Measles is a highly contagious disease that can lead to severe illness, complications and death, especially among young children. Before the availability of a measles vaccine in 1963, approximately half a million cases were reported, and hundreds of deaths occurred annually in the US.1,2 Although measles is no longer endemic in the US, measles remains endemic in much of the Eastern Hemisphere, and substantial outbreaks continue to occur in Europe, Asia and Africa.4,6 Consequently, during the past decade, the vast majority of measles cases in the US have been importations associated with unvaccinated and undervaccinated travelers and their contacts. An MMWR article reported that during the first 8 months of 2013, approximately 99% of 159 US cases were imported from other countries, with approximately half of the imported cases coming from Europe.7 Although 2-dose measles vaccine coverage (with measles-mumps-rubella [MMR] vaccine) in the US remains relatively high at approximately 90% (recommended at 12–15 months and 4–6 years), the overall coverage rate can mask groups of underimmunized persons in communities who are more susceptible to measles introduction and spread.

Prompt recognition and containment of measles cases in the US is imperative to prevent outbreaks. Economic analyses of measles exposures have included containment costs incurred by hospitals caring for patients with measles and costs incurred by public health departments in investigating cases and controlling further spread. Other studies have focused on the cost-effectiveness of vaccination, which demonstrates that prevention through vaccination is more cost-effective than treatment and containment.11–13 No study has evaluated the economic effect of measles exposures on outpatient pediatric practices, although these clinics are often the first to treat a patient with measles.

In August 2013, an unvaccinated 13-year-old male who had recently returned home from travel in Europe, presented to his primary pediatric clinic with a temperature of 104°F, malaise, cough, coryza, conjunctivitis and 2 days of rash. He arrived in the waiting room of his pediatric clinic for an appointment during the busiest time of day and was escorted into a clinic room without being masked, although surgical masks are recommended for all patients with respiratory symptoms old enough for the patients to wear a mask.24 Upon evaluation, measles was suspected. After the patient left the clinic, the exam room was not used during the next 2 hours. Caregivers were asked to isolate the child at home until 4 days after rash onset. The diagnosis was confirmed by both positive measles-specific IgM and reverse transcription-polymerase chain reaction. During the course of the clinic visit, multiple patients and their caregivers, health care providers and clinic staff were exposed to measles. We studied costs of measles case response actions related to the ambulatory clinic exposure to more fully understand economic consequences of measles cases for outpatient health care providers and the health care system.

**MATERIALS AND METHODS**

**Definitions**

Measles cases were identified and classified using standard case definitions and classifications.15 Measles exposures were defined as having had contact with or having been in the same room as the ill patient up to 2 hours after the patient was present. Investigation activities were defined as time spent by employees in identifying and contacting exposed patients and employees, documenting evidence of immunity to measles, consulting with public health regarding response activities and responding to caretakers’ concerns regarding exposure. Evidence of measles immunity was defined as serologic evidence of immunity, laboratory evidence of disease, birth date before 1957 or written confirmation of receipt of 1 measles vaccine after age 12 months for preschool aged patients and their caregivers or 2 measles vaccines after 12 months for
school age children, adolescents and healthcare workers; health-care personnel without evidence of immunity, regardless of post-exposure vaccine, are excluded from work from days 5 to 21 after their exposure.\textsuperscript{15,16} Costs to the health care system included costs attributed to the vaccine program and to private insurance.

**Cost Calculations**

The costs to the pediatric practice related to investigation, follow-up care and post-exposure prophylaxis response activities. Costs were calculated using data collected with a questionnaire administered to the lead health care worker who managed the response to the measles exposure and identified the personnel involved along with the time allocated to the response.

Activities identified in the response related to post-exposure prophylaxis included arranging passive vaccination with intravenous immunoglobulin (IVIG) for infants aged <6 months and identified ≤6 days after exposure (intramuscular immunoglobulin was unavailable in the local hospital) and active vaccination with MMR vaccine ≤72 hours after exposure for infants aged 6–11 months and for persons aged ≥12 months who did not have acceptable evidence of measles immunity.\textsuperscript{16} Investigation costs were calculated by multiplying the hours each employee spent on specific activities by their hourly wage. Caretakers’ exposures were discussed during the initial phone calls with the families and contributed to the time spent during these phone calls, but caretakers were asked to check their vaccination status and to follow up with their physicians, and caretakers’ vaccination records were not verified by the pediatric clinic. Employee follow-up costs were based on the bills the pediatric clinic paid for MMR vaccine doses and laboratory tests for employees.

