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Vaccination practices among physicians and their children

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ABSTRACT

The purpose of this study was to identify vaccination patterns of both general pediatricians and subspecialists with regards to their own children and projected progeny. A 14 question survey was sent randomly to 1000 members of the Academy of Pediatrics in 2009. Two categories of questions included 1) how physicians with children vaccinated them in the past, and 2) how all respondents would vaccinate a child in 2009. A comparison was made between the answers of general and specialty pediatricians. 582 valid questionnaires were received (58.2% response rate) of which 431 were general pediatricians and 151 subspecialists. No statistical difference was found between general and specialty pediatricians on how they vaccinated their children up until 2009 (95% vs 93%). When asked about vaccinating a future child, a significant proportion of respondents would deviate from CDC guidelines, specialists more than general pediatricians (21% vs 9%). Generalists were more likely to give a future child Hepatitis A (OR: 3.6; 95% CI 1.3 - 10.4), Rotavirus (OR: 2.2; 95% CI 1.1 - 4.4), Meningococcal (OR: 9.9; 95% CI 3.3 - 29.9), and influenza (OR: 5.4; 95% CI 1.1 - 26.7) vaccines. Specialists were more likely to postpone MMR vaccinetion (OR: 4.4 95% CI 2.3 - 8.6). Safety was listed by both groups as the most common reason for altering the recommended immunization schedule. Until 2009, general pediatricians and pediatric specialists have largely adhered to ACIP recommendations, but due to vaccine safety and other concerns, both groups, albeit a higher percentage of specialists, reported greater numbers willing to diverge from these recommendations.

Keywords: Vaccination; Vaccine Adverse Events; Vaccine Schedule; Pediatricians; Preventable Diseases

1. INTRODUCTION

While parents seek information from many sources, physicians remain the most commonly relied on resource of information regarding immunizations [1]. Health care providers influence the rates of immunization by answering parents' questions, addressing misinformation, and ultimately building trust [2-4]. Parents who change their mind from delaying or refusing vaccines for their child most often credit the child's health care provider for this change [5]. This places the pediatrician in a unique position to influence vaccination patterns in the United States.

How pediatricians choose to vaccinate their own children may provide the closest surrogate for their actual beliefs on both the necessity and benefits of immunization and ultimately how they counsel families. Little is documented, however, on how pediatricians vaccinate their children overall [6]. One study in 2005 examined how 93% of Swiss physicians followed immunization recommendations in that country, but no duplicate study has been performed in the United States to date [7]. A number of prior studies have examined reported acceptance of new vaccines including rotavirus, but not their acceptance of the overall vaccine schedule of the Advisory Committee on Immunization Practices (ACIP) [8-11]. Gust and colleagues in 2008 surveyed largely family practitioners and a smaller number of pediatricians and found 11% do not recommend to parents that children receive all available vaccines [12]. Barriers to acceptance have included safety, cost, reimbursement, parental acceptance, as well as a perceived lack of need for a vaccine [8-11]. It is important to first identify physicians' beliefs on vaccines in order to improve the counseling they give to families.

Our study was designed to compare how those physicians involved the most with vaccination, namely general pediatricians, compared to pediatric subspecialists, who were less familiar with both vaccine preventable illnesses and the vaccines themselves, in vaccinating their own children as well as future progeny. It was surmised that those persons most familiar with vaccines would be more likely to fully vaccinate their own children. We also examined which vaccines were most often not given or would not be given to future children.

2. PATIENTS AND METHODS

1000 web based questionnaires (**Figure 1**) were sent to a randomized list of members of the Academy of Pediatrics (AAP). An estimated 80% of board certified pediatricians are members of the AAP. Included in responses were general pediatricians and pediatric subspecialists currently in the United States. The list of participants was generated from the AAP member directory and every 20th name selected alphabetically at random to participate. If the randomized name did not have a working email or mailing address, the next name in the list was used. This occurred in 11 cases. 223 of those emailed responded to the initial email and 55 responded to the 2nd email sent out 3 weeks later. The 722 non responders were sent a questionnaire by mail 3 weeks following the 2nd email request with a $2 incentive enclosed in the envelope as well as a stamped envelope for return of the survey. A total of 657 surveys were completed in all. All responses were anonymous.

1. You are a: ☐ Male ☐ Female

2. In which state do you primarily practice?

3. Which best describes you? ☐ General Pediatrician ☐ Pediatric Subspecialist ☐ Family Medicine Physician ☐ Other: ____

4. When did you complete medical school?
☐ After 2004 ☐ 2000-2003 ☐ 1990-1999 ☐ 1980-1989 ☐ 1970-1979 ☐ 1960-1969 ☐ Before 1960

5. You work: (**check all that apply**)
☐ in private practice ☐ in community clinic ☐ at a hospital ☐ in public administration ☐ for the government
☐ in school of medicine ☐ in the pharmaceutical industry ☐ other professional area

6. Do you have children? ☐ Yes ☐ No (**if no, go to question 12**)

7. How many children do you have? ☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5 or more

8. What ages are your child(ren)? (**check all that apply**) ☐ < 2 years old ☐ 2 - 4 years old ☐ 5 - 10 years old ☐ ≥ 11 years old

9. Did you follow the up-to-date recommended vaccination schedule annually published by the Advisory Committee for Immunization Practices (ACIP) for all of your children as it was written at the time they were vaccinated?
☐ Yes (**if yes go to question 12**) ☐ No ☐ I did not know or refer to the guidelines

10. If you did not elect to follow the vaccination schedule or followed an alternative schedule, which vaccines did you elect to postpone or not give? If a vaccine was not available when your child was vaccinated, do not check it. (**check all that apply**)
☐ DTaP ☐ Hib ☐ Prevnar ☐ IPV ☐ Rotavirus ☐ Hep A ☐ Hep B ☐ MMR
☐ Varicella ☐ Meningococcal (Menactra) ☐ Influenza

11. If you elected to not give a vaccine, or to postpone it, which reasons best describe why. (**check all that apply**)
☐ Medical contraindication
☐ Too many vaccines given at once
☐ Safety concern
☐ Vaccine protects against illness that does not present a risk to your child
☐ Do not believe in efficacy of vaccine
☐ Other (Please explain):_____

12. If you were a "new parent" in 2009-2010, at what age would you give the first dose of MMR to your own children?
☐ < 18 months old ☐ 18 months - 2 years old ☐ 3 - 5 years old ☐ 6 - 10 years old ☐ 11 - 15 years old
☐ > 15 years old ☐ would not vaccinate

13. If you were a "new parent" in 2009-2010, which vaccines would you NOT give to your own children? (**check all that apply**)
☐ None - I would give all of them ☐ DtaP ☐ Hib ☐ Prevnar ☐ IPV ☐ Rotavirus ☐ Hepatitis A
☐ Hepatitis B ☐ MMR ☐ Varicella ☐ Menactra ☐ Influenza ☐ Other (please specify) _____

14. If were a new parent in 2009-2010 and would not give a vaccine, which reasons best describe why. (**check all that apply**)
☐ Medical contraindication ☐ Too many vaccines given at once ☐ Safety concern
☐ Vaccine protects against illness that does not present a risk to the individual ☐ Do not believe in efficacy of vaccine
☐ Other (please explain)_____

Figure 1. Survey sent to physicians.

The 14 question survey was presented on 6 separate pages as a web survey or a single page as a mailed survey. Questions were divided into 3 distinct sections: 1) gathering demographic information; 2) parent physicians were asked how they vaccinated their own children and if not following recommended schedules for which vaccines and why; and 3) all participants were asked what vaccines they would or would not give to a hypothetical new child. In addition to set responses for skipping or not giving a vaccine, open fields were included to allow for participants to provide answers not included in the options given. Web surveys were entered by participants into Survey Monkey and mailed surveys manually entered into this same program and exported to Microsoft Excel.

Using standard descriptive statistics, demographic characteristics of responding participants is shown in **Table 1**. Comparisons of baseline demographics and immunization measures were performed by using chi-square tests where appropriate. Univariate statistical analyses were performed for each variable to determine its relationship to the main independent variable, being a general pediatrician or subspecialist. Logistic-regression analysis was used to calculate the adjusted odds rations (OR) and 95% confidence interval (CI), controlling for any statistically significant demographic variables that might act as a confounder. Differences were considered significant at $P < 0.05$ and when the 95% CI did not include 1.0. SPSS statistical software version 18 (SPSS, Inc., Chicago, IL) was used for the statistical analysis.

3. RESULTS

Of the 1000 surveys sent, a total of 582 were utilized in our analysis. 75 participants did not fit the categorization as a pediatric specialist or general pediatrician and were excluded from analysis. These included 5 family physicians, 33 residents, and 37 persons designating themselves as "other" who could not be categorized. Of those surveys analyzed, 431 were completed by general pediatricians and 151 completed by pediatric subspecialists. Subspecialists included a wide representation including pediatric cardiology, urology, neonatology, and even toxicology. **Table 1** summarizes the demographic characteristics of the participants. General pediatricians were more likely to be female (57%) than subspecialists (40%) and more likely to work in the outpatient setting (73% versus 21%).

Table 1. Characteristics of physicians responding.

	General Pediatrician (n = 431)	Pediatric Specialist (n = 151)	Chi square[a]	P value
Gender (female)	57%	40%	14.06	0.00
Region:				
Northeast	25%	18%		
Southeast	37%	33%	9.40	0.02
Midwest	17%	28%		
West	21%	21%		
Type of activity:				
Outpatient	73%	21%		
Hospital	15%	45%		
Government	2%	3%	147.57	0.00
Medical School	6%	28%		
Other	5%	3%		
Year of medical school completion:				
After 2004	17%	6%		
2000-2003	13%	14%		
1990-1999	32%	27%		
1980-1989	20%	25%	23.97	0.00
1970-1979	11%	20%		
1960-1969	4%	8%		
Before 1960	2%	0%		
Has children	78%	85%	2.82	0.09

[a]Using two-way tables with measures of association.

Overall, out of 466 respondents who reported having children, 438 (94%) stated that they followed ACIP recommendations regarding vaccination. This rate was slightly higher among general pediatricians (95% vs 93%) but the difference was not statistically significant. Overall rates for individual vaccines were considerably high ranging from 97% to 100% for both general pediatricians and specialists (**Table 2**). The lower rate of overall compliance with the ACIP recommendations is likely accounted for by differences among which vaccines physicians elected to skip for their children. One notable trend, however, was that physicians who graduated from medical school prior to 1990 were less likely to vaccinate their own children for rotavirus (OR: 10; 95% CI: 1.1 - 81 P value 0.038).

When asked about how they would vaccinate a potential child in 2009, larger differences emerged between general pediatricians and specialists (**Table 3**). Respondents included both those who have and do not have children (n = 554). Specialists were found to be less likely to follow the overall schedule. 41 generalists (9.9%) and 29 specialists (21%) reported they would skip at least one vaccine for their future child (Chi square = 0.001). Specifically, generalists in 2009 were more likely

Table 2. Reported vaccination practices of respondents who have their own children.

	Generalist (n = 336)	Subspecialist (n = 128)	P value	Adjusted OR[a]	95% CI[b]
Followed ACIP recommendation	95%	92%	0.39	0.7	0.3 - 1.7
DTaP	100%	100%			
Hib	100%	100%			
Pneumococcal	100%	99%	0.79	1.5	0.1 - 27.9
IPV	100%	99%	0.88	1.3	0.1 - 25.9
Rotavirus	98%	98%	0.60	0.6	0.1 - 3.4
Hepatitis A	99%	98%	0.64	1.4	0.3 - 6.9
Hepatitis B	99%	99%	0.55	0.5	0 - 5.5
MMR	98%	100%			
Varicella	99%	97%	0.39	1.9	0.4 - 8.8
Meningococcal	100%	98%			
Influenza	99%	99%	0.51	0.5	0 - 4.8

[a]Using binomial regression model, controlling for the following independent variables: speciality (generalist vs specialist), gender, graduation year (after 1990 or before), living in western states (yes, no), practicing in hospital (yes, no). [b]OR and CI not calculated if the % of one of the outcomes of the dependent variable was ≤1%.

Table 3. Projected pattern of vaccination of all respondents.

	Generalist (n = 416)	Subspecialist (n = 138)	P value	Adjusted OR[a]	95% CI[b]
Would postpone MMR until after 18 months	5%	19%	0.00	4.4	2.3 - 8.6
Would not give DTaP	0.5%	0%			
Would not give Hib	0%	0%			
Would not give Prevnar	0.7%	0%			
Would not give IPV	0.2%	0%			
Would not give Rotavirus	6%	12%	0.03	2.2	1.1 - 4.4
Would not give Hepatitis A	2%	6%	0.02	3.6	1.3 - 10.4
Would not give Hepatitis B	0.2%	1%	0.83	1.4	0.1 - 28.4
Would not give MMR	1%	1%	0.83	0.8	0.1 - 8.7
Would not give Varicella	1%	2%	0.30	2.3	0.5 - 11.6
Would not give Menactra	1%	9%	0.00	9.9	3.3 - 29.9
Would not give Influenza	1%	3%	0.04	5.4	1.1 - 26.7
Would not give Gardasil	1%	1%	0.57	0.5	0.1 - 4.8

[a]Using binomial regression model, controlling for the following independent variables: speciality (generalist vs specialist), gender, graduation year (after 1990 or before), living in western states (yes, no), practicing in hospital (yes, no). [b]OR and CI not calculated if the % of one of the outcomes of the dependent variable was ≤1%.

to give a future child Hepatitis A (OR: 3.6; 95% CI 1.3 - 10.4), Rotavirus (OR: 2.2; 95% CI 1.1 - 4.4), Meningococcal (OR: 9.9; 95% CI 3.3 - 29.9), and Influenza (OR: 5.4; 95% CI 1.1 - 26.7) vaccines. Pediatric specialists reported a stronger desire to postpone future MMR vaccination (OR: 4.4 95% CI 2.3 - 8.6), but even 5% of general pediatricians reported they also would postpone this vaccine beyond 18 months. Of the respondents who would elect to withhold at least one vaccine for future progeny (63 of 70 who actually reported having children), the most common reason given was "safety" and "too many vaccines given at once" (**Table 4**). This pattern was also seen for those respondents who have children and elected not to receive vaccines as recommended by the ACIP (**Table 5**). Place of work such as in "private practice" or "for the government" did not demonstrate to play a role in choosing to vaccinate in either specialists or generalists.

Table 4. Physicians' reasons for withholding immunization of future progeny.

	Generalist (n = 41)	Subspecialist (n = 29)
Medical contraindication	1 (2.4%)	1 (3.4%)
Too many vaccines given at once	4 (9.8%)	3 (10.3%)
Safety concern	12 (29.3%)	12 (41.4%)
Do not believe in efficacy of vaccine	3 (7.3%)	2 (6.9%)
Other	"In developed countries Rotavirus is for the most part treatable and I've seen some side effects."	
	"Rotavirus is negligible in US. More of a problem in 3rd world but vaccine ineffective there."	
	"Very low incidence; vaccination not warranted (Hep A)."	
	"(Gardasil) is not appropriate for USA population, doesn't remove need for exams, better served in other parts of world."	
	"Not important (Gardasil) to my daughter and presumes promiscuity."	
	"Not convinced of need (Hep A)."	
	"1) A newborn does not need Hep B, 2) Hep A is rare in US, and 3) Rotavirus is too new."	
	"Would not bundle vaccines."	
	"New to the market, awaiting long term research (Gardasil)."	
	"Children got H1N1 and protected from disease."	
	"No need to introduce another potentially confounding variable until development is clearly normal. Poor science but good art. (regarding delay of MMR)."	
	"Feel HAV us unnecessary at that age."	
	"Risk is greater than negligible benefit in my family situation (rotavirus)."	
	"Severity of illness does not warrant vaccination (rotavirus)."	

Table 5. Physicians' reasons for withholding immunization of their own children (those who actually have children).

	Generalist (n = 15)	Subspecialist (n = 9)
Medical contraindication	1 (6.7%)	0
Too many vaccines given at once	3 (20%)	3 (33%)
Safety concern	3 (20%)	3 (33%)
Do not believe in efficacy of vaccine	2 (13%)	1 (11%)
Other	"Wanted to see if [child] got chickenpox and ensure lifetime immunity."	
	"Knew baby at low risk [for hepatitis B] at birth, decided to start series at 2 mos checkup."	
	"Not in school,limited exposure,able to space them out."	
	"Risk exceeds benefit in my family (stay at home parent)."	
	"Illness itself is usually not severe enough to warrant vaccination (*i.e.*, rotavirus)."	
	"One child on chemo; other was PDD; other two got everything on schedule."	

4. DISCUSSION

Until now few studies have examined how pediatricians in the US vaccinate their own children [6,7]. The results of this study bridge this gap by confirming that a high percentage, 94% of respondents, vaccinated their own children according to ACIP recommendations through 2009 and will likely continue to do so in the future. This important message of "lead by example" should be communicated to a public who is increasingly concerned over the need and safety of vaccines. For those charged with vaccinating and caring for children, there is a strong uniformity with respect to their own children in the actual practice of immunizing as per ACIP recommendations. One of the most common questions asked to pediatricians is "what would you do with your child?" This study answers this question.

Pediatric specialists and general pediatricians do appear potentially poised to diverge further from ACIP recommendations with future progeny. This trend was much larger in the subspecialist group. This may be due to the greater ignorance of subspecialists with regards to the vaccines and the diseases they prevent. Future studies might look to correlate the specialty with electing not to give certain vaccines. Those physicians responding they would not follow recommendations cited safety as their largest concern. This parallels the trend of increasing safety concerns by parents [13-15]. Reasons for safety concerns given by physicians ranged from claims of vaccines being "too new," of perceived "risk" being "greater than [the] negligible benefit," and even a perceived "risk" in bundling vaccines (**Tables 4** and **5**).

A significant number of subspecialists did not want to give hepatitis A (6%), rotavirus (12%), and meningococcal vaccine (9%) moving forward. Comments of those who would not give hepatitis A included "[I am] not convinced of the need", "[I] feel Hepatitis A vaccination is unnecessary at that age", "severity of [the] illness does not warrant vaccination", and the "risk exceeds the benefit in my family (stay at home parent)". Despite evidence of the enormous cost savings and reduction in rotavirus morbidity and incidence in the United States, many physicians in the study appeared to feel that rotavirus vaccination at the individual level was not appropriate in their future progeny [16,17]. It may be that those physicians who practiced in 1999 are biased against the rotavirus vaccine having witnessed the recall of the rotavirus vaccine, Rotashield, due to an association with intussusception. Older physicians, those graduating prior to 1990, in our study demonstrated to be less inclined to vaccinate with rotavirus compared to their younger counterparts. With meningococcal vaccine, safety again was observed to be the major barrier that needs to be addressed with pediatric specialists. The most significant differential between projected immunizations of children of general pediatricians versus specialists was with meningococcal vaccination. This possibly reflects the greater exposure of general pediatricians with the serious outcomes of the disease caused by this organism.

What is observed from this study is the intent of some general pediatricians (5%) and a higher proportion of specialists (19%) to delay the MMR vaccination beyond 18 months of age despite recent increases in incidence of Measles disease [18]. This is somewhat unexpected given the time and resources spent to discredit any association between MMR and autism, but it does mimic the public trend. One physician even goes so far to comment that there is "no need to introduce another potentially confounding variable (MMR vaccine) until development is clearly normal." This potential trend represents a major threat to effectively combating the current rise in measles. Such physicians may not feel compelled to argue for timely vaccination with MMR.

Electing not to vaccinate leads to poor outcomes for many. In a retrospective cohort study spanning 10 years, unvaccinated children were found to be 22 times more likely to contract measles and 6 times more likely to contract pertussis than vaccinated children [19]. In 2008, the most measles cases since 1996 occurred. 112 of a total of 131 cases were unvaccinated or had unknown vaccination status [20]. In 2009, approximately 0.6% of children between 19 and 35 months received no vaccinations and represents an increase from 0.4% from 2006 [18]. Despite these trends, delaying MMR vaccination based on our findings may increase among pediatric clinicians.

