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Implications of a 2005 Measles Outbreak in Indiana for Sustained Elimination of Measles in the United States

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ABSTRACT

BACKGROUND

Measles was declared eliminated from the United States in 2000 but remains endemic worldwide. In 2005, a 17-year-old unvaccinated girl who was incubating measles returned from Romania, creating the largest documented outbreak of measles in the United States since 1996.

METHODS

We conducted a case-series investigation, molecular typing of viral isolates, surveys of rates of vaccination coverage, interviews regarding attitudes toward vaccination, and cost surveys.

RESULTS

Approximately 500 persons attended a gathering with the index patient one day after her return home. Approximately 50 lacked evidence of measles immunity, of whom 16 (32 percent) acquired measles at the gathering. During the six weeks after the gathering, a total of 34 cases of measles were confirmed. Of the patients with confirmed measles, 94 percent were unvaccinated, 88 percent were less than 20 years of age, and 9 percent were hospitalized. Of the 28 patients who were 5 to 19 years of age, 71 percent were home-schooled. Vaccine failure occurred in two persons. The virus strain was genotype D4, which is endemic in Romania. Although containment measures began after 20 persons were already infectious, measles remained confined mostly to children whose parents had refused to have them vaccinated, primarily out of concern for adverse events from the vaccine. Seventy-one percent of patients were from four households. Levels of measles-vaccination coverage in Indiana were 92 percent for preschoolers and 98 percent for sixth graders. Estimated costs of containing the disease were at least \$167,685, including \$113,647 at a hospital with an infected employee.

CONCLUSIONS

This outbreak was caused by the importation of measles into a population of children whose parents had refused to have them vaccinated because of safety concerns about the vaccine. High vaccination levels in the surrounding community and low rates of vaccine failure averted an epidemic. Maintenance of high rates of vaccination coverage, including improved strategies of communication with persons who refuse vaccination, is necessary to prevent future outbreaks and sustain the elimination of measles in the United States.

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MEASLES IS A HIGHLY INFECTIOUS, acute viral disease that can cause rash, fever, diarrhea, pneumonia, encephalitis, and death. The World Health Organization (WHO) estimates that measles infects 30 million persons and causes 454,000 deaths annually worldwide.¹ Although measles is endemic in most of the world, ongoing transmission of the measles virus was declared eliminated in the United States in 2000, an achievement attributed to high rates of vaccination coverage.²

Prolonged absence of a vaccine-preventable disease can result in increased public focus on adverse events related to the vaccine,³ decreased motivation of parents to vaccinate children,^{4,5} and perhaps, a shortened duration of vaccine-induced immunity due to a lack of antibody boosting from exposure to wild virus.⁶⁻⁸ Explosive outbreaks with devastating clinical and public health consequences can occur in environments that have been free of measles for more than a decade.^{9,10} Transmission of the measles virus, once reestablished, can be very difficult to interrupt.⁹⁻¹³

On May 15, 2005, an unvaccinated 17-year-old girl returned to Indiana after a church-mission trip to a Romanian orphanage where she had unknowingly become infected with measles. Despite having prodromal symptoms, she attended a large gathering of church members the day after her return. Many of the other children at the gathering were also unvaccinated. Two weeks after the gathering, the Indiana State Department of Health was notified that an unvaccinated six-year-old girl, who had attended the gathering, had been hospitalized with measles in another state. Despite vigorous containment efforts, the outbreak became the largest documented measles outbreak in the United States since 1996.¹⁴ We investigated transmission patterns, rates of vaccination coverage, and costs of containment activities related to this outbreak to determine whether new policies are needed to sustain the elimination of measles in the United States.

METHODS

DEFINITIONS

We defined the period of the outbreak as extending from one incubation period (14 days) before the onset of rash in the index patient until one incubation period after the last onset of rash in a patient (that is, from May 2 to July 8, 2005). We

defined a case patient as a person who had symptoms or signs during the outbreak period that were compatible with the standard clinical definition of a case of measles¹⁵ and who either had laboratory-confirmed acute measles infection or was epidemiologically linked to a patient with laboratory-confirmed measles infection. A patient was considered to have laboratory-confirmed measles if a sample of the patient's serum tested positive for anti-measles IgM with the use of the Measles IgM EIA Capture Assay (Chemicon) at the Indiana State Department of Health laboratory,¹⁶ or if a sample of urine tested positive for measles virus by polymerase chain reaction at the Centers for Disease Control and Prevention (CDC) laboratory. Molecular typing of measles isolates was performed at the CDC laboratory according to the protocols recommended by the WHO.^{17,18} A patient was considered to have been infectious from four days before through four days after the onset of rash.¹⁹