Other costs not paid directly by the pediatric clinic but that might contribute to the total cost of the response were also tabulated. For example, because the pediatric clinic did not charge patients for vaccination visits resulting from this measles exposure, the estimated clinic costs were based on the vaccine administration reimbursement by the Centers for Medicare and Medicaid Services (CMS) reimbursement for code 90460 (for vaccination administration for children aged <18 years through any route with counseling by any health care professional).\textsuperscript{17} Cost of the MMR vaccine for patients was based on the private-sector price of purchasing the vaccine in a pediatric clinic.\textsuperscript{18} Additionally, for follow-up care requiring an emergency department (ED) visit for IVIG, estimated charges were based on the lowest possible amount charged for the ED doctor visit, IV placement with medication push and IVIG at the local hospital treating the majority of our patients. These charges were converted into costs by using the Washington State average operating cost-to-charge ratio, which estimates the average monetary value of reimbursement for acute care urban hospitals.\textsuperscript{19}

**Human Subjects Review**

This investigation was conducted as part of a measles case investigation by Public Health—Seattle & King County in collaboration with the affected pediatric clinic. The investigation was classified as nonresearch by the Washington State Institutional Review Board and the Centers for Disease Control and Prevention (CDC).

**RESULTS**

**Patient Care Follow-up Costs**

Fifty-two patients with mean age of 9.6 years (range: 2 months to 19 years) were identified as having been exposed to measles at the pediatric clinic. Of these, 34 (65%) were already fully vaccinated; 18 (35%) were aged <12 months and unvaccinated. Five patients (10%) were aged <6 months and were referred to an ED to receive IVIG (Fig. 1) because it was unavailable at

![FIGURE 1. Post-exposure response for patients and employees exposed to measles.](image-url)

MMR, measles-mumps-rubella; IVIG, intravenous immunoglobulin.
the clinic. Thirteen (25%) exposed infants aged 6–11 months were identified and vaccinated ≤72 hours after exposure at the pediatric clinic. The pediatric clinic has a specific area of the clinic dedicated to vaccinations, and these 13 patients did not need an additional visit with the physician before vaccination. However, the clinic did not charge the families the standard fee for vaccine administration, which is typically reimbursed at $28.80 per patient, amounting to a total loss of $374.40.

Investigation Costs

Four employees spent 23 hours identifying and contacting exposed patients and caretakers, costing $1056 in employee wages. Two employees spent another 5 hours identifying and contacting exposed employees, costing $203 in employee wages. Additionally, 2 employees spent 6 hours in consultation with the local public health department determining a plan of action, costing $352 in employee wages. During the initial investigation, 2 employees worked overtime to promptly identify and contact exposed persons, costing the pediatric clinic $242 in employee overtime wages. Furthermore, 1 health care worker spent 1.5 hours on the telephone responding to employee and patient concerns regarding the measles exposure that cost $107 in employee wages. The total cost of employee wages to the clinic was $1961.

Employee Follow-Up Costs

Ten employees at the pediatric clinic were exposed to measles. One employee had written documentation of 2 doses of MMR vaccine, and 9 required measles titers to determine their immune status and to avoid being excluded from work. Measles titers were obtained at an off-site laboratory and paid for by the pediatric clinic at a total cost of $2704. Five employees (50%), who were either born before 1957 or who had 1 documented previous dose of MMR vaccine, received a dose of MMR vaccine at the pediatric clinic. The clinic spent $616 to acquire adult MMR vaccines for staff. Less than 1 hour was spent vaccinating these staff; employee time spent administering vaccine was not calculated. The total amount the pediatric clinic spent responding to employee exposures was $3320. Titer results demonstrated serologic evidence of immunity among all 9 tested employees. No employees were furloughed in response to the measles exposure.

Other Costs

Because of the unique patient demographics in a pediatric clinic, other costs were incurred as a result of this measles exposure that, in this case, were not paid for by the pediatric clinic but in other situations might be billed to the clinic. All 13 patients who received an outbreak-related MMR vaccine were aged <12 months but will still require 2 subsequent lifetime doses of MMR vaccine. Thus, vaccine administered in response to the measles exposure would be an excess cost to the health care system. In Washington State, all childhood vaccines are paid for through the state vaccination program. However, the private-sector cost that a pediatric clinic elsewhere would pay for 1 MMR vaccine is $56.14, which amounts to a total cost of $730 in extra doses of MMR vaccine not counting toward the recommended 2-dose series.