Our results did show some methodological limitations necessitating caution in interpreting them. Recollection bias may have influenced answers that relied on physicians' recall of past vaccine practices. Also, answers for a hypothetical child, may not necessarily translate into actions once a physician has an actual child. This survey drew from a pool of pediatric providers who were far more likely to be interested in vaccine issues as immunization of all children is a primary stated goal of the AAP. This suggests that compliance of the survey respondents in vaccinating their own children according to ACIP guidelines will be higher than for the general population of pediatric providers in the US. The survey also did not address whether responders were actively charged with vaccinating patients. It is not known whether those working "for the government" or "in a school of medicine" actually vaccinate children in their workplace. It is also possible that questionnaires were sent to pediatricians who were parents of the same child although no physicians bearing the same last name who completed the questionnaire were located in the same state. Unfortunately, from the database it was not possible to elicit relationships of physicians surveyed.

While most pediatricians and pediatric specialists (95% and 93%) have adhered to the recommended ACIP vaccination schedule up until 2009, a potential for change emerged with 10% of pediatricians and 21% of pediatric specialists claiming they would not follow the recommendations for future progeny. Despite their education, physicians in this study expressed concern over the safety of vaccines. This study points to the need to focus on education efforts, including safety data, for those particular vaccines physicians displayed the greatest concern over including hepatitis A, rotavirus, meningococcal, and measles. Pediatric specialists should be included in this education as they have the greatest concerns, may be the most removed from the diseases protected by the immunizations, but also care for some of the most vulnerable populations. It has been shown that the more convinced physicians are of the benefits of vaccines, the more likely they are to immunize their patients [21-23].

Researchers might look to correlate whether patients of physicians who choose not to follow current recommendations are indeed more likely to also not follow the published schedule. Continued control of communicable disease will rely on the success of efforts to educate the public and physicians. Future study should thus focus on how to best address safety concerns which presents the greatest threat to sustained high vaccination level.

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REFERENCES

[1] Smith, P.J., Kennedy, A.M., Wooten, K., Gust, D.A. and Pickering, L.K. (2006) Association between health care providers' influence on parents who have concerns about vaccine safety and vaccination coverage. *Pediatrics*, **118**, e1287-e1292. doi:10.1542/peds.2006-0923

[2] Benin, A.L., Wisler-Scher, D.J., Colson, E., Shapiro, E.D. and Holmboe, E.S. (2006) Qualitative analysis of mothers' decision-making about vaccines for infants: The importance of trust. *Pediatrics*, **117**, 1532-1541. doi:10.1542/peds.2005-1728

[3] Sharkness, C.M., Goun, B.D., Davis, L.A. and Sykes, L.E. (1998) Do we practice what we teach about childhood immunization in New Jersey? *Family Medicine*, **30**, 727-732.

[4] Zimmerman, R.K., Bradford, B.J., Janosky, J.E., Mieczkowski, T.A., DeSensi, E. and Grufferman, S. (1997) Barriers to measles and pertussis immunization: The knowledge and attitudes of Pennsylvania primary care physiccians. *American Journal of Preventative Medicine*, **13**, 89-97.

[5] Gust, D.A., Strine, T.W., Maurice, E., Smith, P., *et al.* (2004) Underimmunization among children: Effects of vaccine safety concerns on immunization status. *Pediatrics*, 2004, **114**, e16-e22. doi:10.1542/peds.114.1.e16

[6] Katz-Sidlow, R.J. and Sidlow, R. (2003) A look at the pediatrician as parent: Experiences with the introduction of varicella vaccine. *Clinical Pediatrics*, **28**, 635-640. doi:10.1177/000992280304200710

[7] Posfay-Barbe, K.M., Heininger, U., Aebi, C., Desgrandchamps, D., Vaudaux, B. and Siegrist, C.A. (2005) How do physicians immunize their own children? Differences among pediatricians and nonpediatricians. *Pediatrics*, **116**, e623-e633. doi:10.1542/peds.2005-0885

[8] Kempe, A., Patel, M.M., Daley, M.F., Crane, L.A., Beaty, B., Stokley, S., Barrow, J., Babbel, C., Dickinson, L.M., Tempte, J.L. and Parashar, U.D. (2009) Adoption of rotavirus vaccination by pediatricians and family medicine physicians in the United States. *Pediatrics*, **124**, e809-e816. doi:10.1542/peds.2008-3832

[9] Davis, M.M., Marin, M., Cowan, A.E., Guris, D. and Clark, S.J. (2007) Physician attitudes regarding breakthrough varicella disease and a potential second dose of varicella vaccine. *Pediatrics*, **119**, 258-264. doi:10.1542/peds.2006-0972

[10] Freed, G.L., Bordley, W.C., Clark, S.J. and Konrad, T.R. (1993) Reactions of pediatricians to a new Centers for Disease Control recommendation for universal immunization of infants with hepatitis B vaccine. *Pediatrics*, **91**, 699-702.

[11] Davis, M.M., Ndiaye, S.M., Freed, G.L., Kim, C.S. and Clark, S.J. (2003) Influence of insurance status and vaccine cost on physicians' administration of pneumococcal conjugate vaccine. *Pediatrics*, **112**, 521-526. doi:10.1542/peds.112.3.521

[12] Gust, D., Weber, D., Weintraub, E., Kennedy, A., Sund, F. and Burns, A. (2008) Physicians who do and do not recommend children get all vaccinations. *Journal of Health Communication: International Perspectives*, **13**, 573-582. doi:10.1080/10810730802281726

[13] Gellin, B.G., Maibach, E.W. and Marcuse, E.K. (2000) Do parents understand immunizations? A national telephone survey. *Pediatrics*, **106**, 1097-1102. doi:10.1542/peds.106.5.1097

[14] Gust, D.A., Darling, N., Kennedy, A. and Schwartz, B. (2008) Parents with doubts about vaccines: Which vaccines and reasons why. *Pediatrics*, **122**, 718-725. doi:10.1542/peds.2007-0538

[15] Freed, G.L., Clark, S.J., Butchart, A.T., Singer, D.C. and Davis, M.M. (2010) Parental vaccine safety concerns in 2009. *Pediatrics*, **125**, 654-659. doi:10.1542/peds.2009-1962

[16] Widdowson, M.-A., Meltzer, M.I., Zhang, X.Z., Bresee, J.S., Parashar, U.D. and Glass, R.I. (2007) Cost-effectiveness and potential impact of rotavirus vaccination in the United States. *Pediatrics*, **119**, 684-697. doi:10.1542/peds.2006-2876

[17] Anderson, E.J., Rupp, A., Shulman, S.T., Wang, D.L., Zheng, X.T. and Noskin, G.A. (2011) Impact of rotavirus vaccination on hospital-acquired rotavirus gastroenteritis in children. *Pediatrics*, **127**, e264-e270.

doi:10.1542/peds.2010-1830

[18] Centers for Disease Control and Prevention (2010) National, state, and local area vaccination coverage levels among children aged 19-35 months—United States, 2009. *Morbidity and Mortality Weekly Report* (*MMWR*), **59**, 1171-1177.

[19] Feiken, D.R., Lezott, D.C., Hamman, R.F., Soloman, D.A., Chen, R.T. and Hoffman, R.E. (2000) Individual and community risks of measles and pertussis associated with personal exemptions to immunization. *The Journal of the American Medical Association*, **284**, 3145-3150. doi:10.1001/jama.284.24.3145

[20] Centers for Disease Control and Prevention (2008) Update: Measles—United States, January-July 2008. *Morbidity and Mortality Weekly Report* (*MMWR*), **57**, 893-896.

[21] Iwamoto, M., Saari, T.N., McMahon, S.R., *et al.* (2003) A survey of pediatricians on the reintroduction of a rotavirus vaccine. *Pediatrics*, **112**, e6-e10. doi:10.1542/peds.112.1.e6

[22] Zimmerman, R.K., Schlesselman, J.J., Baird, A.L. and Mieczkowski, T.A. (1997) A national survey to understand why physicians defer childhood immunizations. *Archives of Pediatrics Adolescent Medicine*, **151**, 657-664. doi:10.1001/archpedi.1997.02170440019004

[23] Zucs, A.P., Crispin, A., Eckl, E., Weitkkunat, R. and Schlipkoter, U. (2004) Risk factors for undervaccination against measles in a large sample of preschool children from rural Bavaria. *Infection*, **32**, 127-133. doi:10.1007/s15010-004-3122-0

Testimony on HB 19-1312

Heather Durfee 4/13/19

Colorado Springs, CO 80911

On exemption forms:

It's my right to

- Avoid signing forms that may imply neglect or harm. Pg 6 line 26.
  Q. What do these standardized forms and certificates for religious and philosophical exemption say? Is there compelled speech? How can you standardize someone else's philosophical reasoning for or against a medical procedure?
- This bill removes our RIGHT to draft our own personal belief statement and infringes on Free Speech! My Rights are being threatened.
- Decide what liability-free product is injected into my children. Pg 9 lines 10-21.
- Protect the privacy of my child's health records. Pg 6 lines 12-13.

- This bill tracks **personal identifiers** (violates spirit of HIPAA) (pg 9 line 26-27 "requires reporting of statistical information and **NAMES of NONCOMPLIERS** by the schools.")

On Supporting Healthy Students, Schools, and Community

- Pg 4 line 2: "vaccine coverage in schools helps to protect the health of students."
  Conversely, Vaccinated persons **asymptomatically shed a live virus vaccine** for at least 7-14 days after vaccination. This is why recently vaccinated persons cannot enter cancer wards in hospitals. (Consider the US Navy ship outbreak, high school outbreak among 98% vaccinated, Marshallese community in AR, all had highly vaccinated populations, and still measles was contracted. All recovered. No severe complications reported.)
- Pg 10 line 1. Q. How would this be "enforced"?
- Q. What might happen if we strengthened the students' own immune systems naturally to help prevent chronic health issues?
- All individuals have the **inherent right to voluntarily choose or deny any medical procedures**, including vaccines, without pressure, coercion or fear (per **Informed Consent and the Right of the Individual to Withdraw**, from **the Nuremberg Code).**

On Civil Rights and Exemption Process

- **Keeping** the current exemption process and sharing **all** the information in a balanced manner (including benefits, risks, adverse reactions and VAERS reporting information) in CO helps establish trust between health workers, medical professionals and elected officials by **offering all the options**. This leads to supporting true informed choice.
- This bill is **discriminatory** (by tracking minority groups), Pg 8 lines 6-8.
- Violates basic **Human Rights and Civil Rights**, to determine what goes into our children's bodies. Pg 10 lines 6-10
- As a mother I **am terrified and will fiercely fight for all our children**. As an American citizen I am appalled at the attack on basic human rights and on minorities.
- To help retain and fight for these freedoms are what each of you as public servants have vowed to uphold. This is what we the people **demand**. This is a **pivotal issue** for vast numbers of voters **on both sides of the aisle.**

What will you do?

On a personal note, 2 grandparents on both sides of my family have died with Alzheimers.

My children are at increased risk to damage from heavy metals in vaccines.

Dr. Hugh Fudenberg, internationally referred to as the founder of clinical immunology. and author of 850 peer-reviewed papers, conducted a ten-yr study from 1980-1990 which found that five consecutive flu shots raised the risk ten-fold of developing cognitive dysfunction (Alzheimers) due to the synergistic effect of aluminum and mercury which exacerbates the neuro- toxicity of these two heavy metals.

Hazards of Vaccines 1 & 2 in Internat. J. Clin. Invest., 2000 & 2004 Dr Hugh Fudenberg, MD

- In just the last few months, I have spent well over **80 hours** studying medical journals, CDC reports and FDA complete inserts on vaccines.
- How much time have you spent **researching for yourself**?

References:

"50 Years Later, The Significance of the Nuremberg Code." *www.nejm.org*, 13 Nov. 1997, www.nejm.org/doi/full/10.1056/NEJM199711133372006.

Fudenberg, MD, Hugh. *Hazards of Vaccines 1 & 2 in Internat. J. Clin. Invest*. Vol. 1-2, 2000, 2004.

"Measles Outbreak in Vaccinated School Population." *www.ncbi.nlm.nih.gov*, www.ncbi.nlm.nih.gov/pmc/articles/PMC1646939/.

"Mumps in a Highly Vaccinated Marshallese Community in AR." *ww.researchgate.net*, The Lancet, 1 Feb. 2019, www.researchgate.net/publication/330252951_Mumps_in_a_highly_vaccinated_Marshallese_community_in_Arkansas_USA_an_outbreak_report.

Starr, Barbara. "US Warship Quarantined." *www.cnn.com*, 13 Mar. 2019, www.cnn.com/2019/03/13/politics/us-warship-quarantined-virus/index.html

THE LANCET

ARTICLES| VOLUME 19, ISSUE 2, P185-192, FEBRUARY 01, 2019

Mumps in a highly vaccinated Marshallese community in Arkansas, USA: an outbreak report

Summary

Background

During 2000–15, Arkansas Department of Health, Little Rock, AR, USA, investigated between one and six cases of mumps each year. From Aug 5, 2016, to Aug 5, 2017, the department received notification of more than 4000 suspected mumps cases in the second largest outbreak in the USA in the past 30 years.

Methods

Arkansas Department of Health investigated all reported cases of mumps to ascertain exposure, travel, and vaccination histories and identify close contacts. Cases were classified as confirmed if the patient had laboratory confirmation of mumps virus or probable if they had clinical symptoms and either a positive serological test or a known epidemiological link to a confirmed case.

Findings

2954 cases of mumps related to the outbreak were identified during the outbreak period: 1665 (56%) were laboratory confirmed, 1676 (57%) were in children aged 5–17 years, and 1692 (57%) were in Marshallese people. Among the 1676 school-aged cases, 1536 (92%) had previously received at least two doses of a vaccine containing the mumps virus. Although 19 cases of orchitis were reported, severe complications were not identified. Unusual occurrences, such as recurrent parotitis and prolonged viral shedding, were observed mostly in Marshallese individuals. Viral samples were characterised as genotype G.

Interpretation

This large-scale outbreak, primarily affecting a marginalised community with intense household crowding, highlights the need for coordinated, interdisciplinary, and non-traditional outbreak responses. This outbreak raises questions about mumps vaccine effectiveness and potential waning immunity.

Funding

Council of State and Territorial Epidemiologists and US Centers for Disease Control and Prevention.

Publication History

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Identification

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Am J Public Health. 1987 April; 77(4): 434–438.

PMCID: PMC1646939

PMID: 3826461

Measles outbreak in a vaccinated school population: epidemiology, chains of transmission and the role of vaccine failures.

B M Nkowane, S W Bart, W A Orenstein, and M Baltier

Abstract

An outbreak of measles occurred in a high school with a documented vaccination level of 98 per cent. Nineteen (70 per cent) of the cases were students who had histories of measles vaccination at 12 months of age or older and are therefore considered vaccine failures. Persons who were unimmunized or immunized at less than 12 months of age had substantially higher attack rates compared to those immunized on or after 12 months of age. Vaccine failures among apparently adequately vaccinated individuals were sources of infection for at least 48 per cent of the cases in the outbreak. There was no evidence to suggest that waning immunity was a contributing factor among the vaccine failures. Close contact with cases of measles in the high school, source or provider of vaccine, sharing common activities or classes with cases, and verification of the vaccination history were not significant risk factors in the outbreak. The outbreak subsided spontaneously after four generations of illness in the school and demonstrates that when measles is introduced in a highly vaccinated population, vaccine failures may play some role in transmission but that such transmission is not usually sustained.

US warship quarantined at sea due to virus outbreak

By Barbara Starr, CNN Pentagon Correspondent

Updated 1:50 PM ET, Wed March 13, 2019

(CNN)A US warship has essentially been quarantined at sea for over two months and has been unable to make a port call due to an outbreak of a viral infection similar to mumps.

Twenty-five sailors and Marines aboard the USS Fort McHenry amphibious warship have been diagnosed with parotitis, which causes symptoms similar to mumps, according to US military officials.

Until CNN asked about the incident, the US military had not disclosed it. The illness first broke out in December, with the most recent case being reported on March 9.

"None of the cases are life-threatening and all have either already made or are expected to make a full recovery," the Fifth Fleet said in a statement provided to CNN.

All seven hundred and three military personnel aboard the ship have received measles, mumps and rubella (MMR) booster vaccinations, according to the US Navy's Fifth Fleet headquartered in Bahrain.

The ship is currently operating in the Persian Gulf region and military medical officials are assessing when it may be deemed medically safe to make a port call.

A US military official tells CNN that when there are major disease outbreaks, a decision may be taken to halt port visits until 30 days after the last reported illness due to varying incubation periods.

But the Fort McHenry did make a port call in early January in Romania when it was in the Black Sea before traveling back through the Mediterranean and into the Middle East.

The ship includes elements of the 22nd Marine Expeditionary Unit. Since the initial case was detected on December 22, 24 of the 25 patients have returned to duty.

After they became ill, the patients were quarantined and treated in the ship's medical facility. Living and work spaces were disinfected.

None of the personnel had to be medevaced off the ship and all are expected to make a full recovery.

However, a military medical team specializing in preventative medical care is expected to deploy in the coming days to make an assessment if further steps may be needed, according to the official.

The ship, which carries Marines to perform amphibious warfare duties did have some of its scheduled training modified to deal with the outbreak's impact.

Source:

Starr, Barbara. "US Warship Quarantined." *www.cnn.com*, 13 Mar. 2019, www.cnn.com/2019/03/13/politics/us-warship-quarantined-virus/index.html

THE SCIENCE BEHIND HERD IMMUNITY

1 Scientific studies show weak seroconversion in regards to immunity, in conjunction with vaccination

WHAT DOES THIS MEAN?

Simply being vaccinated provides no guarantee against developing measles during exposure. Relying on a certain "herd level" ignores the scientific research that clearly shows seroconversion (the time period during which a specific antibody to a pathogen develops and becomes detectable in the blood) is unpredictable. Particularly in the form of a vaccine, illness has been known to occur after exposure to measles even in persons with PRN titers (the sign of viral protection) above the levels thought to be protective.

Source:

R.T. Chen et al., "Measles Antibody: Reevaluation of Protective Titers," Journal of Infectious Diseases, Vol. 162, no 5, November 1990, pp 1036-1042

2 Research shows that the different genetic makeup of individuals cause varied immune responses

WHAT DOES THIS MEAN?

Protective herd immunity relies on a simple assumption: If you are vaccinated, you are fully protected. Unfortunately, this is a wildly over-simplistic assumption that good science calls into question. An antibody that is protective in one host may not be protective in another if the nature of their immune responses to the relevant agent places them on different parts of the damage response curve. This means a vaccine that may work for some, may not work for all. Or put another way: the pharmaceutical industry would like to believe they have a bulletproof answer in vaccines, but they must admit their efficacy in all cases is not equal.

Source:

Sallie R. Permar et al., "Limited Contribution of Humoral Immunity to the Clearance of Measles Viremia in Rhesus Monkeys," Journal of Infectious Disease, vol. 192, no 5, 2005, p. 998

3 Vaccines bring forth induced mutations of pathogens, which undermines the very concept of herd immunity

WHAT DOES THIS MEAN?

Herd immunity is presented as a magical solution, that once reached, ensures we will have unmitigated protection from a disease. Science shows this is not and would not ever actually be the case. For example, the pertussis vaccine is becoming less effective as it causes virulent new strains to emerge. Herd immunity is not an end-game, it's a marketing talking-point backed by weak science and medical hubris on behalf of an industry that finds the medical truth to be inconvenient and bad for business.

Sources:

Stefanelli P, Fazio C, et al. A Natural Pertactin-deficient strain of Bordetella pertussis shows improved entry in human monocyte-derived dendritic cells. New Microbiol. 2009 Apr; 32(2): 159-66.

Otsuka N, Han HJ, et al. Prevalence and genetic characterization of pertactin-deficient Bordetella pertussis in Japan. PLos One. 2012; 7(2): e31985

Concerns regarding the false promises of herd immunity are based on published scientific research that industry and the fear-driven media would prefer we overlook.

