et des services sociaux de l’Estrie, Sherbrooke, Québec), Sara MacMartin (Kingston, Frontenac, and Lennox and Addington Health Unit, Kingston, Ontario), Leslie Warick (Capital Health–Regional Public Health, Edmonton, Alberta), Helen Kelly (Wellington-Dufferin-Guelph Health Unit, Orangeville, Ontario), Karen Urquhart (Public Health Services–Central Region Health Board, Dartmouth, Nova Scotia), and Penny Smith (SHUSS, Laboratory Centre for Disease Control, Health Canada, Ottawa, Ontario).

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