All of our patients requiring IVIG at an ED had private insurance plans that covered the visit costs. The minimum charge for a visit to the ED at the local hospital is $600 for these infants who would have been billed for a brief encounter with a physician. In addition, the minimum charge for intravenous line placement with medication administration is $367, and the charge for the IVIG medication is $480. IVIG is charged according to number of bottles used; the smallest bottle stocked at the hospital contains 3 g of medication, which would be enough to treat infants weighing ≤7.5 kg (recommended dose of 400 mg/kg body weight). Thus, the minimum charge to insurance companies is $1447 per infant. The actual cost of treatment on the basis of the urban cost-to-charge ratio in Washington State of $0.313 would be $452.91 per infant. In the case of uninsured children, the charge of $1447 per infant would be billed to the caretakers or to the pediatric clinic. The minimum total charge for the 5 infants visiting the local ED would be $7235; CMS in an urban Washington State hospital would reimburse a total cost of $2265.

Total Costs

Overall, 122 people were exposed to measles in the pediatric clinic, costing the clinic $5655, the health insurance system at least $2265 and the Washington Vaccine Program $730. The total cost to the health care system was $8650 (Table 1). Approximately 60% of clinic’s costs were attributed to assessing measles immunity status among exposed employees, and the remaining 40% was the cost of identifying and treating exposed infants aged <12 months.

DISCUSSION

We documented substantial costs incurred by an ambulatory care pediatric clinic and others in the health care system responding to a single measles exposure from an unvaccinated adolescent,

<table>
<thead>
<tr>
<th>TABLE 1.</th>
<th>Costs Related to measles Exposure in a Pediatric Clinic</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Costs to Pediatric Clinic ($)</strong></td>
<td><strong>Costs to Private Insurance ($)</strong></td>
</tr>
<tr>
<td>Identifying or contacting patients</td>
<td>1056.17</td>
</tr>
<tr>
<td>Identifying or contacting employees</td>
<td>203.35</td>
</tr>
<tr>
<td>Working with PHSKC</td>
<td>352.10</td>
</tr>
<tr>
<td>Employee overtime</td>
<td>241.85</td>
</tr>
<tr>
<td>Responding to concerns</td>
<td>107.33</td>
</tr>
<tr>
<td>Costs of investigation</td>
<td>1960.80</td>
</tr>
<tr>
<td>MMR vaccine administration</td>
<td>347.40</td>
</tr>
<tr>
<td>MMR vaccine</td>
<td></td>
</tr>
<tr>
<td>Patient ED visits for IVIG</td>
<td>2264.56</td>
</tr>
<tr>
<td>Costs of patient follow-up</td>
<td>374.40</td>
</tr>
<tr>
<td>Employee MMR</td>
<td>616</td>
</tr>
<tr>
<td>Employee laboratory tests</td>
<td>2704</td>
</tr>
<tr>
<td>Costs of employee follow-up</td>
<td>3320</td>
</tr>
<tr>
<td>Total costs</td>
<td>5655.20</td>
</tr>
</tbody>
</table>

PHSKC, Public Health—Seattle & King County.
resulting in 122 additional exposures of patients, caregivers and employees. These exposures occurred in addition to multiple community exposures in Washington and Oregon that were investigated by 6 state health departments, 30 local health departments and at least 1 Canadian health department. Secondary cases and additional costs at the pediatric clinic might have been avoided because the illness was quickly diagnosed and isolated after the clinic visit, and all eligible clinic patients and employees were previously immune. However, the health care costs of this exposure were high, costing approximately $140 per exposure. The loss of a clinic room for 2 hours during the busiest point of the day additionally affected clinic operations, although these costs were not able to be evaluated. Approximately half of the total costs to the pediatric clinic resulted from assessing measles immunity among employees; this cost could have been eliminated if the clinic had documentation of measles immunity status, including vaccination, for staff. For new employees without documented immunity, vaccination or titers could be obtained before employment, such that the results will be immediately available in the case of a measles exposure. CDC recommends that all persons working in medical facilities should be vaccinated for measles because of the potential for these workers to contract measles and transmit the disease to patients.20 However, there are no requirements for healthcare providers in Washington State to provide their employers with documented MMR vaccination. Our analysis indicates that it can be financially prudent for ambulatory pediatric clinics to maintain a database of employee evidence of immunity status.