Public policy should be based on facts and logic

Suggestions for Amendments to HB19-1312

Page 6 lines 1-5, 14-15, 24-27, and page 7 lines 1-25
Remove the entire process of issuing a certificate and placing child's info in a database. Colorado residents should bring a letter or CDPHE's form as written in current state law into the CDPHE's office annually. CDPHE staff verifies that the letter to the school has all required info according to state law, or the form is completed in full. They then document the numbers and types of exemptions, but no personal data. They sign and date the letter or the original form that the parent brings in, and the parent turns in that letter or form to their school, as per current state law. This will dissuade any parents who are doing the exemption out of laziness, protect Coloradan's privacy, and allow Colorado to more accurately track exemption rates.

Page 8 lines 11-15
Remove lines 11-15 of the bill.

Page 9 lines 10-21
These regulations will result in higher exemption rates for Colorado. I am deeply concerned, because I have heard rumors from multiple sources that the Governor, and members of the Legislature have received threats against their persons and families if the exemption rates don't go down in Colorado. The two vaccines that are of particular concern are FLU and Gardasil. After a review of the FLU vaccine rates in Colorado, it indicates that exemption rates for that vaccine alone, could spike up to 40-50%. Gardasil has extremely dangerous side effects, and many people are declining this vaccine. Because the side effects are paralyzing and deadly, parents are not going to budge on this vaccine. Including these in the required vaccines will backfire.

Source: https://www.colorado.gov/pacific/cdphe/immunization-rates-reports-and-data

Giving the authority to the State to add any vaccines to the schedule goes too far. Line 21 is of concern as it unchecked authority to the CDC, Federal Department of HHS, or any successor entity. Vaccine exemptions are an established State's Rights issue, and authority should not be given, unchecked, to anyone, even CDPHE.

COLORADO
Department of Public Health & Environment

COLORADO
Department of Education

April 12, 2017

Regarding School Responsibility and Immunization Exemptions

In response to several requests from schools for support and clarity around the usage of immunization exemption forms, the Colorado Department of Public Health and Environment (CDPHE) and the Colorado Department of Education jointly issue this memo.

Schools are required to have an immunization record on file for every student enrolled. Immunization records are the official certificate of immunization, the official medical exemption form or a documented non-medical exemption. The certificate of immunization is located here: www.colorado.gov/pacific/cdphe/immunization-forms. Medical and nonmedical exemption forms are located here: www.colorado.gov/vaccineexemption.

We encourage the use of the CDPHE non-medical exemption form when possible. However, recognizing that some families may prefer not to use this form, a parent/guardian or emancipated student or student over the age of 18 may submit a signed non-medical statement of exemption per section 25-4-903(2)(b), C.R.S. Such a statement should include the following information: student's full name, age or date of birth, date the exemption was submitted, the vaccines declined, and which type of non-medical exemption is being taken (personal belief or religious).

Additionally, schools are not required to share immunization records with CDPHE but may do so if the parent has provided written consent, per the Family Educational Rights and Privacy Act (FERPA). Parents/guardians/students may choose to submit immunization and exemption forms directly to CDPHE for inclusion in the Colorado Immunization Information System (CIIS), the state's secure, confidential immunization registry. Once a record is in CIIS, schools can retrieve immunization or exemption records for their students at any time. All information contained in CIIS is kept confidential per section 25-4-2403, C.R.S. Parents/guardians/students can opt out of CIIS at any time by following the procedures here: www.colorado.gov/pacific/cdphe/ciis-opt-out-procedures.

Larry Wolk, MD, MSPH
Executive Director and Chief Medical Officer
Colorado Department of Public Health and Environment

Katy Anthes, Ph.D.
Commissioner
Colorado Department of Education

Immunization

Non-Medical Exemption Form (Religious and Personal Belief)

Vaccines are one of the greatest public health achievements of the past century and save an estimated 3 million children's lives every year. The Colorado Department of Public Health and Environment strongly supports vaccination as one of the easiest and most effective tools in preventing diseases that can cause serious illness and even death. For nearly all children, the benefits of preventing disease with a vaccine far outweigh the risks. Declining to follow the Centers for Disease Control and Prevention's Advisory Committee on Immunization Practices (ACIP) immunization schedule for number, space and timing of doses, may endanger an unvaccinated child's health and others who come into contact with him/her. Some vaccine-preventable diseases are common in other countries and unvaccinated children could easily get one of these diseases while traveling or from a traveler.

Colorado law C.R.S. § 25-4-902 requires all students attending any school in the state of Colorado to be vaccinated against certain vaccine-preventable diseases as established by Colorado Board of Health rule 6 CCR 1009-2, unless an exemption is filed. This law applies to students attending public, private and parochial kindergarten, elementary and secondary schools through 12th grade, colleges or universities, and child care facilities licensed by the Colorado Department of Human Services including child care centers, school-age child care centers, preschools, day camps, resident camps, day treatment centers, family child care homes, foster care homes, and Head Start programs. Prior to kindergarten, a non-medical exemption must be filed each time a student is due for vaccines according to the schedule developed by the ACIP.[1,2] From kindergarten through 12th grade, a non-medical exemption must be filed every year during the student's school enrollment/registration process.[1] Students with a recorded immunization exemption may be kept out of a child care facility or school during a disease outbreak; the length of time will vary depending on the type of the disease and the circumstances of the outbreak.

Please complete all required fields below; incomplete forms will not be accepted. *All fields are required unless noted optional.*

Type of Non-Medical Exemption Claimed: □ Personal Belief □ Religious

Student Information:

Last Name:	First Name:	(optional) Middle Name:
Gender: □ Female □ Male	Date of Birth:	
Street #:	Street Name:	Street Type (e.g. Ave.):
Unit #:	P.O. Box:	
City:	State:	Zip Code:
Email Address:		County:
Phone Number:		□ Home □ Cell

Parent/Guardian Completing This Form: □ Check if an emancipated student or student over 18 years old

Last Name:	First Name:	(optional) Middle Name:
Relationship to student: □ Mother □ Father □ Guardian		
Street #:	Street Name:	Street Type (e.g. Ave.):
Unit #:	P.O. Box:	
City:	State:	Zip Code:
Email Address:		County:
Phone Number:		□ Home □ Cell

School/Licensed Child Care Facility Information:

School Name/Licensed Child Care Facility:		
School District:		□ Check if Not Applicable
Address:		
City:	State:	Zip Code:
Phone Number:		Grade of Student:

[1] Colorado Board of Health rule 6 CCR 1009-2: https://www.sos.state.co.us/CCR/GenerateRulePdf.do?ruleVersionId=7698&fileName=6%20CCR%201009-2.

[2] 2018 Recommended Immunizations from Birth through 6 Years Old: www.cdc.gov/vaccines/parents/downloads/parent-ver-sch-0-6yrs.pdf. Based on this schedule, a non-medical exemption would be submitted at 2 months, 4 months, 6 months, 12 months and 18 months of age.

Vaccine Preventable Disease Information

The information provided below is to ensure parents/guardians/students are informed about the risks of not vaccinating.

Diphtheria, tetanus, pertussis (DTaP, Tdap) - Unvaccinated children may be at increased risk of developing diphtheria, tetanus and/or pertussis if exposed to these diseases. Serious symptoms and effects of diphtheria include heart failure, paralysis, breathing problems, coma, and death. Serious symptoms and effects of tetanus include "locking" of the jaw, difficulty swallowing and breathing, seizures, painful tightening of muscles in the head and neck, and death. Serious symptoms and effects of pertussis (whooping cough) include severe coughing fits that can cause vomiting and exhaustion, pneumonia, seizures, brain damage, and death. For more information: http://www.cdc.gov/vaccines/hcp/vis/vis-statements/dtap.pdf and http://www.cdc.gov/vaccines/hcp/vis/vis-statements/tdap.pdf
Haemophilus influenzae type b (Hib) - Unvaccinated children may be at increased risk of developing invasive Hib disease if exposed to this disease. Serious symptoms and effects include bacterial meningitis, pneumonia, severe swelling in the throat, brain damage, deafness, infections of the blood, joints, bones, and covering of the heart, and death. For more information: http://www.cdc.gov/vaccines/hcp/vis/vis-statements/hib.pdf
Hepatitis B - Unvaccinated children may be at increased risk of developing hepatitis B if exposed to this disease. Serious symptoms and effects include jaundice, life-long liver problems such as liver damage, scarring, liver cancer, and death. For more information: http://www.cdc.gov/vaccines/hcp/vis/vis-statements/hep-b.pdf
Inactivated poliovirus (IPV) - Unvaccinated children may be at increased risk of developing polio if exposed to this disease. Serious symptoms and effects include paralysis of muscles that control breathing, meningitis, permanent disability, and death. For more information: http://www.cdc.gov/vaccines/hcp/vis/vis-statements/ipv.pdf
Measles, mumps, rubella (MMR) - Unvaccinated children may be at increased risk of developing measles, mumps, and/or rubella if exposed to these diseases. Serious symptoms and effects of measles include pneumonia, seizures, brain damage, and death. Serious symptoms and effects of mumps include meningitis, painful swelling of the testicles or ovaries, sterility, deafness, and death. Serious symptoms and effects of rubella include rash, arthritis, and muscle or joint pain. If a pregnant woman gets rubella, she could have a miscarriage or her baby could be born with serious birth defects such as deafness, heart problems, and mental retardation. For more information: http://www.cdc.gov/vaccines/hcp/vis/vis-statements/mmr.pdf
Pneumococcal conjugate (PCV13) - Unvaccinated children may be at increased risk of developing pneumococcal disease if exposed to this disease. Serious symptoms and effects include pneumonia, lung infections, blood infections, meningitis and death. For more information: http://www.cdc.gov/vaccines/hcp/vis/vis-statements/pcv13.pdf.
Varicella (chickenpox) - Unvaccinated children may be at increased risk of developing varicella if exposed to this disease. Serious symptoms and effects include severe skin infections, pneumonia, brain damage, and death. For more information: http://www.cdc.gov/vaccines/hcp/vis/vis-statements/varicella.pdf

Required Vaccines for School Entry - Place an "X" next to each vaccine you are declining.

	Diphtheria, tetanus, pertussis (DTaP)		Inactivated poliovirus (IPV)
	Tetanus, diptheria, pertussis (Tdap)		Measles, mumps, rubella (MMR)
	Haemophilus influenzae type b (Hib)		Pneumococcal conjugate (PCV13)
	Hepatitis B		Varicella (chickenpox)

Statement of Exemption

I am the parent/guardian of the above-named student or am the student himself/herself (emancipated or over 18 years of age) and am declining the vaccine(s) indicated above due to a religious or personal belief that is opposed to vaccines. The information I have provided on this form is complete and accurate.

- I may change my mind at any time and accept vaccination(s) for my child/myself in the future.
- I can review evidence-based vaccine information at www.colorado.gov/cdphe/immunization-education, or www.ImmunizeforGood.com for additional information on the benefits and risks of vaccines and the diseases they prevent.
- I can contact the Colorado Immunization Information System (CIIS) at www.ColoradoIIS.com or my health care provider to locate my child's/my immunization record.[3]

I acknowledge that I have read this document in its entirety.

Parent/Guardian/Student (emancipated or over 18 yrs old) signature: _____ Date: _____

(Optional) I authorize my/my student's school to share my/my student's immunization records with state/local public health agencies and the Colorado Immunization Information System, the state's secure, confidential immunization registry.

Parent/Guardian/Student (emancipated or over 18 yrs old) signature: _____ Date: _____

[3] Under Colorado law, you have the option to exclude your child's/your information from CIIS at any time. To opt out of CIIS, go to www.colorado.gov/cdphe/ciis-opt-out-procedures. Please be advised you will be responsible for maintaining your child's/your immunization records to ensure school compliance.

Can People Receiving Live Virus Vaccines Transmit Vaccine Strain Virus to Others?

Public health officials say that unvaccinated children pose a big danger to those around them and even threaten the health of fully vaccinated children and adults because vaccines can fail to prevent infection in vaccinated persons.[1] Today, the most common argument used to justify "no exceptions" mandatory vaccination laws is that unvaccinated people pose a serious health threat to others who "cannot be vaccinated," such as the immunocompromised.[2]

Some parents of unvaccinated children are asking the opposite question:

Could my *unvaccinated* or *immune compromised* child get sick from coming in contact with a recently vaccinated person?

When it comes to live virus vaccines, the short answer is: Yes.

During a viral infection, live virus is shed in the body fluids of those who are infected for varying amounts of time and can be transmitted to others. [3] [4] [5] Vaccine strain live virus is also shed for varying amounts of time in the body fluids of vaccinated people and can be transmitted to others. [6] [7] [8]

Although public health officials maintain that live attenuated virus vaccines rarely cause complications in the vaccinated person and that vaccine strain viral shedding rarely causes disease in close contacts of the recently vaccinated, it is important to be aware that vaccine strain live virus infection *can* sometimes cause serious complications in vaccinated persons and vaccine strain live viruses *can* be shed and transmitted to others with serious or even fatal consequences.

Viruses: Microbes That Help, Harm and Evolve

Unlike bacteria, viruses are microbes that that cannot multiply on their own but need a human, animal or other living host to replicate. Viruses inject their genetic material into the cells of humans and other living hosts (including plants, insects and bacteria) in order to replicate.

Many viruses have developed various molecular mechanisms to evade the immune responses of their host. There is great diversity among viruses and they often mutate and recombine with other viruses while continually being shed and transmitted in body fluids and waste products of animals and humans. [9]

There is an ongoing debate among scientists about where viruses came from and how they evolved and are still evolving. [10] One virologist observed that replicating and mutating viruses are the "world's leading source of genetic innovation:"

> *"The huge population of viruses, combined with their rapid rates of replication and mutation, makes them the world's leading source of genetic innovation: they*

> *constantly "invent" new genes. And unique genes of viral origin may travel, finding their way into other organisms and contributing to evolutionary change."* [11]

Discussing the co-evolution of viruses with humans and other living organisms, another virologist wrote in 2012 that during epidemics viruses evolve. Genetic and environmental co-factors make some individuals more or less likely to die from or survive the infection, producing an increase of the numbers of resistant individuals in the population:

> *"Viruses can become particularly dangerous when they evolve to acquire the possibility to infect new animal species. The defense systems of the new host may be generally unable to counteract the new pathogen and many individuals will die. In any epidemic, there are also individuals showing little sensitivity to or complete resistance to the particular pathogen. Both increased sensitivity and resistance to the infection are specified by the individual's genetic makeup and various environmental factors. Accordingly, mass epidemics not only produce new virus variants but also alter the host population structure: highly sensitive individuals die, while the portion of resistant individuals in the population increases. Therefore, the coevolution of the virus and the host is a mutually dependent process."* [12]

Viral Infections Both Trigger and Are Protective Against Autoimmunity

Most people fear and view viruses as dangerous microbes that only cause sickness and death. However, emerging evidence has revealed that viruses play an integral role in helping us stay well, too.

Healthy infants experience many different kinds of wild-type viral infections and shed virus without showing any clinical symptoms of illness. In addition to the protection they receive from maternal antibodies, viruses help the infant's immune system develop and gives them early protection against more serious viral infections in infancy and later in life. [13] [14] [15]

Depending upon individual genetic variability, viral infections have been associated with the triggering of autoimmune disorders like type 1 diabetes in some individuals; however, for many other people viral infections appear to be protective against development of autoimmunity. [16]

Public Health Policies & the Hygiene Hypothesis

According to scientists discussing the 'hygiene hypothesis,' increased sanitation and public health interventions in modern societies have reduced the diversity of early experiences with viral and bacterial infections among infants and children and one negative outcome has been an increase in autoimmune and allergic diseases. [17] They suggest that some infectious microbes, especially those that have co-evolved with humans, protect against a wide spectrum of immune-related disorders. [18]

The Human Microbiome: Viruses R Us

Viruses are part of the human microbiome, which is composed of trillions of non-human microbial cells and genetic material from bacteria, fungi and viruses that are present in and on the human body, including the nose, throat, gastrointestinal and urogenital tracts and skin. Microbes add another 100 trillion cells to the 10 million cells that make up the human body and resident microbes have about 8 million genes which interact with 21,000 human genes to help our body grow, digest food, develop and mount immune responses and perform many other normal bodily functions. [19] [20]

There is mounting evidence that the microbiome is a powerful ally in helping us resist disease. [21] Viruses, bacteria and other microbes populating the human microbiome play an important role in preparing a baby developing inside the womb for survival outside the womb. [22]

In 2014, researchers in Ireland studying the microbiome, stress, health and disease observed that the microbiome is established during the first three years of life but that it evolves throughout our lives as we constantly respond to our environment:

> *"The microbiome is a dynamic entity that is under continuous evolution throughout the host's lifetime in particular during the first three years of life during which time a stable microbiome is established. It is sensitive to a whole array of manipulations such as diet, stress, infection, pharmacological interventions and thus is it clear that the composition of the microbiota is distinct at different milestones of life."* [23]

One prominent physician writing about the importance of maintaining the health of the human microbiome from childhood said recently that "modern medical practices" have interfered with microbiome health and changed how children develop:

> "*With the modern advances of modern life, including modern medical practices, we have been disrupting the microbiome. And there's evidence for that, especially early in life, and it's changing how our children develop… Just as today the kids are lining up for the vaccines, in the future, maybe the kids are going to be drinking certain organisms so that we can replace the ones that they've lost."* [24]

Microbiome Differences Between Individuals

Viruses and bacteria always present in the body are constantly interacting with each other in a complex and dynamic process from infancy through adulthood. [25] In 2012 a consortium of scientists analyzing the structure, function and diversity of the human microbiome confirmed that biodiversity and the uniqueness of each individual human being is important to individual and human health. They found that the microbiomes of "*even healthy individuals differ remarkably*" and that *"much of this diversity remains unexplained, although diet, environment, host genetics and early microbial exposure have all been implicated."* [26]

Testimonial, Monday the 15th of April at the Capitol to the Health and Insurance Committee:
Dear Madam Chair, Dear Representatives,

I am Dr. Katia Meier; I have been a MD for 20 years.

It is a fact that some children have complex medical and genetic vulnerabilities to vaccine injury.

I strongly oppose this bill, because it would endanger the medically and genetically vulnerable by eliminating the Doctor/Patient relationship and ignoring a Doctors' particular experience. I refer specifically to section 3 part (a) (II), where this bill would ELIMINATE all medical exemptions that could PREVENT a serious life threatening and permanently damaging vaccine reaction and would instead throw the genetically and medically vulnerable minority of children under the bus.

A parent would be forced to play Russian roulette with their child and risk an anaphylactic reaction, or permanent lifelong serious brain damage before a medical exemption can be written, if the child survives at all. And how can it be determined, which vaccine has caused the reaction if given with multiple other vaccines at the same time.
To save their children from harm, a Parent would have to seek other exemptions, therefore this bill would obscure the REAL reason a child is exempt.

This bill would block doctors from abiding to their Oath of First Do No Harm because children would have to be put into harm's way before a medical exemption can be written for each one out of 53 different vaccines and 72 doses by the time a child is 18 years old.

This bill would make Colorado be the FIRST and ONLY state that allows someone without a medical degree, without a medical license, who has never seen the child, to override the medical judgement of a Colorado licensed Physician who is taking care of the child.

The medically and genetically vulnerable deserve to be PROTECTED, not put in harm's way by ill-conceived state regulations.

I urge you to vote against this dangerous bill.

Sincerely,

Katia Meier M.D.
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VIROLOGY

Rapid Identification of Measles Virus Vaccine Genotype by Real-Time PCR

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ABSTRACT During measles outbreaks, it is important to be able to rapidly distinguish between measles cases and vaccine reactions to avoid unnecessary outbreak response measures such as case isolation and contact investigations. We have developed a real-time reverse transcription-PCR (RT-PCR) method specific for genotype A measles virus (MeV) (MeVA RT-quantitative PCR [RT-qPCR]) that can identify measles vaccine strains rapidly, with high throughput, and without the need for sequencing to determine the genotype. We have evaluated the method independently in three measles reference laboratories using two platforms, the Roche LightCycler 480 system and the Applied Biosystems (ABI) 7500 real-time PCR system. In comparison to the standard real-time RT-PCR method, the MeVA RT-qPCR showed 99.5% specificity for genotype A and 94% sensitivity for both platforms. The new assay was able to detect RNA from five currently used vaccine strains, AIK-C, CAM-70, Edmonston-Zagreb, Moraten, and Shanghai-191. The MeVA RT-qPCR assay has been used successfully for measles surveillance in reference laboratories, and it could be readily deployed to national and subnational laboratories on a wide scale.