PATIENTS AND HOUSEHOLD CONTACTS

Information on the demographic characteristics of patients and family members, morbidity, and the setting of transmission was obtained by interviews with patients and household contacts. The vaccination status of all patients was verified by reviews of their vaccination records. Proof of immunity was evaluated according to the standards of the Public Health Service's Advisory Committee on Immunization Practices (ACIP).²⁰ Persons were considered eligible for the vaccine if they lacked proof of immunity and were at least 12 months of age (the minimum age for routine measles vaccination). Church officials were interviewed to obtain estimates of the number of persons in the congregation who refused to be vaccinated. Families who refused vaccination were interviewed to obtain information about their reasons for refusal.

LEVELS OF VACCINATION COVERAGE

We examined the rates of measles vaccination in Indiana for the period from 1995 to 2004 according to the records of the National Immunization Survey, which annually supplies provider-verified, population-based rates of immunization with 95 percent confidence intervals for children 19 to 35 months of age.^{21,22} We also examined aggregate data from 2004 and 2005 that were sent to the Indiana State Department of Health from primary

schools in Indiana, which annually survey the vaccination records of their kindergarteners and sixth graders.

CONTAINMENT MEASURES AND COSTS

From a health care perspective, we examined time spent by personnel, materials, and direct costs related to containing the measles virus for a period extending from recognition in the index patient until containment efforts ceased (i.e., from May 29 to July 22, 2005). Ninety-nine public health officers and infection-control personnel working in 12 health departments and health care facilities completed surveys of the hours of person-time spent and resources used, with a response rate of 100 percent. We calculated personnel costs by multiplying a person's gross wage by the time spent on the measles outbreak. Since data on fringe benefits were not collected, we calculated overhead costs as a proportion of wages. We obtained unitary costs for expenses including vaccines, immune globulin, and miles traveled. No direct medical costs were included.

RESULTS

IDENTIFICATION OF PATIENTS

During the outbreak period, 66 persons who were suspected to have measles were identified, of whom 32 (48 percent) were determined not to have measles because they either had a negative laboratory test for acute measles infection or were not epidemiologically linked to a patient with laboratory-confirmed measles. Of the remaining 34 persons, 14 (41 percent) had laboratory-confirmed measles and 20 (59 percent) were epidemiologically linked to a laboratory-confirmed case. All epidemiologically linked patients had the characteristic maculopapular rash and at least two of the following symptoms: fever, cough, coryza, conjunctivitis, otitis media, or diarrhea. We obtained specimens for viral isolation and molecular characterization from 14 patients, and measles virus was isolated in 6. All molecular sequences from the outbreak were identical, and all were members of genotype D4, which is endemic in Romania, as well as in other areas of Eastern Europe, the Indian subcontinent, the Middle East, and Eastern Africa.¹⁸ A representative sequence from the outbreak, MVs/Indiana.USA/23.05 [D4] (GenBank accession number DQ355989), was most closely related to sequences obtained from con-

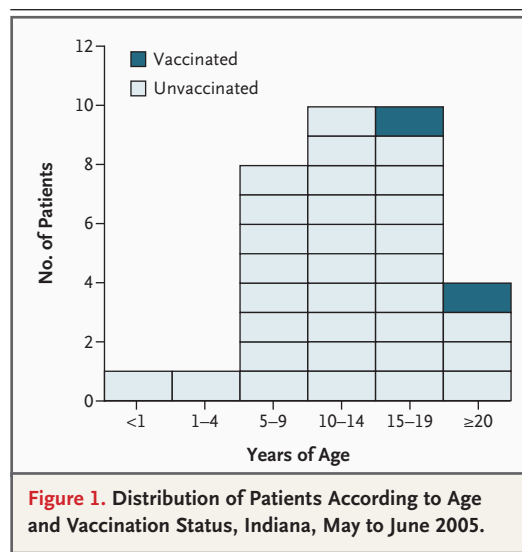
temporary measles viruses isolated from patients in Romania.