Post-exposure measures to prevent exposed infants from experiencing measles accounted for the majority of the total cost to the public health response activities, including investigation, emergency response and materials for limited outbreaks, have been substantial. Vaccination of all eligible persons according to recommendations and are often first recognized and evaluated in outpatient settings and are therefore likely to be first evaluated and where susceptible infants aged <12 months are often present. For example, the San Diego example of 2008 included an exposure in a pediatric clinic where 6 children were exposed to measles, 5 of which were unvaccinated and 4 of whom became ill, including 3 infants <12 months and one 2-year-old.26 Outbreaks of infectious diseases in ambulatory care clinics have been previously reported.22 In such outbreaks, persons at particular risk for contracting a severe case of measles include unvaccinated persons (including infants aged <12 months), pregnant women and immunocompromised persons.14 Exposure of susceptible patients to vaccine-preventable diseases in the ambulatory pediatric setting might be an increasing problem. A 2005 investigation reported that 85% of pediatricians had encountered a child during the preceding 12 months whose caretakers had refused at least 1 vaccination;21 and in 2011, surveyed pediatricians reported a 62% increase in vaccination refusals during the previous 5 years.24 The most commonly refused vaccinations include MMR, varicella and influenza.24 Persons who have not received MMR vaccine account for the vast majority of measles cases during outbreaks in the US.7,21 To reduce spread of measles in the health care setting, the American Academy of Pediatrics recommends triaging patients at the time of scheduling or arrival to identify patients with symptomatic infections (especially suspected measles or varicella) and directing symptomatic patients to a separate entrance to avoid potentially exposing others in the waiting area. American Academy of Pediatrics also recommends prominently displaying signs at the clinic entrance instructing caretakers to immediately notify staff if their child has a rash or respiratory symptoms (or exposure to someone with similar symptoms) and providing surgical masks for any coughing persons.17 Furthermore, employees should be vaccinated and be alert to recognize respiratory illnesses and enforce masking and isolation of such patients. Finally, contaminated rooms in which patients with suspected measles were treated should be cleaned and not used for ≥2 hours after the infectious person has left. In our case, the majority of exposed persons (71%) had evidence of measles immunity, and measles containment was successful, with no secondary cases of measles reported.

This cost analysis had some limitations. Cost questionnaires were completed retrospectively, and therefore, they are subject to recall bias. We do not expect the error to be substantial because we asked the clinic to track time spent responding to the exposure while the investigation was occurring. The cost of purchasing MMR vaccine in private clinics was estimated using 2013 data published by CDC28 and might differ from private sector prices. A 2009 report regarding vaccine purchase price and reimbursements per dose noted substantial differences among 67 private pediatric and family medicine practices studied.25 We calculated charges for ED visits that were based on minimum charges for each component of the services provided from the billing department of the local hospital that treated our patients. Actual charges might have been considerably higher if patients had received more than the minimal billable services. We also estimated costs of ED visits using CMS reimbursement rates, which are likely lower than what private insurance companies pay. One study reported that in 2008 in Washington State, physician services were reimbursed by private insurance companies at 113% of that amount reimbursed by Medicare.29 Therefore, our analysis potentially underestimates costs and time incurred by ambulatory pediatric clinics responding to measles exposures within their clinics. Our analysis highlights the need for documentation of employee vaccination status and vaccination of eligible patients in accordance with the recommended vaccination schedule.

Imported measles infections remain a threat to U.S. populations and are often first recognized and evaluated in outpatient clinics. Costs to prevent outbreaks related to these clinic exposures are substantial. Vaccination of all eligible persons according to the recommended vaccination schedule remains the most important method for preventing outbreaks and containing costs. Other methods for mitigating costs include preemptively documenting employee vaccination status and promptly instituting infection control measures when a case of measles is suspected.
after weaning) was more similar to that of controls.

tent and increased bone area. By contrast, the body composition of adult
expression of genes involved in adipogenesis, decreased bone mineral con-
are particularly vulnerable to exposure to low-dose penicillin during a criti-
testinal microbiota and for metabolic development. Cox et al found that mice
...tors have but partial roles in the development of obesity. The focus in recent
dition is more complex than commonly assumed. Dietary and genetic fac-
Jess T. Microbiota, Antibiotics, and Obesity

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Cox et al also studied whether treatment with prenatally adminis-
tered penicillin added to the effect of a high-fat diet in the development of
obesity. Low-dose penicillin and high-fat diet were found to have independ-
ent selective effects on the microbiota and body mass of male mice. Expos-
ure to penicillin also resulted in substantially more fat mass in female mice
fed a high-fat diet, when compared with penicillin-exposed female mice fed
a low-fat diet. Penicillin and high-fat diet in combination, but not separately,
increased fasting insulin levels.

Whether penicillin-moderated gut microbiota would have similar
effects on body composition and metabolism if transferred to germ-free
mice was also examined by Cox et al. Cecal microbiota were transferred
from 18-week-old controls and penicillin-treated mice to 3-week-old germ-
free mice. The young mice that received penicillin-altered microbiota
gained total mass and fat mass at a significantly faster rate than did the mice
that received microbiota from controls.

Comment: The studies by Cox et al provide evidence for the existence of
a critical window in early life, when the intestinal microbiota can influence
the development of persisting metabolic traits. Currently, however, there is
no direct evidence for a causal relation in humans. The translation of find-
ings from mouse to humans is challenging.