KEYWORDS measles, PCR, genotyping, measles vaccine, molecular methods

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Endemic transmission of measles virus (MeV) was interrupted in the Americas in 2002 (1), but since then, importations of measles from areas of endemicity have caused frequent and sometimes large outbreaks (2–6) and a recent transitory suspension of the elimination status (7). An important component of the public health response to a measles outbreak is vaccination of unimmunized contacts (8). Since approximately 5% of recipients of measles virus-containing vaccine experience rash and fever which may be indistinguishable from measles (9), it is very important to identify vaccine reactions to avoid unnecessary isolation of the patient, as well as the need for contact tracing and other labor-intensive public health interventions. Recent measles outbreaks in the Canadian provinces of Alberta and British Columbia have emphasized the need for rapid differentiation of vaccine reactions (18, 19) from reactions to infection with the wild-type virus. During the measles outbreak in California in 2015, a large number of suspected cases occurred in recent vaccinees (3). Of the 194 measles virus sequences obtained in the United States in 2015, 73 were identified as vaccine sequences (R. J. McNall, unpublished data). In contrast, only 11 of 542 cases genotyped in the National Reference Center for Measles, Mumps, and Rubella in Germany were associated with the vaccine virus.

vaccine strain caused the measles

Genotyping is used to confirm the origin of an outbreak and to exclude endemic circulation, but it is also the only way to distinguish vaccine strains from wild-type viruses. Genetic characterization of MeV is accomplished by sequencing of the 450

TABLE 1 The lower limit of detection of MeVA RT-qPCR compared to MeV RT-qPCR was determined by testing serial dilutions of synthetic MeV RNA with a known copy number

Assay	Copy no.	No. of samples with positive results/total no. of samples tested	% positive results
MeVA RT-qPCR	10^3	18/18	100
	10^2	18/18	100
	10^1	13/20	65
	10^0	1/18	6
	10^{-1}[a]	0/3	0
MeV RT-qPCR	10^3	18/18	100
	10^2	18/18	100
	10^1	18/18	100
	10^0	4/18	22
	10^{-1}[a]	0/3	0

[a]This concentration was tested only 3 times since it is undetectable by both assays and therefore was not informative in the determination of the lower limit of detection.

nucleotides (nt) coding for the COOH terminal 150 amino acids of the nucleoprotein (N-450) (10). The WHO currently recognizes 24 genotypes of measles virus, and all of the vaccine strains are in a single genotype, genotype A. Wild-type viruses of genotype A are no longer circulating (11).

It is difficult, especially during outbreaks, to perform rapid confirmation of vaccine reactions by sequencing, and there is interest in developing rapid molecular tests to detect vaccine strains (12). Here, we describe a real-time reverse transcription-PCR (RT-PCR) method that detects the vaccine genotype (MeVA RT-quantitative PCR [RT-qPCR]) and that can provide rapid discrimination between wild-type-virus infections and vaccine reactions. The method was developed initially on the Roche LightCycler 480 platform at the Canadian National Microbiology Laboratory (NML) and then independently evaluated at the Robert Koch-Institute (RKI) in Germany using the same platform and at the US Centers for Disease Control (CDC) using the Applied Biosystems 7500 platform.

RESULTS

Assay development and evaluation at the NML. The analytical sensitivity of the MeVA RT-qPCR on the Roche LightCycler 480 platform was established using the synthetic RNA standard, which was serially diluted from 10^3 to 10^{-1} copies per reaction and tested in triplicate in at least 6 separate assays in parallel with the MeV RT-qPCR. The lower limit of detection of the MeVA RT-qPCR was 10 to 100 copies per reaction, compared to a sensitivity of 1 to 10 copies per reaction for the MeV RT-qPCR (Table 1).

Eighty-eight surveillance specimens that were previously genotyped as genotype A, 96 specimens of nonvaccine measles virus genotypes (B3, C2, D3, D4, D6, D7, D8, D9, E, H1, and H2), and isolates for genotypes B2, C1, D2, D5, D6, D7, D10, G1, G2, and H2 (WHO Measles Strain Bank, US Centers for Disease Control, Atlanta, GA, USA) were tested with MeVA RT-qPCR and produced no false-positive results. The amplification curves of 33 wild-type measles virus samples, including all the genotypes listed above, did not rise significantly in comparison to the curves of samples containing vaccine strain RNA (Fig. 1). However, 3 of 88 genotype A specimens were not detected by the MeVA RT-qPCR (Table 2). These three specimens were near the lower limit of detection (crossing-point [Cp] value, >35) for the MeV RT-qPCR. The sensitivity of the MeVA RT-qPCR in relation to the MeV RT-qPCR was 97% (90% to 99%, 95% confidence interval [CI]), and the specificity was 100% (95% to 100%, 95% CI) (Table 3). Specificity was further evaluated by testing a panel of other viral agents from cell culture-derived material or clinical specimens (parvovirus B19, dengue virus serotypes 1 to 4, influenza virus H3N2, poliovirus Sabin 1 species C, enterovirus D68-2 [EV-D68-2] species D, Coxsackie virus, EV71, parechovirus, echovirus 18, herpes simplex virus 1 [HSV1], HSV2, Epstein-Barr virus [EBV], cytomegalovirus [CMV], human herpesvirus 6 [HHV-6], HHV7,

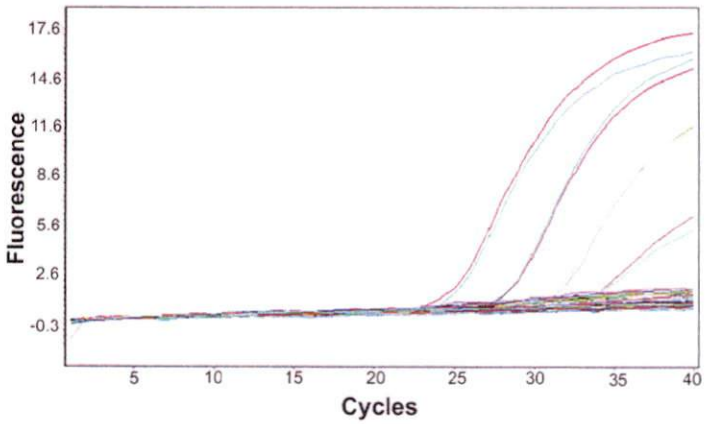

FIG 1 Amplification curve from the MeVA RT-qPCR on the Roche LightCycler 480 system. The bundle of the flat curves includes 33 wild-type measles virus specimens comprising the following genotypes: B2, B3, C1, C2, D2, D3, D4, D5, D6, D7, D8, D9, D10, G1, G2, E, H1, and H2. The amplification curves are from MeV vaccine RNA from 10^2 to 10^5 copy numbers, assessed in duplicate. The QuantiTect Probe RT-PCR kit was used for these reactions.

varicella zoster virus [VZV], rubella virus, and mumps virus). All specimens were negative by MeVA RT-qPCR.

Fifty specimens that were positive for vaccine strain A were tested in parallel by MeVA RT-qPCR and MeV RT-qPCR, and there was a good correlation of the Cp values between the two methods, with a slope of 0.88 (0.82 to 0.94, 95% CI). The slope was significantly different from 1.00, and a *y* intercept of 4.1 (2.2 to 6.0, 95% CI) confirmed that the sensitivity and limit of detection of the MeVA RT-qPCR method were lower than those of the MeV RT-qPCR (Fig. 2).

Assay evaluation at RKI. The MeVA qPCR was also independently evaluated at RKI by testing 46 archival measles virus specimens of genotype A and 112 samples containing wild-type MeV, including genotypes B3, D4, D5, D6, D8, D9, D10, G2, and H1. The same LightCycler 480 platform was used. The MeV RT-qPCR (16) includes the SuperScript III Platinum One-Step qRT-PCR kit (Invitrogen), so an evaluation was performed comparing the SuperScript III and QuantiTect reagent kits. The SuperScript III PCR kit produced suboptimal results, with significant increases of the amplification baseline of nonvaccine measles virus genotypes D10, D8, and B3 (Fig. 3A).

When the QuantiTect Probe RT-PCR kit was used for the MeVA RT-qPCRs, the test was 89% sensitive and 99.5% specific for genotype A measles virus (Table 3), with amplification curves comparable to those shown in Fig. 1. There was a single false-positive result from a genotype D5 wild-type strain, which produced amplification with

TABLE 2 Comparison of MeVA RT-PCR and MeV RT-qPCR in three reference laboratories

Reference laboratory and MeVA RT-qPCR result	No. of MeV RT-qPCR samples		Total no. of samples
	Genotype A	Not genotype A	
NML			
Positive	85	0	85
Negative	3	96	99
Total	88	96	184
CDC			
Positive	12	0	15
Negative	1	12	13
Total	13	12	28
RKI			
Positive	41	1	42
Negative	5	111	116
Total	46	112	158

TABLE 3 Summary of sensitivity and specificity of MeVA RT-qPCR for the detection of MeV genotype A

Center	No. of samples	% sensitivity (95% CI)	% specificity (95% CI)	Genotypes tested
NML	184	97 (90–99)	100 (95–100)	B3, B2, C1, D2, C2, D3, D4, D5 D6, D7, D8, D9, D10, G1, G2, E, H1, H2
RKI	158	89 (0.76–0.96)	99 (94–100)	B3, D4, D5, D6, D8, D9, D10, G2, H1
CDC	28	92 (66–100)	100 (70–100)	B3, D4, D8, D9, G3, H1, AIK, CAM-70, Edmonston-Zagreb, Moraten, Shanghai-191[a]
Overall	370	94 (88–97)	99 (97–100)	

[a]Genotypes D4 and G3 and the non-Edmonston vaccine strains, tested using synthetic RNAs and culture lysate, respectively, were not included in the sensitivity and specificity calculations.

the MeVA RT-qPCR. The region targeted by the MeVA assay was sequenced, and the sequence differed from the vaccine strain sequence by a G at position 517 in the probe region (conserved in all wild-type genotypes listed in Fig. 4), by a C at position 538 in the reverse primer region (similar to genotypes D4, D7, and D8), and by a T at position 548, at the 5′ terminus of the reverse primer (similar to genotypes B3 and D6). These genotypes did not produce any cross-reactivity with the MeVA-specific assay, and the reason for the false-positive result for this D5 specimen is unclear.

Assay evaluation at CDC on the ABI 7500 platform. The MeVA RT-qPCR method was independently evaluated at the CDC on the ABI 7500 instrument, which is a commonly used instrument in state public health laboratories and is available in many laboratories in the WHO Measles Rubella Laboratory Network (14). Similarly to the results seen with the LightCycler 480 platform, the MeVA RT-qPCR assay performed suboptimally with the SuperScript III kit with respect to the resulting amplification curves for wild-type measles virus genotypes (Fig. 3B).

The MeVA RT-qPCR and MeV qPCR were compared using the ABI 7500 platform and the QuantiTect kit, and the samples included synthetic MeV RNAs serially diluted from 10^5 to 10^1 copies per reaction. The dilutions were tested in duplicate on at least four separate assays. The results were similar to those obtained from the Roche LightCycler 480 system (Table 1) in that the lower limit of detection of the MeVA RT-qPCR assay was approximately 1 Log_{10} higher than for the MeV RT-qPCR assay.

To assess the specificity of the MeVA RT-qPCR assay on the ABI 7500 platform and to compare it to the performance of the MeV RT-qPCR assay, three sets of samples were used, i.e., synthetic RNAs containing the entire N gene open reading frames from six currently circulating wild-type genotypes (B3, D4, D8, D9, G3, and H1) (B. Bankamp, unpublished data), RNA from cell culture lysates from five vaccine strains (AIK-C, CAM-70, Edmonston-Zagreb, Moraten, and Shanghai-191), and RNA extracted from 28

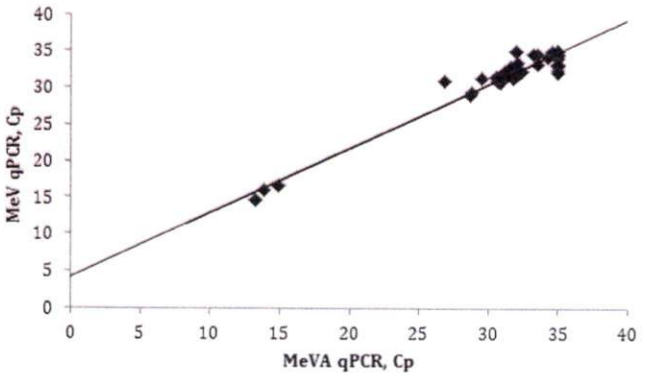

FIG 2 Correlation between Cp values of 50 genotype A measles virus specimens tested by MeVA RT-qPCR and the standard MeV RT-qPCR method. The regression line has a slope of 0.88 (0.82 to 0.94, 95% CI), a y intercept of 4.1 (2.2 to 6.0, 95% CI) and an R^2 value of 0.949 ($P < 0.0001$). The QuantiTect Probe RT-PCR kit was used for these reactions.

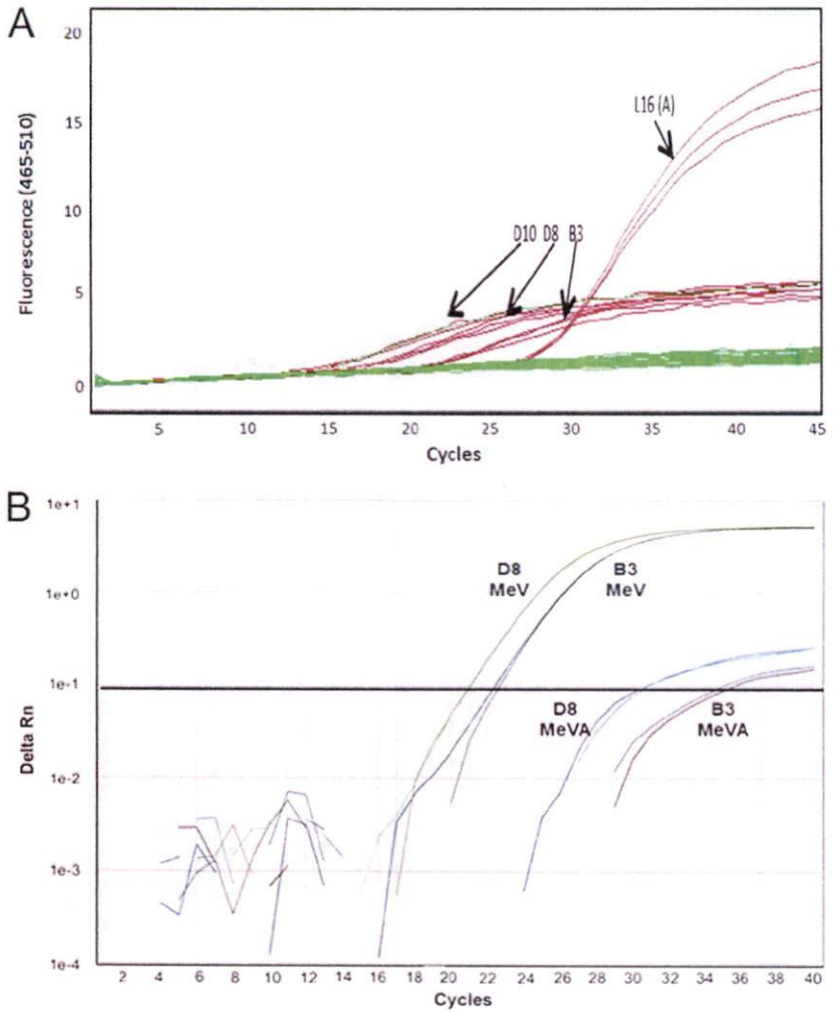

FIG 3 Negative effect of the use of the SuperScript III Platinum One-Step quantitative RT-PCR kit on the specificity of the MeVA RT-qPCR for the vaccine genotype. (A) The use of SuperScript III on the Roche LightCycler 480 platform caused a significant rise in the baseline of the amplification curves for genotype D10, D8, and B3. (B) Results of the use of SuperScript III on an ABI 7500 platform in amplification curves from wild-type measles virus RNA.

archival respiratory swabs and urine specimens that were submitted to the CDC for routine surveillance. Three archival specimens were negative by MeV RT-qPCR, and the other 25 were positive by MeV RT-qPCR and included clinical specimens from measles cases and vaccine reactions (with threshold cycle [C_T] values ranging from 14 to 36).

Of the positive archival specimens, all specimens with wild-type genotypes ($n = 12$) were negative in the MeVA RT-qPCR assay but positive in the MeV RT-qPCR assay and 12 of 13 specimens from vaccine reactions were positive in both assays (Table 2). Three of the specimens from the vaccine reactions had C_T values ranging from 38 to 40 in the MeV RT-qPCR assay and from 38 to 40 in the MeVA RT-qPCR.

The RNA from all five vaccine strains was detected in both assays with slightly lower sensitivity (C_T value, 2 to 3) in the MeVA RT-qPCR assay than in the MeV RT-qPCR assay (data not shown). In addition, the MeVA RT-qPCR assay did not produce a positive signal in samples containing high copy numbers of synthetic RNA from the six commonly circulating wild-type genotypes (Fig. 5).

If we consider all samples that were amplified within 40 PCR cycles, as was done at NML and RKI for the LightCycler platform, the sensitivity of the MeVA test on the ABI 7500 platform was 94% and the specificity was 100% (Table 3).

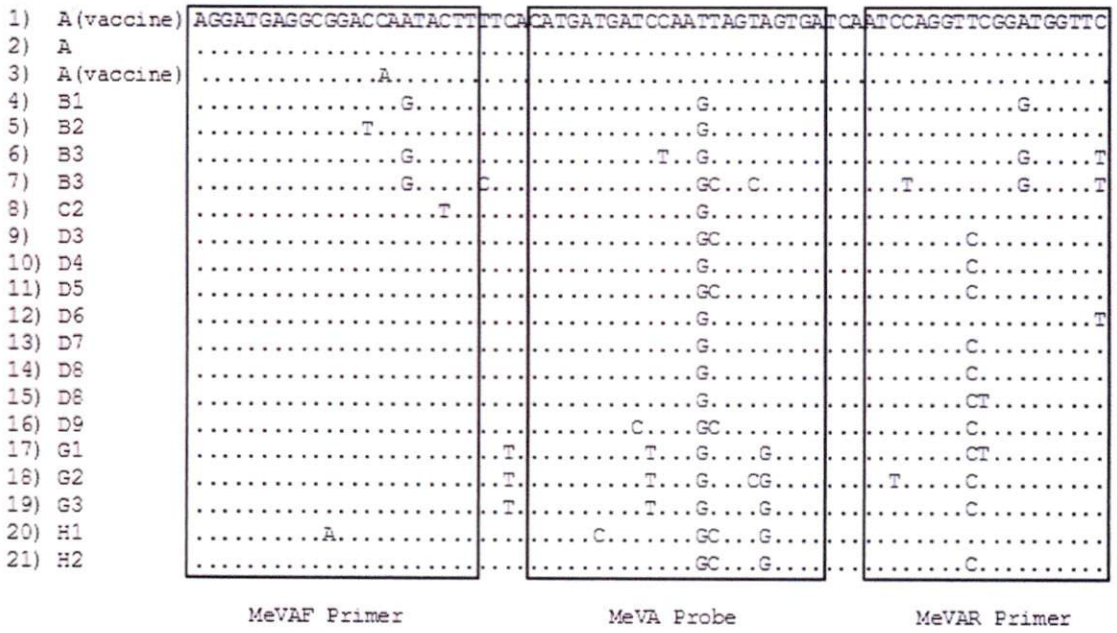

FIG 4 Alignment of the N gene region (positions 478 to 548) amplified by the MeVA RT-qPCR. The alignment includes examples of each genotype available on GenBank for this region, except for genotype D9, which was sequenced from one of our archival specimens. Row 1, 31 identical sequences from various vaccine strains; row 2, MVi/Maryland.USA/54 (A); row 3, two vaccine strains showing a 1-nt difference in the forward primer region; row 4, MVi/Yaounde.CMR/12.83 (B1); row 5, MVi/Libreville.GAB/84 (B2); row 6, MVi/Ibadan.NIE/971 (B3); row 7, MVi/New_York.USA/94 (B3); row 8, MVi/Maryland.USA/77 (C2); row 9, MVi/Illinois.USA/89/1 (D3); row 10, MVi/Montreal.CAN/89 (D4); row 11, Bankok.THA/12.93 (D5); row 12, MVi/New_Jersey.USA/94/1 (D6); row 13, MVs/Dundee.UNK/82 (D7); row 14, MVi/BritishColumbia.CAN/13.10/1 (D8); row 15, MVi/Manchester.GBR/30.94 (D8); row 16, MVs/Ontario.CAN/14.14 (D9); row 17, MVi/Berkeley.USA/83 (G1); row 18, MVi/Amsterdam.NLD/49.97 (G2); row 19, MVi/Gresik.IDN/17.02 (G3); row 20, MVi/Hunan.CHN/93/7 (H1); row 21, MVi/Beijing.CHN/94/1 (H2).