DEMOGRAPHIC CHARACTERISTICS AND VACCINATION STATUS OF PATIENTS

Of the 34 patients, 33 (97 percent) were self-declared non-Hispanic white, 33 (97 percent) were members of the church that held the gathering, 28 (82 percent) were 5 to 19 years of age (of these, 20 [71 percent] were home-schooled), and 32 (94 percent) lacked evidence of measles vaccination (Fig. 1). Of the 32 patients without evidence of vaccination, 2 were ineligible for routine vaccination (1 was born before 1957 and 1 was less than 12 months of age) and 2 had a vaccination status that could not be determined.

VACCINE FAILURE

Vaccine failure, which was defined as confirmed measles disease in a person who had been documented to have previously received measles vaccine, occurred in two patients. A 16-year-old student attended the church gathering and 14 days later had a morbilliform rash after having had prodromal fever, cough, and coryza. She was epidemiologically linked to a patient with laboratory-confirmed measles, but no specimen was obtained from her for laboratory confirmation. She had received a dose of measles vaccine at 13 months of age and a dose at 4.5 years of age, which are within the age ranges recommended by the ACIP for school-age children.²⁰ Neither this patient nor anyone else at the gathering had been offered postexposure prophylaxis, since the exposure to



measles had not been recognized until two weeks after the gathering, which was beyond the period of prophylaxis effectiveness.²⁰ The other patient with vaccine failure was a 34-year-old hospital phlebotomist who was hospitalized for severe measles. Serum drawn four days after the onset of rash was positive for anti-measles IgM and IgG. Her direct source of exposure could not be identified, but she worked at the hospital where two of the patients with measles had been treated. She had received one dose of measles vaccine at 12 months of age but did not have documentation of a second dose and had not been tested for serologic evidence of immunity on employment. The ACIP recommends either proof of measles vaccination with two doses or evidence of immunity for health care workers.²⁰

COMPLICATIONS

Three patients (9 percent) were hospitalized — a 45-year-old man and a 6-year-old girl required intravenous rehydration, and the hospital phlebotomist, who had no coexisting conditions but did have a history of smoking, required six days of ventilator support for pneumonia complicated by the acute respiratory distress syndrome. Sixteen patients (47 percent) had diarrhea, and

two (6 percent) had otitis media. No deaths occurred.

PATTERNS OF TRANSMISSION

Three generations of the spread of measles occurred during a six-week period (Fig. 2). Thirty-two cases (94 percent) occurred in Indiana Counties A and B, one in Indiana County C, and one in Illinois. An estimated 500 persons had attended the church gathering; approximately 50 lacked evidence of measles immunity, and of these 50, 16 (32 percent) acquired measles at the gathering. Of the estimated 450 other persons, 2 (<1 percent) acquired measles at the gathering (an adult born before 1957 and the student described above who had received two documented doses of measles vaccine). Of the 34 patients, 19 (56 percent) were infected directly by the index patient (18 at the gathering and 1 during a visit with a neighbor), and 13 (38 percent) were infected by household contact with a person infected by the index patient. Although 20 patients were infectious and interacted with the surrounding community before public health authorities were notified and instituted measures to contain the disease, no known transmission occurred in community or health care settings, with the exception of the hospital