DISCUSSION

In response to the need for prompt differentiation between vaccine reactions and wild-type measles virus infection cases, laboratories have been developing methods that do not require sequencing of N-450. A method targeting a region on the hemagglutinin gene has been described and tested with a small number of vaccine and wild-type specimens or isolates (15). Here, we describe the development and validation of a measles virus genotype A-specific RT-qPCR, MeVA RT-qPCR, that targets the N gene of MeV. This assay produces rapid results and is capable of high throughput. The MeVA RT-qPCR was thoroughly tested at three global reference laboratories. Two RT-qPCR platforms and over 300 samples were included in the evaluation. Overall, our data show very high (99.5%) specificity for the A genotype, albeit with lower (94%) sensitivity than the standard MeV RT-qPCR (16). Because of the lower sensitivity, the MeVA RT-qPCR is intended to be used as a tool for rapid detection of genotype A sequences and not as a primary diagnostic test. The MeVA RT-qPCR should be performed in parallel with the MeV RT-qPCR method. Multiplexing of the two tests is in progress to increase the efficiency of this method.

We have shown that the MeVA RT-qPCR can be used on both the Roche LightCycler 480 and the ABI 7500 platforms, which are available in a large number of laboratories around the world. We also demonstrated that the QuantiTect kit gave optimal performance on both platforms.

An alignment of the nt 478 to 548 region used for the MeVA RT-qPCR (Fig. 4) shows that some wild-type strains differ only by a single nucleotide in the probe region, a G at position 517, although other mismatches that may favor specificity are present in the primer regions. This point mutation may be stable, since it results in an amino acid change (serine in wild-type strains to isoleucine in vaccine strains), but it is conceivable that wild-type strains may arise with a mutation in this position that cross-reacts with the MeVA assay. Therefore, we currently still confirm every MeVA RT-qPCR result by WHO-recommended sequencing of the N-450 region.

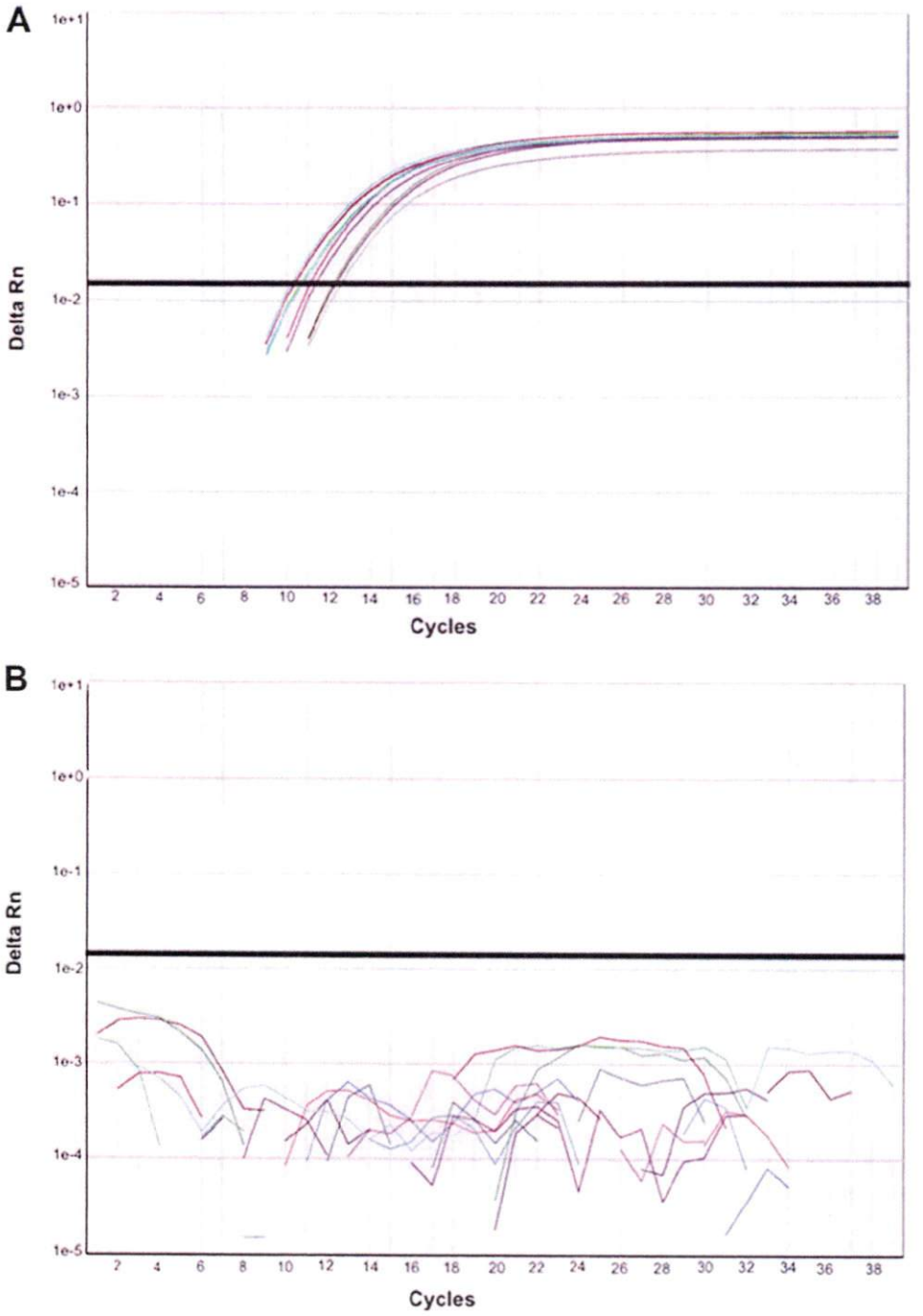

FIG 5 Specificity of the MeVA RT-qPCR assay, using an Applied Biosystems 7500 platform. Synthetic RNA from the six active wild-type measles virus genotypes (B3, D4, D8, D9, G3, and H1) was tested. Panel A shows detection of 10^7 copies of RNA/reaction in the MeV qPCR assay, and panel B shows the lack of amplification of 10^7 copies of RNA/reaction in the MeVA RT-qPCR assay. The QuantiTect Probe RT-PCR kit was used for these reactions.

The specificity of the test has been assessed on most of the measles virus genotypes currently circulating in the world (except D11 and G3) (11, 14), and there was only one genotype D5 specimen that gave a false-positive result. The sequence of the MeVA RT-qPCR target region of this genotype D5 virus differed from that of the vaccine strains by the G at position 517, conserved in all measles virus wild-type strains, and by two additional nucleotides in the reverse primer. Genotypes D4, D6, and D8 have the same sequence as this D5 strain in the probe region and one fewer difference in the reverse

primer region (Fig. 4), but they did not cross-react with the MeVA RT-qPCR. Another genotype D5 strain, tested at the NML, and 12 additional D5 strains, tested at the RKI, were not amplified by the MeVA RT-qPCR. Therefore, the reasons for this false-positive result remain unclear.

During measles outbreak investigations, rapid detection of measles vaccine reactions is necessary to avoid unnecessary public health interventions. In Canada, the NML has been using the MeVA and MeV RT-qPCRs with a turnaround time of 2 days. Therefore, local health authorities can initiate appropriate public health responses without waiting for sequencing results, which often take several days to obtain. The MeVA RT-qPCR is especially useful during large measles outbreaks, when it is difficult for laboratories to perform sequencing on a large number of specimens in a timely manner. Similarly, recent measles outbreaks in the United States have reinforced the need for rapid confirmation of vaccine reactions. In countries such as Germany, which is still experiencing frequent measles outbreaks, this RT-PCR-based method has already proven to be a valuable tool for guiding the public health responses. The MeVA RTqPCR assay is a straightforward application of real-time RT-PCR methodology, and the two platforms evaluated here are available in many laboratories. This assay could be readily deployed to national and subnational laboratories on a wide scale.

MATERIALS AND METHODS

Primers, probes, and control RNA. The primers and probe for the vaccine-specific assays were designed following analysis of 31 sequences available on GenBank from Edmonston-derived and non-Edmonston-derived vaccine strains. These sequences are identical in the target region of MeVA RT-qPCR (the 3′ region of the MeV N gene between nt 478 and nt 548 of the Edmonston strain [GenBank accession no. AF266288.2]), including the more divergent non-Edmonston-derived strains Shanghai-191 and CAM-70 (Fig. 4) (15). Two vaccine strains, Schwarz FF-8 (GenBank AB591381.1) and Edmonston AIK-C (GenBank S58435.1), have a 1-nt difference in the sequence of the forward primer, but they are identical to the other vaccine strains in the probe region (Fig. 4). The primers (Invitrogen) for reverse transcription and cDNA amplification were 5′-AGGATGAGGCGGACCAATACTT-3′ (MeVAF) and 5′-GAACCATCCGAACC TGGAT-3′ (MeVAR). Both primers were used at a concentration of 0.9 μM. Amplification was detected by a TaqMan probe (TIB Molbiol) with 6-carboxyfluorescein (FAM) as a fluorophore, at a concentration of 0.25 μM. The probe had the sequence 5′-FAM-CATGATGATCCAATTAGTAGTGA-BBQ-3′ (MeVA probe [BBQ, black berry quencher]), where the underlined characters indicate locked nucleic acid bases containing a 2′O,4-C methylene bridge which has the effect of increasing the melting temperature (T_m) and potentiating the destabilizing effect of a nucleotide mismatch (17).

As a standard for the measurement of MeV copy numbers, synthetic measles virus RNA was prepared by *in vitro* transcription, using a MEGAscript T7 transcription kit (Invitrogen, Life Technologies Inc.), either from a plasmid containing the open reading frame of the N gene of genotype A (16) or from PCR amplicons that included the T7 promoter in the forward primer (Bankamp, unpublished). DNase-treated RNA was purified with a MEGAclear transcription cleanup kit (Ambion, Life Technologies Inc.) and quantitated fluorometrically (Qubit, Life Technologies Inc.). The absence of residual DNA was verified by real-time RT-PCR (MeV RT-qPCR) (16) in the presence or absence of the reverse transcriptase.

Samples tested. For this study, 370 samples were tested to evaluate the sensitivity and specificity of the MeVA RT-PCR. The majority of these were clinical samples that were submitted to NML, CDC, or RKI as part of routine surveillance activities for measles.

Roche LightCycler 480 platform. Archival nasopharyngeal swabs and urine specimens sent to the NML for molecular surveillance were used. These specimens tested positive for measles virus by MeV RT-qPCR using a previously described method (16) and were genotyped using the N-450 target (10, 11). RNA was extracted using the QIAamp viral RNA minikit (Qiagen; catalog no. 52904) or the MagNA Pure liquid chromatograph (LC) total nucleic acid isolation kit—high performance (Roche Diagnostics; catalog no. 05323738001) on the MagNA Pure LC 2.0 instrument (Roche Diagnostics). For RT-PCR, 2 μl of extracted RNA was subjected to one-step reverse transcription and qPCR using the QuantiTect Probe RT-PCR kit (Qiagen; catalog no. 204443) according the instructions of the manufacturer. The RT-qPCR mixtures (total volume, 20 μl) were incubated at 50°C for 20 min (RT step) and 95°C for 15 min (activation of the polymerase) and subjected to 40 cycles of amplification (95°C for 5 s and 60°C for 1 min) on the Roche LightCycler 480 instrument. The RT-qPCR result was considered positive if there was amplification within 40 cycles, but crossing-point (Cp) values were recorded for only the first 35 cycles.

At the National Reference Center for Measles, Mumps, and Rubella at the RKI, archival surveillance specimens were extracted using the QIAamp viral RNA minikit (Qiagen; catalog no. 52906) and amplified by using the SuperScript III Platinum One-Step quantitative RT-PCR kit (Invitrogen; catalog no. 11732-088) or the QuantiTect Probe RT-PCR kit (Qiagen; catalog no. 20443). MeVA RT-qPCR, MeV RT-qPCR, and genotyping at the N-450 region were performed as described above. The RT-PCR result was considered positive if amplification was detected within 40 cycles.

Applied Biosystems 7500 platform. At the CDC, RNA was extracted with the QIAamp viral RNA minikit as described above. The MeV RT-qPCR was performed using the same reaction conditions and primers and probes (16). As for the Roche LightCycler 480, the SuperScript III and QuantiTect reagent kits were evaluated as described in Results. For the comparisons described in this report, the RT-qPCR result was considered positive if there was amplification within 40 cycles; however, during routine use of this assay at the CDC, specimens with threshold cycle (C_T) values between 38 and 40 are considered to represent equivocal results.

Statistical analyses. Sensitivity and specificity of MeVA RT-qPCR were calculated using the VassarStats website (13). Linear regression and related statistics were calculated using an online calculator developed by GraphPad Software, Inc. (http://www.graphpad.com/quickcalcs/linear1) and graphed using Microsoft Excel.

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The findings and conclusions in this report are ours and do not necessarily represent the official position of the Centers for Disease Control and Prevention. Names of specific vendors, manufacturers, or products are included for public health and informational purposes; inclusion does not imply endorsement of the vendors, manufacturers, or products by the Centers for Disease Control and Prevention or the US Department of Health and Human Services.

REFERENCES

1. Strebel PM, Cochi SL, Hoekstra E, Rota PA, Featherstone D, Bellini WJ, Katz SL. 2011. A world without measles. J Infect Dis 204(Suppl 1):S1–S3. https://doi.org/10.1093/infdis/jir111.
2. De Serres G, Desai S, Shane A, Hiebert J, Ouakki M, Severini A. 2015. Measles in Canada between 2002 and 2013. Open Forum Infect Dis 2:ofv048. https://doi.org/10.1093/ofid/ofv048.
3. Zipprich J, Winter K, Hacker J, Xia D, Watt J, Harriman K, Centers for Disease Control and Prevention (CDC). 2015. Measles outbreak–California, December 2014-February 2015. MMWR Morb Mortal Wkly Rep 64:153–154.
4. Jost M, Luzi D, Metzler S, Miran B, Mutsch M. 2015. Measles associated with international travel in the region of the Americas, Australia and Europe, 2001–2013: a systematic review. Travel Med Infect Dis 13:10–18. https://doi.org/10.1016/j.tmaid.2014.10.022.
5. Clemmons NS, Gastanaduy PA, Fiebelkorn AP, Redd SB, Wallace GS, Centers for Disease Control and Prevention (CDC). 2015. Measles - United States, January 4–April 2, 2015. MMWR Morb Mortal Wkly Rep 64:373–376.
6. Rocha HA, Correia LL, Campos JS, Silva AC, Andrade FO, Silveira DI, Machado MM, Leite AJ, Cunha AJ. 26 July 2015. Factors associated with non-vaccination against measles in northeastern Brazil: clues about causes of the 2015 outbreak. Vaccine https://doi.org/10.1016/j.vaccine.2015.07.027.
7. Leite RD, Barreto JL, Sousa AQ. 2015. Measles reemergence in Ceara, northeast Brazil, 15 years after elimination. Emerg Infect Dis 21:1681–1683. https://doi.org/10.3201/eid2109.150391.
8. Measles and Rubella Elimination Working Group. 2013. Guidelines for the prevention and control of measles outbreaks in Canada. Can Commun Dis Rep 39:ACS-3.
9. Berggren KL, Tharp M, Boyer KM. 2005. Vaccine-associated "wild-type" measles. Pediatr Dermatol 22:130–132. https://doi.org/10.1111/j.1525-1470.2005.22208.x.
10. Anonymous. 1998. Expanded Programme on Immunization (EPI). Standardization of the nomenclature for describing the genetic characteristics of wild-type measles viruses. Wkly Epidemiol Rec 73:265–269.
11. Anonymous. 2015. Genetic diversity of wild-type measles viruses and the global measles nucleotide surveillance database (MeaNS). Wkly Epidemiol Rec 90:373–380.
12. Xu CP, Li MH, He HQ, Lu YY, Feng Y. 19 November 2015. Laboratory diagnosis of vaccine-associated measles in Zhejiang Province, China. J Microbiol Immunol Infect https://doi.org/10.1016/j.jmii.2015.10.004.
13. Lowry R. VassarStats: website for statistical computation. http://vassarstats.net.
14. Anonymous. 2006. Global distribution of measles and rubella genotypes–update. Wkly Epidemiol Rec 81:474–479.
15. Rota JS, Wang ZD, Rota PA, Bellini WJ. 1994. Comparison of sequences of the H, F, and N coding genes of measles virus vaccine strains. Virus Res 31:317–330. https://doi.org/10.1016/0168-1702(94)90025-6.
16. Hummel KB, Lowe L, Bellini WJ, Rota PA. 2006. Development of quantitative gene-specific real-time RT-PCR assays for the detection of measles virus in clinical specimens. J Virol Methods 132:166–173. https://doi.org/10.1016/j.jviromet.2005.10.006.
17. Petersen M, Wengel J. 2003. LNA: a versatile tool for therapeutics and genomics. Trends Biotechnol 21:74–81. https://doi.org/10.1016/S0167-7799(02)00038-0.
18. Murti M, Krajden M, Petric M, Hiebert J, Hemming F, Hefford B, Bigham M, Van Buynder P. 2013. Case of vaccine-associated measles five weeks post-immunisation, British Columbia, Canada, October 2013. Euro Surveill 18:pii=20649. https://doi.org/10.2807/1560-7917.ES2013.18.49.20649.
19. Nestibo L, Lee BE, Fonseca K, Beirnes J, Johnson MM, Sikora CA. 2012. Differentiating the wild from the attenuated during a measles outbreak. Paediatr Child Health 17:e32–e33.

↓ Full text

Association between MTHFR gene polymorphisms and the risk of autism spectrum disorders: a meta-analysis.

Pu D, et al. Autism Res. 2013.
Show full citation

Abstract

Methylenetetrahydrofolate reductase (MTHFR) is essential for DNA biosynthesis and the epigenetic process of DNA methylation, and its gene polymorphisms have been implicated as risk factors for birth defects, neurological disorders, and cancers. However, reports on the association of MTHFR polymorphisms with autism spectrum disorders (ASD) are inconclusive. Therefore, we investigated the relationship of the MTHFR polymorphisms (C677T and A1298C) and the risk of ASD by meta-analysis. Up to December 2012, eight case-control studies involving 1672 patients with ASD and 6760 controls were included for meta-analysis. The results showed that the C677T polymorphism was associated with significantly increased ASD risk in all the comparison models [T vs. C allele (frequency of allele): odds ratio (OR) = 1.42, 95% confidence interval (CI): 1.09-1.85; CT vs. CC (heterozygote): OR = 1.48, 95% CI: 1.09-2.00; TT vs. CC (homozygote): OR = 1.86, 95% CI: 1.08-3.20; CT+TT vs. CC (dominant model): OR = 1.56, 95% CI: 1.12-2.18; and TT vs. CC+CT (recessive model): OR = 1.51, 95% CI: 1.02-2.22], whereas the A1298C polymorphism was found to be significantly associated with reduced ASD risk but only in a recessive model (CC vs. AA+AC: OR = 0.73, 95% CI: 0.56-0.97). In addition, we stratified the patient population based on whether they were from a country with food fortification of folic acid or not. The meta-analysis showed that the C677T polymorphism was found to be associated with ASD only in children from countries without food fortification. Our study indicated that the MTHFR C677T polymorphism contributes to increased ASD risk, and periconceptional folic acid may reduce ASD risk in those with MTHFR 677C>T polymorphism.

PMID: 23653228 [Indexed for MEDLINE]

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See all

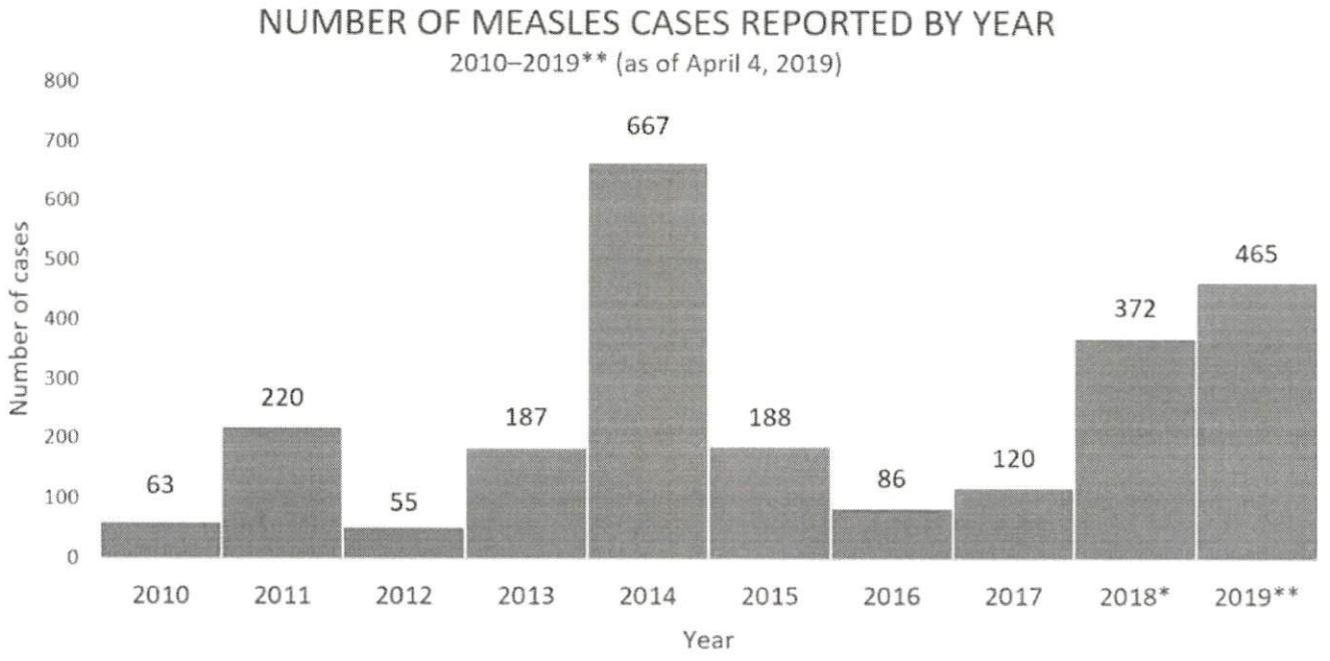
CDC Bar Graph below tracks measles outbreaks. https://www.cdc.gov/measles/cases-outbreaks.html

Cyclical. Small numbers of measles cases occur annually and are successfully contained every year.

Spikes. The CDC reports (link above) that the years with larger numbers had outbreaks in religious communities (e.g., Amish in 2014, Somali-Americans in 2017 and Orthodox Jews is 2018). These communities chose to be unvaccinated.

What happened with Disneyland? 147 cases of measles. Extremely successful containment even though kindergarten vaccination rates for MMR that year were below "herd immunity" guidelines (California's MMR rates were reported 92.6% the year of the outbreak). The case study shows outbreaks can be successfully contained even when "herd immunity" guidelines are not met.

How many deaths? Zero in all the years below. Measles is treatable in developed countries like the USA.



A "challenge" reported by the California Department of Public Health: "Two dose MMR recipients and IgG+ people can and did develop measles"

(https://www.hhs.gov/sites/default/files/nvpo/nvac/meetings/pastmeetings/2015/2014-2015_california_measles_outbreak.pdf)

Conflicts of Interest in Vaccine Policy Making
Majority Staff Report
Committee on Government Reform
U.S. House of Representatives
June 15, 2000

Section I
Introduction

In August 1999, the Committee on Government Reform initiated an investigation into Federal vaccine policy. Over the last six months, this investigation has focused on possible conflicts of interest on the part of Federal policy-makers. Committee staff has conducted an extensive review of financial disclosure forms and related documents, and interviewed key officials from the Department of Health and Human Services, including the Food and Drug Administration and the Centers for Disease Control and Prevention.

This staff report focuses on two influential advisory committees utilized by Federal regulators to provide expert advice on vaccine policy:
1. The FDA's Vaccines and Related Biological Products Advisory Committee (VRBPAC); and
2. The CDC's Advisory Committee on Immunizations Practices (ACIP).

The VRBPAC advises the FDA on the licensing of new vaccines, while the ACIP advises the CDC on guidelines to be issued to doctors and the states for the appropriate use of vaccines.

Members of the advisory committees are required to disclose any financial conflicts of interest and recuse themselves from participating in decisions in which they have an interest. The Committee's investigation has determined that conflict of interest rules employed by the FDA and the CDC have been weak, enforcement has been lax, and committee members with substantial ties to pharmaceutical companies have been given waivers to participate in committee proceedings. Among the specific problems identified in this staff report:

§ The CDC routinely grants waivers from conflict of interest rules to every member of its advisory committee.

§ CDC Advisory Committee members who are not allowed to vote on certain recommendations due to financial conflicts of interest are allowed to participate in committee deliberations and advocate specific positions.

§ The Chairman of the CDC's advisory committee until very recently owned 600 shares of stock in Merck, a pharmaceutical company with an active vaccine division.

§ Members of the CDC's advisory Committee often fill out incomplete financial disclosure statements, and are not required to provide the missing information by CDC ethics officials.

§ Four out of eight CDC advisory committee members who voted to approve guidelines for the rotavirus vaccine in June 1998 had financial ties to pharmaceutical companies that were developing different versions of the vaccine.

§ 3 out of 5 FDA advisory committee members who voted to approve the rotavirus vaccine in December 1997 had financial ties to pharmaceutical companies that were developing different versions of the vaccine.

A more complete discussion of specific conflict of interest problems identified by Government

Testimony by Margaret Sachsenmaier

M-M-R® II
(MEASLES, MUMPS, and RUBELLA VIRUS VACCINE LIVE)

DESCRIPTION

M-M-R® II (Measles, Mumps, and Rubella Virus Vac
against measles (rubeola), mumps, and rubella (German

M-M-R II is a sterile lyophilized preparation of (1) ATT
attenuated line of measles virus, derived from Enders'
chick embryo cell culture; (2) MUMPSVAX® (Mumps V
of mumps virus propagated in chick embryo cell cultu
Live), the Wistar RA 27/3 strain of live attenuated rub
fibroblasts.{1,2}

The growth medium for measles and mumps is Medium
vitamins and amino acids and supplemented with fetal bovine serum,
phosphate, glutamate, and recombinant human albumin) as stabilizer and neomycin.

The growth medium for rubella is Minimum Essential Medium (MEM) [a buffered salt solution containing vitamins and amino acids and supplemented with fetal bovine serum] containing recombinant human albumin and neomycin. Sorbitol and hydrolyzed gelatin stabilizer are added to the individual virus harvests.

The cells, virus pools, and fetal bovine serum are all screened for the absence of adventitious agents.

The reconstituted vaccine is for subcutaneous administration. Each 0.5 mL dose contains not less than 1,000 $TCID_{50}$ (tissue culture infectious doses) of measles virus; 12,500 $TCID_{50}$ of mumps virus; and 1,000 $TCID_{50}$ of rubella virus. Each dose of the vaccine is calculated to contain sorbitol (14.5 mg), sodium phosphate, sucrose (1.9 mg), sodium chloride, hydrolyzed gelatin (14.5 mg), recombinant human albumin (≤0.3 mg), fetal bovine serum (<1 ppm), other buffer and media ingredients and approximately 25 mcg of neomycin. The product contains no preservative.

Before reconstitution, the lyophilized vaccine is a light yellow compact crystalline plug. M-M-R II, when reconstituted as directed, is clear yellow.

CLINICAL PHARMACOLOGY

Measles, mumps, and rubella are three common childhood diseases, caused by measles virus, mumps virus (paramyxoviruses), and rubella virus (togavirus), respectively, that may be associated with serious complications and/or death. For example, pneumonia and encephalitis are caused by measles. Mumps is associated with aseptic meningitis, deafness and orchitis; and rubella during pregnancy may cause congenital rubella syndrome in the infants of infected mothers.

The impact of measles, mumps, and rubella vaccination on the natural history of each disease in the United States can be quantified by comparing the maximum number of measles, mumps, and rubella cases reported in a given year prior to vaccine use to the number of cases of each disease reported in 1995. For measles, 894,134 cases reported in 1941 compared to 288 cases reported in 1995 resulted in a 99.97% decrease in reported cases; for mumps, 152,209 cases reported in 1968 compared to 840 cases reported in 1995 resulted in a 99.45% decrease in reported cases; and for rubella, 57,686 cases reported in 1969 compared to 200 cases reported in 1995 resulted in a 99.65% decrease.{3}

Clinical studies of 284 triple seronegative children, 11 months to 7 years of age, demonstrated that M-M-R II is highly immunogenic and generally well tolerated. In these studies, a single injection of the vaccine induced measles hemagglutination-inhibition (HI) antibodies in 95%, mumps neutralizing antibodies in 96%, and rubella HI antibodies in 99% of susceptible persons. However, a small percentage (1-5%) of vaccinees may fail to seroconvert after the primary dose (see also INDICATIONS AND USAGE, *Recommended Vaccination Schedule*).

A study{4} of 6-month-old and 15-month-old infants born to vaccine-immunized mothers demonstrated that, following vaccination with ATTENUVAX, 74% of the 6-month-old infants developed detectable neutralizing antibody (NT) titers while 100% of the 15-month-old infants developed NT. This rate of seroconversion is higher than that previously reported for 6-month-old infants born to naturally immune mothers tested by HI assay. When the 6-month-old infants of immunized mothers were revaccinated at 15

months, they developed antibody titers equivalent to the 15-month-old vaccinees. The lower seroconversion rate in 6-month-olds has two possible explanations: 1) Due to the limit of the detection level of the assays (NT and enzyme immunoassay [EIA]), the presence of trace amounts of undetectable maternal antibody might interfere with the seroconversion of infants; or 2) The immune system of 6-month-olds is not always capable of mounting a response to measles vaccine as measured by the two antibody assays.

There is some evidence to suggest that infants who are born to mothers who had wild-type measles and who are vaccinated at less than one year of age may not develop sustained antibody levels when later revaccinated. The advantage of early protection must be weighed against the chance for failure to respond adequately on reimmunization.{5,6}

Efficacy of measles, mumps, and rubella vaccines was established in a series of double-blind controlled field trials which demonstrated a high degree of protective efficacy afforded by the individual vaccine components.{7-12} These studies also established that seroconversion in response to vaccination against measles, mumps, and rubella paralleled protection from these diseases.{13-15}

Following vaccination, antibodies associated with protection can be measured by neutralization assays, HI, or ELISA (enzyme linked immunosorbent assay) tests. Neutralizing and ELISA antibodies to measles, mumps, and rubella viruses are still detectable in most individuals 11 to 13 years after primary vaccination.{16-18} See INDICATIONS AND USAGE, *Non-Pregnant Adolescent and Adult Females*, for Rubella Susceptibility Testing.

The RA 27/3 rubella strain in M-M-R II elicits higher immediate post-vaccination HI, complement-fixing and neutralizing antibody levels than other strains of rubella vaccine{19-25} and has been shown to induce a broader profile of circulating antibodies including anti-theta and anti-iota precipitating antibodies.{26,27} The RA 27/3 rubella strain immunologically simulates natural infection more closely than other rubella vaccine viruses.{27-29} The increased levels and broader profile of antibodies produced by RA 27/3 strain rubella virus vaccine appear to correlate with greater resistance to subclinical reinfection with the wild virus,{27,29-31} and provide greater confidence for lasting immunity.

INDICATIONS AND USAGE

Recommended Vaccination Schedule

M-M-R II is indicated for simultaneous vaccination against measles, mumps, and rubella in individuals 12 months of age or older.

Individuals first vaccinated at 12 months of age or older should be revaccinated prior to elementary school entry. Revaccination is intended to seroconvert those who do not respond to the first dose. The Advisory Committee on Immunization Practices (ACIP) recommends administration of the first dose of M-M-R II at 12 to 15 months of age and administration of the second dose of M-M-R II at 4 to 6 years of age.{32} In addition, some public health jurisdictions mandate the age for revaccination. Consult the complete text of applicable guidelines regarding routine revaccination including that of high-risk adult populations.

Measles Outbreak Schedule

Infants Between 6 to 12 Months of Age

Local health authorities may recommend measles vaccination of infants between 6 to 12 months of age in outbreak situations. This population may fail to respond to the components of the vaccine. Safety and effectiveness of mumps and rubella vaccine in infants less than 12 months of age have not been established. The younger the infant, the lower the likelihood of seroconversion (see CLINICAL PHARMACOLOGY). Such infants should receive a second dose of M-M-R II between 12 to 15 months of age followed by revaccination at elementary school entry.{32}

Unnecessary doses of a vaccine are best avoided by ensuring that written documentation of vaccination is preserved and a copy given to each vaccinee's parent or guardian.

Other Vaccination Considerations

Non-Pregnant Adolescent and Adult Females

Immunization of susceptible non-pregnant adolescent and adult females of childbearing age with live attenuated rubella virus vaccine is indicated if certain precautions are observed (see below and PRECAUTIONS). Vaccinating susceptible postpubertal females confers individual protection against subsequently acquiring rubella infection during pregnancy, which in turn prevents infection of the fetus and consequent congenital rubella injury.{33}

Women of childbearing age should be advised not to become pregnant for 3 months after vaccination and should be informed of the reasons for this precaution.

The ACIP has stated "If it is practical and if reliable laboratory services are available, women of childbearing age who are potential candidates for vaccination can have serologic tests to determine susceptibility to rubella. However, with the exception of premarital and prenatal screening, routinely performing serologic tests for all women of childbearing age to determine susceptibility (so that vaccine is given only to proven susceptible women) can be effective but is expensive. Also, 2 visits to the health-care provider would be necessary — one for screening and one for vaccination. Accordingly, rubella vaccination of a woman who is not known to be pregnant and has no history of vaccination is justifiable without serologic testing — and may be preferable, particularly when costs of serology are high and follow-up of identified susceptible women for vaccination is not assured."{33}

Postpubertal females should be informed of the frequent occurrence of generally self-limited arthralgia and/or arthritis beginning 2 to 4 weeks after vaccination (see ADVERSE REACTIONS).

Postpartum Women

It has been found convenient in many instances to vaccinate rubella-susceptible women in the immediate postpartum period (see PRECAUTIONS, *Nursing Mothers*).

Other Populations

Previously unvaccinated children older than 12 months who are in contact with susceptible pregnant women should receive live attenuated rubella vaccine (such as that contained in monovalent rubella vaccine or in M-M-R II) to reduce the risk of exposure of the pregnant woman.

Individuals planning travel outside the United States, if not immune, can acquire measles, mumps, or rubella and import these diseases into the United States. Therefore, prior to international travel, individuals known to be susceptible to one or more of these diseases can either receive the indicated monovalent vaccine (measles, mumps, or rubella), or a combination vaccine as appropriate. However, M-M-R II is preferred for persons likely to be susceptible to mumps and rubella; and if monovalent measles vaccine is not readily available, travelers should receive M-M-R II regardless of their immune status to mumps or rubella.{34-36}

Vaccination is recommended for susceptible individuals in high-risk groups such as college students, health-care workers, and military personnel.{33,34,37}

According to ACIP recommendations, most persons born in 1956 or earlier are likely to have been infected with measles naturally and generally need not be considered susceptible. All children, adolescents, and adults born after 1956 are considered susceptible and should be vaccinated, if there are no contraindications. This includes persons who may be immune to measles but who lack adequate documentation of immunity such as: (1) physician-diagnosed measles, (2) laboratory evidence of measles immunity, or (3) adequate immunization with live measles vaccine on or after the first birthday.{34}

The ACIP recommends that "Persons vaccinated with inactivated vaccine followed within 3 months by live vaccine should be revaccinated with two doses of live vaccine. Revaccination is particularly important when the risk of exposure to wild-type measles virus is increased, as may occur during international travel."{34}

Post-Exposure Vaccination

Vaccination of individuals exposed to wild-type measles may provide some protection if the vaccine can be administered within 72 hours of exposure. If, however, vaccine is given a few days before exposure, substantial protection may be afforded.{34,38,39} There is no conclusive evidence that vaccination of individuals recently exposed to wild-type mumps or wild-type rubella will provide protection.{33,37}

Use With Other Vaccines

See DOSAGE AND ADMINISTRATION, *Use With Other Vaccines*.

CONTRAINDICATIONS

Hypersensitivity to any component of the vaccine, including gelatin.{40}

Do not give M-M-R II to pregnant females; the possible effects of the vaccine on fetal development are unknown at this time. If vaccination of postpubertal females is undertaken, pregnancy should be avoided for three months following vaccination (see INDICATIONS AND USAGE, *Non-Pregnant Adolescent and Adult Females* and PRECAUTIONS, *Pregnancy*).

Anaphylactic or anaphylactoid reactions to neomycin (each dose of reconstituted vaccine contains approximately 25 mcg of neomycin).

Febrile respiratory illness or other active febrile infection. However, the ACIP has recommended that all vaccines can be administered to persons with minor illnesses such as diarrhea, mild upper respiratory infection with or without low-grade fever, or other low-grade febrile illness.{41}

Patients receiving immunosuppressive therapy. This contraindication does not apply to patients who are receiving corticosteroids as replacement therapy, e.g., for Addison's disease.

Individuals with blood dyscrasias, leukemia, lymphomas of any type, or other malignant neoplasms affecting the bone marrow or lymphatic systems.

Primary and acquired immunodeficiency states, including patients who are immunosuppressed in association with AIDS or other clinical manifestations of infection with human immunodeficiency viruses;{41-43} cellular immune deficiencies; and hypogammaglobulinemic and dysgammaglobulinemic states. Measles inclusion body encephalitis{44} (MIBE), pneumonitis{45} and death as a direct consequence of disseminated measles vaccine virus infection have been reported in immunocompromised individuals inadvertently vaccinated with measles-containing vaccine.

Individuals with a family history of congenital or hereditary immunodeficiency, until the immune competence of the potential vaccine recipient is demonstrated.

WARNINGS

Due caution should be employed in administration of M-M-R II to persons with a history of cerebral injury, individual or family histories of convulsions, or any other condition in which stress due to fever should be avoided. The physician should be alert to the temperature elevation which may occur following vaccination (see ADVERSE REACTIONS).