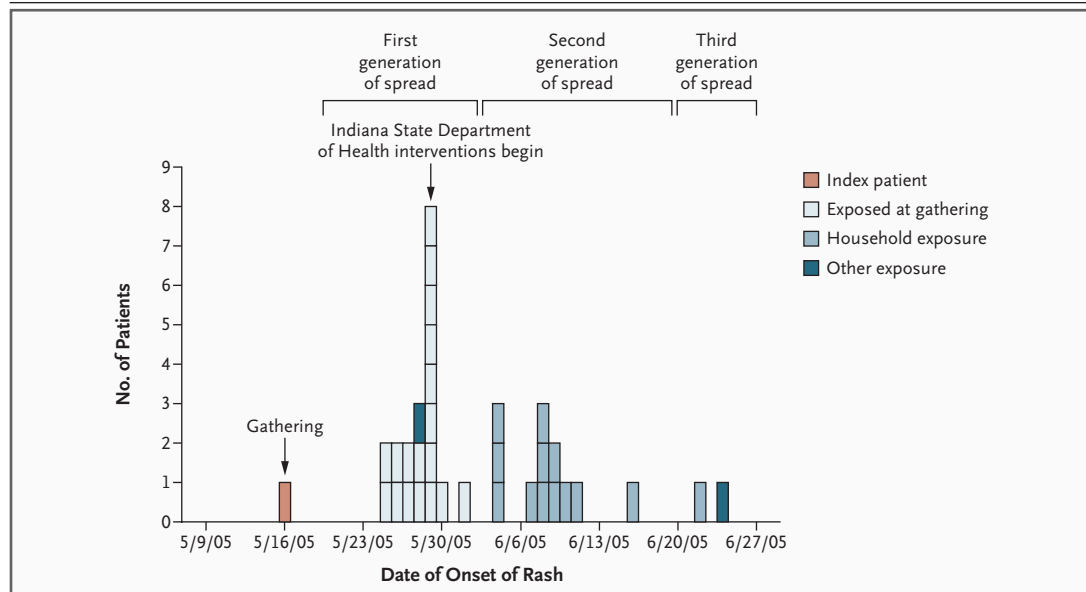


Figure 2. Patients with Measles According to the Day of Onset of Rash, Indiana, May to June 2005.

The first generation of spread consisted of 19 patients who were exposed to the index patient (18 at the gathering and 1 during a visit with a neighbor). The second generation consisted of 12 patients who had household contact with a person infected by the index patient. The third generation consisted of two patients, one with household exposure and one hospital worker who had an unknown exposure.

phlebotomist. Four households accounted for 24 of the 34 patients (71 percent) (Table 1). Of 69 persons in the 11 affected households, 56 (81 percent) lacked evidence of immunity according to the ACIP standards. Of these, 32 (57 percent) acquired measles; 18 of the remaining 24 reported a history of measles disease or vaccination but lacked the documentation needed to meet ACIP criteria for immunity, 4 met none of the criteria for immunity, and 2 had unknown vaccination or disease status.

RATES OF VACCINATION COVERAGE IN THE COMMUNITY

The National Immunization Survey estimated that the 2004 rate of first doses of measles-vaccination coverage among children 19 to 35 months of age in Indiana was 92 percent (95 percent confidence interval, 88.1 to 95.9 percent). The lowest estimate in the previous 10 years was 86 percent (95 percent confidence interval, 82 to 90 percent) for 1996.²² The rate of two-dose measles-vaccination coverage in Indiana for the 2004 to 2005 school survey was 98 percent of kindergarteners (78,637 of 80,495) and 98 percent of sixth graders (83,252 of 84,523); the proportion of children not

vaccinated for religious, philosophical, or medical reasons was less than 1 percent. In Counties A and B, where 94 percent of the patients resided, similar rates of two-dose coverage were reported — 98 percent of kindergarteners (2100 of 2139) and nearly 100 percent of sixth graders (2299 of 2307).

PERSONS DECLINING VACCINATION

On notification of the first recognized case of measles, personnel at the Indiana State Department of Health contacted church officials. The church had no position on immunization, and its officials actively cooperated with measures to contain the disease. The church reported its membership at approximately 500 persons, most of whom were characterized by church officials as white, middle class, and well educated. The church estimated that 35 of its members declined vaccination, primarily out of concern for adverse events. Of these, 31 (89 percent) became infected. According to representatives of six families who declined vaccination, issues considered important in their decision to refuse the vaccine were media reports of the dangers of the vaccine (e.g., the putative association between measles vaccination and au-

Table 1. Characteristics of All Households in Which a Person with Confirmed Measles Resided.

Family No.	Church Membership	State of Residence	County of Residence	Total	Lacked Proof of Immunity*	Infected with Measles	Acquired Measles and Were Home-Schooled
					<i>no. of persons in household</i>		
1	Yes	Indiana	B	11	11	10	9
2	Yes	Indiana	A	12	12	6	6
3	Yes	Indiana	B	6	6	4	2
4	Yes	Indiana	A	8	6	4	1
5	Yes	Indiana	B	6	5	3	1
6	Yes	Indiana	A	5	5	2	1
7	Yes	Indiana	A	8	3	1	0
8	Yes	Illinois	D	5	2	1	0
9	Yes	Indiana	A	3	1	1	0
10	Yes	Indiana	A	3	3	1	0
11	No	Indiana	C	2	2	1	0
Total	—	—	—	69	56	34	20