Hypersensitivity to Eggs

Live measles vaccine and live mumps vaccine are produced in chick embryo cell culture. Persons with a history of anaphylactic, anaphylactoid, or other immediate reactions (e.g., hives, swelling of the mouth and throat, difficulty breathing, hypotension, or shock) subsequent to egg ingestion may be at an enhanced risk of immediate-type hypersensitivity reactions after receiving vaccines containing traces of chick embryo antigen. The potential risk to benefit ratio should be carefully evaluated before considering vaccination in such cases. Such individuals may be vaccinated with extreme caution, having adequate treatment on hand should a reaction occur (see PRECAUTIONS).{46}

However, the AAP has stated, "Most children with a history of anaphylactic reactions to eggs have no untoward reactions to measles or MMR vaccine. Persons are not at increased risk if they have egg allergies that are not anaphylactic, and they should be vaccinated in the usual manner. In addition, skin testing of egg-allergic children with vaccine has not been predictive of which children will have an immediate hypersensitivity reaction...Persons with allergies to chickens or chicken feathers are not at increased risk of reaction to the vaccine."{47}

Hypersensitivity to Neomycin

The AAP states, "Persons who have experienced anaphylactic reactions to topically or systemically administered neomycin should not receive measles vaccine. Most often, however, neomycin allergy manifests as a contact dermatitis, which is a delayed-type (cell-mediated) immune response rather than anaphylaxis. In such persons, an adverse reaction to neomycin in the vaccine would be an erythematous, pruritic nodule or papule, 48 to 96 hours after vaccination. A history of contact dermatitis to neomycin is not a contraindication to receiving measles vaccine."{47}

Thrombocytopenia

Individuals with current thrombocytopenia may develop more severe thrombocytopenia following vaccination. In addition, individuals who experienced thrombocytopenia with the first dose of M-M-R II (or its component vaccines) may develop thrombocytopenia with repeat doses. Serologic status may be evaluated to determine whether or not additional doses of vaccine are needed. The potential risk to benefit ratio should be carefully evaluated before considering vaccination in such cases (see ADVERSE REACTIONS).

PRECAUTIONS

General

Adequate treatment provisions, including epinephrine injection (1:1000), should be available for immediate use should an anaphylactic or anaphylactoid reaction occur.

Special care should be taken to ensure that the injection does not enter a blood vessel.

Children and young adults who are known to be infected with human immunodeficiency viruses and are not immunosuppressed may be vaccinated. However, vaccinees who are infected with HIV should be monitored closely for vaccine-preventable diseases because immunization may be less effective than for uninfected persons (see CONTRAINDICATIONS).{42,43}

Vaccination should be deferred for 3 months or longer following blood or plasma transfusions, or administration of immune globulin (human).{47}

Excretion of small amounts of the live attenuated rubella virus from the nose or throat has occurred in the majority of susceptible individuals 7 to 28 days after vaccination. There is no confirmed evidence to indicate that such virus is transmitted to susceptible persons who are in contact with the vaccinated individuals. Consequently, transmission through close personal contact, while accepted as a theoretical possibility, is not regarded as a significant risk.{33} However, transmission of the rubella vaccine virus to infants via breast milk has been documented (see *Nursing Mothers*).

There are no reports of transmission of live attenuated measles or mumps viruses from vaccinees to susceptible contacts.

It has been reported that live attenuated measles, mumps and rubella virus vaccines given individually may result in a temporary depression of tuberculin skin sensitivity. Therefore, if a tuberculin test is to be done, it should be administered either before or simultaneously with M-M-R II.

Children under treatment for tuberculosis have not experienced exacerbation of the disease when immunized with live measles virus vaccine;{48} no studies have been reported to date of the effect of measles virus vaccines on untreated tuberculous children. However, individuals with active untreated tuberculosis should not be vaccinated.

As for any vaccine, vaccination with M-M-R II may not result in protection in 100% of vaccinees.

The health-care provider should determine the current health status and previous vaccination history of the vaccinee.

The health-care provider should question the patient, parent, or guardian about reactions to a previous dose of M-M-R II or other measles-, mumps-, or rubella-containing vaccines.

Information for Patients

The health-care provider should provide the vaccine information required to be given with each vaccination to the patient, parent, or guardian.

The health-care provider should inform the patient, parent, or guardian of the benefits and risks associated with vaccination. For risks associated with vaccination see WARNINGS, PRECAUTIONS, and ADVERSE REACTIONS.

Patients, parents, or guardians should be instructed to report any serious adverse reactions to their health-care provider who in turn should report such events to the U.S. Department of Health and Human Services through the Vaccine Adverse Event Reporting System (VAERS), 1-800-822-7967.{49}

Pregnancy should be avoided for 3 months following vaccination, and patients should be informed of the reasons for this precaution (see INDICATIONS AND USAGE, *Non-Pregnant Adolescent and Adult Females*, CONTRAINDICATIONS, and PRECAUTIONS, *Pregnancy*).

Laboratory Tests

See INDICATIONS AND USAGE, *Non-Pregnant Adolescent and Adult Females*, for Rubella Susceptibility Testing, and CLINICAL PHARMACOLOGY.

Drug Interactions

See DOSAGE AND ADMINISTRATION, *Use With Other Vaccines*.

Immunosuppressive Therapy

The immune status of patients about to undergo immunosuppressive therapy should be evaluated so that the physician can consider whether vaccination prior to the initiation of treatment is indicated (see CONTRAINDICATIONS and PRECAUTIONS).

The ACIP has stated that "patients with leukemia in remission who have not received chemotherapy for at least 3 months may receive live virus vaccines. Short-term (<2 weeks), low- to moderate-dose systemic corticosteroid therapy, topical steroid therapy (e.g. nasal, skin), long-term alternate-day treatment with low to moderate doses of short-acting systemic steroid, and intra-articular, bursal, or tendon injection of corticosteroids are not immunosuppressive in their usual doses and do not contraindicate the administration of [measles, mumps, or rubella vaccine]."{33,34,37}

Immune Globulin

Administration of immune globulins concurrently with M-M-R II may interfere with the expected immune response.{33,34,47}

See also PRECAUTIONS, *General*.

Carcinogenesis, Mutagenesis, Impairment of Fertility

M-M-R II has not been evaluated for carcinogenic or mutagenic potential, or potential to impair fertility.

Pregnancy

Animal reproduction studies have not been conducted with M-M-R II. It is also not known whether M-M-R II can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity. Therefore, the vaccine should not be administered to pregnant females; furthermore, pregnancy should be avoided for 3 months following vaccination (see INDICATIONS AND USAGE, *Non-Pregnant Adolescent and Adult Females* and CONTRAINDICATIONS).

In counseling women who are inadvertently vaccinated when pregnant or who become pregnant within 3 months of vaccination, the physician should be aware of the following: (1) In a 10-year survey involving over 700 pregnant women who received rubella vaccine within 3 months before or after conception (of whom 189 received the Wistar RA 27/3 strain), none of the newborns had abnormalities compatible with congenital rubella syndrome;{50} (2) Mumps infection during the first trimester of pregnancy may increase the rate of spontaneous abortion. Although mumps vaccine virus has been shown to infect the placenta and fetus, there is no evidence that it causes congenital malformations in humans;{37} and (3) Reports have indicated that contracting wild-type measles during pregnancy enhances fetal risk. Increased rates of spontaneous abortion, stillbirth, congenital defects and prematurity have been observed subsequent to infection with wild-type measles during pregnancy.{51,52} There are no adequate studies of the attenuated (vaccine) strain of measles virus in pregnancy. However, it would be prudent to assume that the vaccine strain of virus is also capable of inducing adverse fetal effects.

Nursing Mothers

It is not known whether measles or mumps vaccine virus is secreted in human milk. Recent studies have shown that lactating postpartum women immunized with live attenuated rubella vaccine may secrete the virus in breast milk and transmit it to breast-fed infants.{53} In the infants with serological evidence of rubella infection, none exhibited severe disease; however, one exhibited mild clinical illness typical of acquired rubella.{54,55} Caution should be exercised when M-M-R II is administered to a nursing woman.

Pediatric Use

Safety and effectiveness of measles vaccine in infants below the age of 6 months have not been established (see also CLINICAL PHARMACOLOGY). Safety and effectiveness of mumps and rubella vaccine in infants less than 12 months of age have not been established.

Geriatric Use

Clinical studies of M-M-R II did not include sufficient numbers of seronegative subjects aged 65 and over to determine whether they respond differently from younger subjects. Other reported clinical experience has not identified differences in responses between the elderly and younger subjects.

ADVERSE REACTIONS

The following adverse reactions are listed in decreasing order of severity, without regard to causality, within each body system category and have been reported during clinical trials, with use of the marketed vaccine, or with use of monovalent or bivalent vaccine containing measles, mumps, or rubella:

Body as a Whole

Panniculitis; atypical measles; fever; syncope; headache; dizziness; malaise; irritability.

Cardiovascular System

Vasculitis.

Digestive System

Pancreatitis; diarrhea; vomiting; parotitis; nausea.

Endocrine System

Diabetes mellitus.

Hemic and Lymphatic System

Thrombocytopenia (see WARNINGS, *Thrombocytopenia*); purpura; regional lymphadenopathy; leukocytosis.

Immune System

Anaphylaxis and anaphylactoid reactions have been reported as well as related phenomena such as angioneurotic edema (including peripheral or facial edema) and bronchial spasm in individuals with or without an allergic history.

Musculoskeletal System

Arthritis; arthralgia; myalgia.

Arthralgia and/or arthritis (usually transient and rarely chronic), and polyneuritis are features of infection with wild-type rubella and vary in frequency and severity with age and sex, being greatest in adult females and least in prepubertal children. This type of involvement as well as myalgia and paresthesia, have also been reported following administration of MERUVAX II.

Chronic arthritis has been associated with wild-type rubella infection and has been related to persistent virus and/or viral antigen isolated from body tissues. Only rarely have vaccine recipients developed chronic joint symptoms.

Following vaccination in children, reactions in joints are uncommon and generally of brief duration. In women, incidence rates for arthritis and arthralgia are generally higher than those seen in children (children: 0-3%; women: 12-26%),{17,56,57} and the reactions tend to be more marked and of longer duration. Symptoms may persist for a matter of months or on rare occasions for years. In adolescent girls, the reactions appear to be intermediate in incidence between those seen in children and in adult women. Even in women older than 35 years, these reactions are generally well tolerated and rarely interfere with normal activities.

Nervous System

Encephalitis; encephalopathy; measles inclusion body encephalitis (MIBE) (see CONTRAINDICATIONS); subacute sclerosing panencephalitis (SSPE); Guillain-Barré Syndrome (GBS); acute disseminated encephalomyelitis (ADEM); transverse myelitis; febrile convulsions; afebrile convulsions or seizures; ataxia; polyneuritis; polyneuropathy; ocular palsies; paresthesia.

Encephalitis and encephalopathy have been reported approximately once for every 3 million doses of M-M-R II or measles-, mumps-, and rubella-containing vaccine administered since licensure of these vaccines.

The risk of serious neurological disorders following live measles virus vaccine administration remains less than the risk of encephalitis and encephalopathy following infection with wild-type measles (1 per 1000 reported cases).{58,59}

In severely immunocompromised individuals who have been inadvertently vaccinated with measles-containing vaccine; measles inclusion body encephalitis, pneumonitis, and fatal outcome as a direct consequence of disseminated measles vaccine virus infection have been reported (see CONTRAINDICATIONS). In this population, disseminated mumps and rubella vaccine virus infection have also been reported.

There have been reports of subacute sclerosing panencephalitis (SSPE) in children who did not have a history of infection with wild-type measles but did receive measles vaccine. Some of these cases may have resulted from unrecognized measles in the first year of life or possibly from the measles vaccination. Based on estimated nationwide measles vaccine distribution, the association of SSPE cases to measles vaccination is about one case per million vaccine doses distributed. This is far less than the association with infection with wild-type measles, 6-22 cases of SSPE per million cases of measles. The results of a retrospective case-controlled study conducted by the Centers for Disease Control and Prevention suggest that the overall effect of measles vaccine has been to protect against SSPE by preventing measles with its inherent higher risk of SSPE.{60}

Cases of aseptic meningitis have been reported to VAERS following measles, mumps, and rubella vaccination. Although a causal relationship between the Urabe strain of mumps vaccine and aseptic meningitis has been shown, there is no evidence to link Jeryl Lynn™ mumps vaccine to aseptic meningitis.

Respiratory System

Pneumonia; pneumonitis (see CONTRAINDICATIONS); sore throat; cough; rhinitis.

Skin

Stevens-Johnson syndrome; erythema multiforme; urticaria; rash; measles-like rash; pruritis.

Local reactions including burning/stinging at injection site; wheal and flare; redness (erythema); swelling; induration; tenderness; vesiculation at injection site; Henoch-Schönlein purpura; acute hemorrhagic edema of infancy.

Special Senses — Ear

Nerve deafness; otitis media.

Special Senses — Eye

Retinitis; optic neuritis; papillitis; retrobulbar neuritis; conjunctivitis.

Urogenital System

Epididymitis; orchitis.

Other

Death from various, and in some cases unknown, causes has been reported rarely following vaccination with measles, mumps, and rubella vaccines; however, a causal relationship has not been established in healthy individuals (see CONTRAINDICATIONS). No deaths or permanent sequelae were reported in a published post-marketing surveillance study in Finland involving 1.5 million children and adults who were vaccinated with M-M-R II during 1982 to 1993.{61}

Under the National Childhood Vaccine Injury Act of 1986, health-care providers and manufacturers are required to record and report certain suspected adverse events occurring within specific time periods after vaccination. However, the U.S. Department of Health and Human Services (DHHS) has established a Vaccine Adverse Event Reporting System (VAERS) which will accept all reports of suspected events.{49} A VAERS report form as well as information regarding reporting requirements can be obtained by calling VAERS 1-800-822-7967.

DOSAGE AND ADMINISTRATION

FOR SUBCUTANEOUS ADMINISTRATION

Do not inject intravascularly.

The dose for any age is 0.5 mL administered subcutaneously, preferably into the outer aspect of the upper arm.

The recommended age for primary vaccination is 12 to 15 months.

Revaccination with M-M-R II is recommended prior to elementary school entry. See also INDICATIONS AND USAGE, *Recommended Vaccination Schedule*.

Children first vaccinated when younger than 12 months of age should receive another dose between 12 to 15 months of age followed by revaccination prior to elementary school entry.{32} See also INDICATIONS AND USAGE, *Measles Outbreak Schedule*.

Immune Globulin (IG) is not to be given concurrently with M-M-R II (see PRECAUTIONS, *General* and PRECAUTIONS, *Drug Interactions*).

CAUTION: A sterile syringe free of preservatives, antiseptics, and detergents should be used for each injection and/or reconstitution of the vaccine because these substances may inactivate the live virus vaccine. A 25 gauge, 5/8" needle is recommended.

To reconstitute, use only the diluent supplied, since it is free of preservatives or other antiviral substances which might inactivate the vaccine.

Single Dose Vial — First withdraw the entire volume of diluent into the syringe to be used for reconstitution. Inject all the diluent in the syringe into the vial of lyophilized vaccine, and agitate to mix thoroughly. If the lyophilized vaccine cannot be dissolved, discard. Withdraw the entire contents into a syringe and inject the total volume of restored vaccine subcutaneously.

It is important to use a separate sterile syringe and needle for each individual patient to prevent transmission of hepatitis B and other infectious agents from one person to another.

Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration whenever solution and container permit. M-M-R II, when reconstituted, is clear yellow.

Use With Other Vaccines

M-M-R II should be given one month before or after administration of other live viral vaccines.

M-M-R II has been administered concurrently with VARIVAX® [Varicella Virus Vaccine Live (Oka/Merck)], and PedvaxHIB® [*Haemophilus b* Conjugate Vaccine (Meningococcal Protein Conjugate)] using separate injection sites and syringes. No impairment of immune response to individually tested vaccine antigens was demonstrated. The type, frequency, and severity of adverse experiences observed with M-M-R II were similar to those seen when each vaccine was given alone.

Routine administration of DTP (diphtheria, tetanus, pertussis) and/or OPV (oral poliovirus vaccine) concurrently with measles, mumps and rubella vaccines is not recommended because there are limited data relating to the simultaneous administration of these antigens.

However, other schedules have been used. The ACIP has stated "Although data are limited concerning the simultaneous administration of the entire recommended vaccine series (i.e., DTaP [or DTwP], IPV [or OPV], Hib with or without Hepatitis B vaccine, and varicella vaccine), data from numerous studies have

indicated no interference between routinely recommended childhood vaccines (either live, attenuated, or killed). These findings support the simultaneous use of all vaccines as recommended."{62}

HOW SUPPLIED

No. 4681 — M-M-R II is supplied as follows: (1) a box of 10 single-dose vials of lyophilized vaccine (package A), **NDC** 0006-4681-00; and (2) a box of 10 vials of diluent (package B). To conserve refrigerator space, the diluent may be stored separately at room temperature.

Storage

To maintain potency, M-M-R II must be stored between -58°F and +46°F (-50°C to +8°C). Use of dry ice may subject M-M-R II to temperatures colder than -58°F (-50°C).

Protect the vaccine from light at all times, since such exposure may inactivate the viruses.

Before reconstitution, store the lyophilized vaccine at 36°F to 46°F (2°C to 8°C). The diluent may be stored in the refrigerator with the lyophilized vaccine or separately at room temperature. **Do not freeze the diluent.**

It is recommended that the vaccine be used as soon as possible after reconstitution. Store reconstituted vaccine in the vaccine vial in a dark place at 36°F to 46°F (2°C to 8°C) and discard if not used within 8 hours.

For information regarding stability under conditions other than those recommended, call 1-800-MERCK-90.

REFERENCES

1. Plotkin, S.A.; Cornfeld, D.; Ingalls, T.H.: Studies of immunization with living rubella virus: Trials in children with a strain cultured from an aborted fetus, Am. J. Dis. Child. *110:* 381-389, 1965.
2. Plotkin, S.A.; Farquhar, J.; Katz, M.; Ingalls, T.H.: A new attenuated rubella virus grown in human fibroblasts: Evidence for reduced nasopharyngeal excretion, Am. J. Epidemiol. *86:* 468-477, 1967.
3. Monthly Immunization Table, MMWR *45*(1): 24-25, January 12, 1996.
4. Johnson, C.E.; et al: Measles Vaccine Immunogenicity in 6- Versus 15-Month-Old Infants Born to Mothers in the Measles Vaccine Era, Pediatrics, *93*(6): 939-943, 1994.
5. Linneman, C.C.; et al: Measles Immunity After Vaccination: Results in Children Vaccinated Before 10 Months of Age, Pediatrics, *69*(3): 332-335, March 1982.
6. Stetler, H.C.; et al: Impact of Revaccinating Children Who Initially Received Measles Vaccine Before 10 Months of Age, Pediatrics *77*(4): 471-476, April 1986.
7. Hilleman, M.R.; Buynak, E.B.; Weibel, R.E.; et al: Development and Evaluation of the Moraten Measles Virus Vaccine, JAMA *206*(3): 587-590, 1968.
8. Weibel, R.E.; Stokes, J.; Buynak, E.B.; et al: Live, Attenuated Mumps Virus Vaccine 3. Clinical and Serologic Aspects in a Field Evaluation, N. Engl. J. Med. *276:* 245-251, 1967.
9. Hilleman, M.R.; Weibel, R.E.; Buynak, E.B.; et al: Live, Attenuated Mumps Virus Vaccine 4. Protective Efficacy as Measured in a Field Evaluation, N. Engl. J. Med. *276:* 252-258, 1967.
10. Cutts, F.T.; Henderson, R.H.; Clements, C.J.; et al: Principles of measles control, Bull WHO *69*(1): 1-7, 1991.
11. Weibel, R.E.; Buynak, E.B.; Stokes, J.; et al: Evaluation Of Live Attenuated Mumps Virus Vaccine, Strain Jeryl Lynn, First International Conference on Vaccines Against Viral and Rickettsial Diseases of Man, World Health Organization, No. 147, May 1967.
12. Leibhaber, H.; Ingalls, T.H.; LeBouvier, G.L.; et al: Vaccination With RA 27/3 Rubella Vaccine, Am. J. Dis. Child. *123:* 133-136, February 1972.
13. Rosen, L.: Hemagglutination and Hemagglutination-Inhibition with Measles Virus, Virology *13:* 139-141, January 1961.
14. Brown, G.C.; et al: Fluorescent-Antibody Marker for Vaccine-Induced Rubella Antibodies, Infection and Immunity *2*(4): 360-363, 1970.
15. Buynak, E.B.; et al: Live Attenuated Mumps Virus Vaccine 1. Vaccine Development, Proceedings of the Society for Experimental Biology and Medicine, *123:* 768-775, 1966.
16. Weibel, R.E.; Carlson, A.J.; Villarejos, V.M.; Buynak, E.B.; McLean, A.A.; Hilleman, M.R.: Clinical and Laboratory Studies of Combined Live Measles, Mumps, and Rubella Vaccines Using the RA 27/3 Rubella Virus, Proc. Soc. Exp. Biol. Med. *165:* 323-326, 1980.