* According to the recommendations of the Advisory Committee on Immunization Practices,²⁰ proof of immunity to measles was defined as documentation of at least one of the following: adequate vaccination with measles-containing vaccine (i.e., one dose for preschool children and adults not at high risk, and two doses for school-age children and adults at high risk, such as international travelers, persons who work in health care facilities, and students at post-secondary educational institutions), laboratory evidence of immunity, birth before 1957, or physician-diagnosed measles.

tism, as well as the perceived effects of the vaccine preservative thimerosal) and a preference for naturally acquired immunity. The group that refused the vaccine was considered to be well integrated into the general community, creating the potential for multiple exposures and generalized transmission.

CONTAINMENT MEASURES AND COSTS

Efforts were made to contact all families who had been present at the church gathering. Patients were advised to remain in isolation for 4 days after the onset of rash, and nonimmune family members were asked to be voluntarily quarantined for up to 18 days after exposure. Ten families in the church congregation who declined vaccination had at least one family member who was eligible for the measles vaccine before the outbreak. Although 9 of the 10 families still had members who were eligible for vaccination during efforts to control the outbreak, only 2 families agreed to vaccination. However, no legal actions were required to enforce other containment measures. Local health care facilities administered 148 doses of the measles, mumps, and rubella (MMR) vaccine to exposed, nonimmune persons. Hospital A, which employed the infected phlebotomist, had not previously required written documentation of the vaccination status of its employees. Therefore, daily screening of all staff for rash and fever was instituted at shift changes for one incubation period. Hospital A administered 317 doses of MMR vaccine and 210 doses of prophylactic immune globulin.

In aggregate, containment activities involved approximately 3650 person-hours, 4800 telephone calls, 5500 miles driven, and 550 laboratory specimens tested (Table 2). Costs of containment were \$167,685 (\$4,932 per patient). The hospital employing the infected health care worker accrued 68 percent of the costs, creating a hospital-specific cost of more than \$113,647.

DISCUSSION

This outbreak of measles in the United States was caused by the importation of measles from abroad into a population of children whose parents objected to vaccination, primarily out of concern for adverse events related to the vaccine. Most patients were active young persons who had the potential to create hundreds of additional exposures in the

two weeks before the Indiana State Department of Health was notified and efforts to contain the virus began. Despite this, the spread of disease outside the at-risk population was minimal because vaccination levels in the surrounding community were high. Only two instances of vaccine failure occurred. The outbreak was the largest documented outbreak in nearly a decade, created substantial health risks, and required a vigorous and expensive public health response.

The ACIP recommends two doses of measles vaccine or proof of measles immunity for persons traveling abroad, school-age children, and health care workers.²⁰ The measles outbreak in Indiana occurred because these recommendations were not followed. The index patient had not been vaccinated before traveling abroad, home-schooled children had not been vaccinated, and a hospital had not required documentation ensuring that all its employees were either fully vaccinated or had proof of measles immunity.

Although measles has been declared eliminated from the United States,² import-associated outbreaks of measles continue to occur sporadically because of the persistence of endemic measles in other countries and the high volume of international travel.²⁴ However, no nation currently requires measles vaccination for entry or return,²⁵ and U.S. international-travel recommendations for vaccination depend on voluntary compliance.²⁰ Measles imported into the United States may be the first indication of outbreaks occurring elsewhere.²⁶ At the time of the index patient's travel, Romania had not reported a measles outbreak, but several months later, it reported more than 4000 cases.²⁷ Thus, the potential for rapid, unpredictable dissemination of communicable diseases requires travelers and travel clinics to place a greater emphasis on routine vaccinations, including vaccination for measles.

In the Indiana outbreak, 71 percent of school-age patients were home-schooled, although home-schooled children were estimated to constitute 1 percent of school-age children in Indiana (similar to estimates in other states).²⁸ Although every state requires two doses of measles vaccine for school attendance, only West Virginia has a similar requirement for home-schooled children.²⁹ Refusing vaccination, rather than limited access to vaccination services, was a primary reason that many patients in the outbreak in Indiana were unvaccinated. Concern about adverse events, par-

ticularly related to media reports of a putative association between vaccinations and autism and of the dangers of thimerosal, appeared to play a major role in the decision of these families to decline vaccination. Most families with these concerns continued to decline vaccination, even in the midst of an outbreak involving hospitalizations among their own community members. Although measles can cause severe sequelae and death,³⁰ public concern in other developed nations about adverse events associated with vaccines has been shown to reduce vaccination coverage to levels low enough to facilitate ongoing

disease transmission.^{5,31} In the United States, efforts to raise immunization rates have focused on improving preventive care for disadvantaged children,^{32,33} but different approaches may be necessary for populations such as this one, where belief systems, rather than access to health care, are the primary barrier to vaccination.

In the Indiana outbreak, 68 percent of the costs related to containment of the disease were incurred by a single hospital, where an undervaccinated employee potentially exposed children below the age of vaccination, immunocompromised patients, and employees of unknown vac-

Table 2. Estimated Direct Costs of Containing Measles during the Outbreak in Indiana.*

Variable	Indiana State Department of Health	Illinois State Health Department	County Health Departments†	Hospital A	Outpatient Care	Total
No. of personnel directly involved	18	2	9	66	4	99
Time spent per activity (hr)‡						
Investigation	298	—	53	422	13	786
Emergency response	535	74	374	1078	19	2080
Laboratory work	135	—	—	481	—	616
Other	61	—	2	96	33	192
Total	1029	74	429	2077	65	3674
Materials or activities						
No. of telephone calls	1422	11	1630	1581	167	4811
Doses of MMR vaccine	—	—	141	317	7	465
Doses of immune globulin	—	—	5	210	1	216
No. of specimen-collection kits or tests§	51	3	—	508	15	577
Travel (miles)	5298	127	129	—	—	5554
Estimated costs (U.S. \$)						
Wages and salaries	21,972	1,813	12,284	70,948	1,575	108,592
Overhead	5,339	440	2,985	21,284	383	30,431
MMR vaccine and immune globulin¶	0	0	2,372	19,185	135	21,692
Mileage	1,536	37	37	0	0	1,610
Other	3,074	0	56	2,230	0	5,360
Total costs (U.S. \$)	31,921	2,290	17,734	113,647	2,093	167,685
Proportion of total (%)	19	1	11	68	1	100

* Dashes denote not applicable, and MMR measles, mumps, and rubella. To convert miles to kilometers, multiply by 1.6.

† Counties A, B, and C are in Indiana; County D is in Illinois; and County E is in Ohio. No patients lived in County E, but one patient was hospitalized there.

‡ Activities included in the “investigation” category were finding and interviewing patients and tracing contacts. Activities in the “emergency response” category included planning and coordinating responses, vaccinating contacts, administering immune globulin to contacts, collecting specimens, enforcing isolation and quarantines, developing and analyzing databases, developing information for the public, preparing reports, answering public inquiries, and working with the media.

§ Specimen collection includes blood-collection kits, swabs, urine tests, and serologic tests for anti-measles IgM and IgG.

¶ Except for the cost of vaccines in Hospital A, unitary costs are adapted from Dayan et al.²³ 2005 costs were \$15.99 per dose of MMR vaccine and \$23.50 per dose of immune globulin.

|| Mileage costs are adapted from Dayan et al.²³ and were calculated as \$0.29 per mile.

ination status. During the resurgence of measles in the United States in 1989 to 1991, medical settings were primary sites of measles transmission.³⁴ Nevertheless, as of July 2005, only four states (Maine, New York, Oklahoma, and Rhode Island) had laws mandating that all health care workers in hospitals have proof of measles immunity (CDC: unpublished data).

This investigation was limited in several respects. Only 41 percent of cases were laboratory-confirmed. The total extent of community exposure to disease was unknown. Church officials estimated the size of the population that refused vaccination. Costs of containment were measured retrospectively and did not include patient care or indirect costs.

Measles was eliminated in the United States through high rates of routine childhood vaccination coverage. The outbreak in Indiana shows that states, localities, and health care organizations need to implement more effective policies to protect persons traveling abroad, home-schooled children, and health care workers against measles and other vaccine-preventable diseases. In addition,

to preclude the experience of those countries where vaccine-preventable diseases have become epidemic through the refusal of vaccination, better communication strategies are needed concerning the adverse events associated with vaccines. These efforts will be necessary to sustain the elimination of measles in the United States.

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The findings and conclusions expressed are those of the authors and do not necessarily represent the views of the CDC.

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