17. Unpublished data from the files of Merck Research Laboratories.

18. Watson, J.C.; Pearson, J.S.; Erdman, D.D.; et al: An Evaluation of Measles Revaccination Among School-Entry Age Children, 31st Interscience Conference on Antimicrobial Agents and Chemotherapy, Abstract #268, 143, 1991.

19. Fogel, A.; Moshkowitz, A.; Rannon, L.; Gerichter, Ch.B.: Comparative trials of RA 27/3 and Cendehill rubella vaccines in adult and adolescent females, Am. J. Epidemiol. *93:* 392-393, 1971.

20. Andzhaparidze, O.G.; Desyatskova, R.G.; Chervonski, G.I.; Pryanichnikova, L.V.: Immunogenicity and reactogenicity of live attenuated rubella virus vaccines, Am. J. Epidemiol. *91:* 527-530, 1970.

21. Freestone, D.S.; Reynolds, G.M.; McKinnon, J.A.; Prydie, J.: Vaccination of schoolgirls against rubella. Assessment of serological status and a comparative trial of Wistar RA 27/3 and Cendehill strain live attenuated rubella vaccines in 13-year-old schoolgirls in Dudley, Br. J. Prev. Soc. Med. *29:* 258-261, 1975.

22. Grillner, L.; Hedstrom, C.E.; Bergstrom, H.; Forssman, L.; Rigner, A.; Lycke, E.: Vaccination against rubella of newly delivered women, Scand. J. Infect. Dis. *5:* 237-241, 1973.

23. Grillner, L.: Neutralizing antibodies after rubella vaccination of newly delivered women: a comparison between three vaccines, Scand. J. Infect. Dis. *7:* 169-172, 1975.

24. Wallace, R.B.; Isacson, P.: Comparative trial of HPV-77, DE-5 and RA 27/3 live-attenuated rubella vaccines, Am. J. Dis. Child. *124:* 536-538, 1972.

25. Lalla, M.; Vesikari, T.; Virolainen, M.: Lymphoblast proliferation and humoral antibody response after rubella vaccination, Clin. Exp. Immunol. *15:* 193-202, 1973.

26. LeBouvier, G.L.; Plotkin, S.A.: Precipitin responses to rubella vaccine RA 27/3, J. Infect. Dis. *123:* 220-223, 1971.

27. Horstmann, D.M.: Rubella: The challenge of its control, J. Infect. Dis. *123:* 640-654, 1971.

28. Ogra, P.L.; Kerr-Grant, D.; Umana, G.; Dzierba, J.; Weintraub, D.: Antibody response in serum and nasopharynx after naturally acquired and vaccine-induced infection with rubella virus, N. Engl. J. Med. *285:* 1333-1339, 1971.

29. Plotkin, S.A.; Farquhar, J.D.; Ogra, P.L.: Immunologic properties of RA 27/3 rubella virus vaccine, J. Am. Med. Assoc. *225:* 585-590, 1973.

30. Liebhaber, H.; Ingalls, T.H.; LeBouvier, G.L.; Horstmann, D.M.: Vaccination with RA 27/3 rubella vaccine. Persistence of immunity and resistance to challenge after two years, Am. J. Dis. Child. *123:* 133-136, 1972.

31. Farquhar, J.D.: Follow-up on rubella vaccinations and experience with subclinical reinfection, J. Pediatr. *81:* 460-465, 1972.

32. Measles, Mumps, and Rubella — Vaccine Use and Strategies for Elimination of Measles, Rubella, and Congenital Rubella Syndrome and Control of Mumps: Recommendations of the Advisory Committee on Immunization Practices (ACIP), MMWR *47*(RR-8): May 22, 1998.

33. Rubella Prevention: Recommendation of the Immunization Practices Advisory Committee (ACIP), MMWR *39*(RR-15): 1-18, November 23, 1990.

34. Measles Prevention: Recommendations of the Immunization Practices Advisory Committee (ACIP), MMWR *38*(S-9): 5-22, December 29, 1989.

35. Jong, E.C., The Travel and Tropical Medicine Manual, W.B. Saunders Company, p. 12-16, 1987.

36. Committee on Immunization Council of Medical Societies, American College of Physicians, Phila., PA, Guide for Adult Immunization, First Edition, 1985.

37. Recommendations of the Immunization Practices Advisory Committee (ACIP), Mumps Prevention, MMWR *38*(22): 388-400, June 9, 1989.

38. King, G.E.; Markowitz, L.E.; Patriarca, P.A.; et al: Clinical Efficacy of Measles Vaccine During the 1990 Measles Epidemic, Pediatr. Infect. Dis. J. *10*(12): 883-888, December 1991.

39. Krasinski, K.; Borkowsky, W.: Measles and Measles Immunity in Children Infected With Human Immunodeficiency Virus, JAMA *261*(17): 2512-2516, 1989.

40. Kelso, J.M.; Jones, R.T.; Yunginger, J.W.: Anaphylaxis to measles, mumps, and rubella vaccine mediated by IgE to gelatin, J. Allergy Clin. Immunol. *91:* 867-872, 1993.

41. General Recommendations on Immunization, Recommendations of the Advisory Committee on Immunization Practices, MMWR *43*(RR-1): 1-38, January 28, 1994.

42. Center for Disease Control: Immunization of Children Infected with Human T-Lymphotropic Virus Type III/Lymphadenopathy-Associated Virus, Annals of Internal Medicine, *106:* 75-78, 1987.

43. Krasinski, K.; Borkowsky, W.; Krugman, S.: Antibody following measles immunization in children infected with human T-cell lymphotropic virus-type III/lymphadenopathy associated virus (HTLV-III/LAV) [Abstract]. In: Program and abstracts of the International Conference on Acquired Immunodeficiency Syndrome, Paris, France, June 23-25, 1986.

44. Bitnum, A.; et al: Measles Inclusion Body Encephalitis Caused by the Vaccine Strain of Measles Virus. Clin. Infect. Dis. *29:* 855-861, 1999.

45. Angel, J.B.; et al: Vaccine Associated Measles Pneumonitis in an Adult with AIDS. Annals of Internal Medicine, *129:* 104-106, 1998.

46. Isaacs, D.; Menser, M.: Modern Vaccines, Measles, Mumps, Rubella, and Varicella, Lancet *335:* 1384-1387, June 9, 1990.

47. Peter, G.; et al (eds): Report of the Committee on Infectious Diseases, Twenty-fourth Edition, American Academy of Pediatrics, 344-357, 1997.

48. Starr, S.; Berkovich, S.: The effect of measles, gamma globulin modified measles, and attenuated measles vaccine on the course of treated tuberculosis in children, Pediatrics *35:* 97-102, January 1965.

49. Vaccine Adverse Event Reporting System — United States, MMWR *39*(41): 730-733, October 19, 1990.

50. Rubella vaccination during pregnancy — United States, 1971-1981. MMWR *31*(35): 477-481, September 10, 1982.

51. Eberhart-Phillips, J.E.; et al: Measles in pregnancy: a descriptive study of 58 cases. Obstetrics and Gynecology, *82*(5): 797-801, November 1993.

52. Jespersen, C.S.; et al: Measles as a cause of fetal defects: A retrospective study of ten measles epidemics in Greenland. Acta Paediatr Scand. *66:* 367-372, May 1977.

53. Losonsky, G.A.; Fishaut, J.M.; Strussenber, J.; Ogra, P.L.: Effect of immunization against rubella on lactation products. II. Maternal-neonatal interactions, J. Infect. Dis. *145:* 661-666, 1982.

54. Landes, R.D.; Bass, J.W.; Millunchick, E.W.; Oetgen, W.J.: Neonatal rubella following postpartum maternal immunization, J. Pediatr. *97:* 465-467, 1980.

55. Lerman, S.J.: Neonatal rubella following postpartum maternal immunization, J. Pediatr. *98:* 668, 1981. (Letter)

56. Gershon, A.; et al: Live attenuated rubella virus vaccine: comparison of responses to HPV-77-DE5 and RA 27/3 strains, Am. J. Med. Sci. *279*(2): 95-97, 1980.

57. Weibel, R.E.; et al: Clinical and laboratory studies of live attenuated RA 27/3 and HPV-77-DE rubella virus vaccines, Proc. Soc. Exp. Biol. Med. *165:* 44-49, 1980.

58. Bennetto, L; Scolding, N. Inflammatory/post-infectious encephalomyelitis. J Neurol Neurosurg Psychiatry 2004;75(Suppl 1):i22-8.

59. Fenichel, GM. Neurological complications of immunization. AnnNeurol 1982;12(2):119-28.

60. CDC, Measles Surveillance, Report No. 11, p. 14, September 1982.

61. Peltola, H.; et al: The elimination of indigenous measles, mumps, and rubella from Finland by a 12-year, two dose vaccination program. N. Engl. J. Med. *331:* 1397-1402, 1994.

62. Centers for Disease Control and Prevention. Recommended childhood immunization schedule — United States, January-June 1996, MMWR *44*(51 & 52): 940-943, January 5, 1996.

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- Colorado reportable disease data.

Measles cases in Colorado, 2014-2018	
2014	1
2015	1
2016	2
2017	0
2018	0
2019	1*

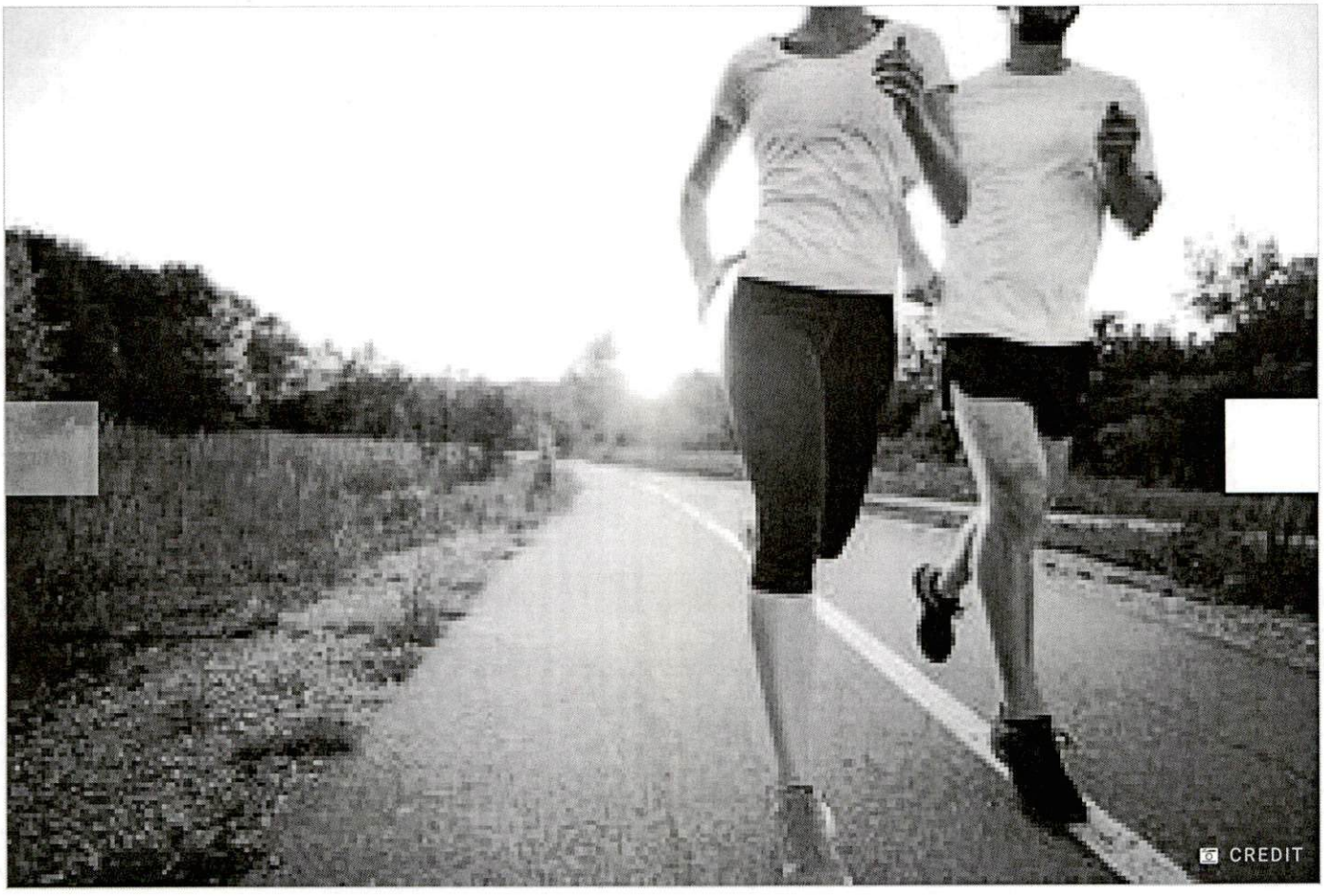
*As of Feb.27, 2018

U.S.News & WORLD REPORT CIVIC

10 Healthiest States in the U.S.

Eastern and Pacific states are among the healthiest in the country, while states in the South lag.

By **Andrew Soergel**, Senior Reporter Aug. 6, 2018



Where Public Health Prospers

The U.S. spends more on its citizens' health care in any given year than much of the rest of the world. And although America is hardly the top country globally in terms of life expectancy or overall health – with elevated obesity statistics and relatively high infant and maternal mortality numbers for such a wealthy nation – the U.S. is still regarded as one of the better countries in the world to receive sporadic or ongoing treatment.

Geography and health care results are closely intertwined, both in[illegible] nationally and on a state-by-state basis. Some states, predominately those in the Northeast and along the

Pacific Coast, enjoy significantly lower mortality, obesity and smoking rates than other parts of the country.

As part of its annual Best States rankings, U.S. News evaluated states' public health – looking at variables such as overall mortality, infant mortality, obesity, rates of smoking, and suicide and mental health.

The findings showed room for improvement in the geographic South, in particular, with the bottom eight states on the index classified as "Southern" by the Census Bureau. At the top of the list, four states sit on the East Coast, three are categorized as Pacific, two are Mountain states and one is in the Midwest.

See which states are considered to be the healthiest in the country:

NEXT: 10. Utah

1 of 12

Andrew Soergel, Senior Reporter

Andrew Soergel is a Senior Reporter at U.S. News. You can connect with him on LinkedIn, follow ... **READ MORE »**

2019 CHILDHOOD VACCINE SCHEDULE

1962

OPV
Smallpox
DTP

5 Doses

1983

DTP (2 months)
OPV (2 months)
DTP (4 months)
OPV (4 months)
DTP (6 months)
MMR (15 months)
DTP (18 months)
OPV (18 months)
DTP (4 years)
OPV (4 years)
Td (15 years)

24 Doses

2019

Influenza *(pregnancy)*
Tdap *(pregnancy)*
Hep B (birth)
Hep B (2 months)
Rotavirus (2 months)
DTaP (2 months)
HIB (2 months)
PCV (2 months)
IPV (2 months)
Rotavirus (4 months)
DTaP (4 months)
HIB (4 months)
PCV (4 months)
IPV (4 months)
Hep B (6 months)
Rotavirus (6 months)
DTaP (6 months)
HIB (6 months)
PCV (6 months)
IPV (6 months)
Influenza (6 months)
Influenza (7 months)
HIB (12 months)
PCV (12 months)
MMR (12 months)
Varicella (12 months)
Hep A (12 months)
DTaP (18 months)
Influenza (18 months)
Hep A (18 months)
Influenza (30 months)
Influenza (42 months)
DTaP (4 years)
IPV (4 years)
MMR (4 years)
Varicella (4 years)
Influenza (5 years)
Influenza (6 years)
Influenza (7 years)
Influenza (8 years)
Influenza (9 years)
HPV (9 years)
Influenza (10 years)
HPV (10 years)
Influenza (11 years)
HPV (11 years)
Tdap (12 years)
Influenza (12 years)
Meningococcal (12 years)
Influenza (13 years)
Influenza (14 years)
Influenza (15 years)
Influenza (16 years)
Meningococcal (16 years)
Influenza (17 years)
Influenza (18 years)

72 Doses

WHAT HAPPENED IN 1986?

- In 1986, Reagan passed a law that gave legal immunity to vaccine manufacturers.
- They could no longer be sued for injuries or death caused by their products. Safe vaccines wouldn't need such protection.
- Once that law passed, we suddenly 'needed' 48 additional doses of vaccines. (Do you remember any outbreaks in 1989?)
- Also, since that law was passed, U.S. Federal Government has paid out more than $4 Billion in vaccine injury compensation, and that's only a fraction of actual injuries.
- The U.S. gives more vaccines than most developed countries, yet we have the sickest kids

GUESS WHAT?

The CDC has only ever tested MMR and Thimerosal for a link to autism. The remaining 15 vaccines and 37 common ingredients remain untested for links to autism.

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CONSUMER ADVOCACY | EDUCATION | EMPOWERMENT

For more information and sources, please visit www.InformedChoiceUSA.org

THERE ARE RISKS | YOU HAVE CHOICES

Emily
Mattoni
~~testifying next(?)~~

Data Table

Location	Infant Mortality Rate (Click for Rankings)	Deaths (Click for Rankings)
Alabama	7.4	434
Alaska	5.6	59
Arizona	5.7	469
Arkansas	8.2	307
California	4.2	1,973
Colorado	4.5	291
Connecticut	4.5	160
Delaware	6.6	72
Florida	6.1	1,358
Georgia	7.2	932
Hawaii	5.3	92
Idaho	4.6	102
Illinois	6.1	912
Indiana	7.3	600
Iowa	5.3	203
Kansas	6.1	221
Kentucky	6.5	355
Louisiana	7.1	431
Maine	5.7	70
Maryland	6.4	460
Massachusetts	3.7	262
Michigan	6.8	755
Minnesota	4.8	328
Mississippi	8.6	322
Missouri	6.2	456
Montana	5.4	64
[illegible]	[illegible]	144
[illegible]	[illegible]	208
[illegible]	[illegible]	51
[illegible]	[illegible]	453
[illegible]	[illegible]	140
[illegible]	[illegible]	1,047
[illegible]	[illegible]	847
[illegible]	[illegible]	46
[illegible]	[illegible]	983
[illegible]	7.7	387
Oregon	5.4	236
Pennsylvania	6.1	841
Rhode Island	6.2	66
South Carolina	6.5	371
South Dakota	7.7	94
Tennessee	7.4	597
Texas	5.9	2,237
Utah	5.9	285
Vermont	4.8	27
Virginia	5.9	592
Washington	3.9	341
West Virginia	7.0	131
Wisconsin	6.4	414
Wyoming	4.6	32

Why aren't children in the UK vaccinated against chickenpox?

The chickenpox vaccine is not part of the routine UK **childhood vaccination programme** (https://www.nhs.uk/conditions/vaccinations/childhood-vaccines-timeline/) because **chickenpox** (https://www.nhs.uk/conditions/chickenpox/) is usually a mild illness, particularly in children.

There's also a worry that introducing chickenpox vaccination for all children could increase the risk of chickenpox and **shingles** (https://www.nhs.uk/conditions/shingles/) in adults.

Chickenpox in adults

In adults, chickenpox tends to be more severe and the risk of complications increases with age.

If a childhood chickenpox vaccination programme was introduced, people would not catch chickenpox as children because the infection would no longer circulate in areas where the majority of children had been vaccinated.

This would leave unvaccinated children susceptible to contracting chickenpox as adults, when they are more likely to get a more serious infection, or in pregnancy, where there is a risk of the infection harming the baby.

Shingles in adults

We could also see a significant increase in cases of shingles in adults.

Being exposed to chickenpox as an adult – for example, through contact with infected children – boosts your immunity to shingles.

If you vaccinate children against chickenpox, you lose this natural boosting, so immunity in adults will drop and more shingles cases will occur.

So when is chickenpox vaccine given?

The chickenpox vaccine is used to immunise people who may pass the infection on to someone who is at risk of serious complications from chickenpox.

The vaccine may be given on the NHS to:

- healthcare workers who are not immune to chickenpox
- people in close contact with someone who has a weakened immune system

In this way, the chickenpox vaccine protects people at risk who are unable to themselves be vaccinated against chickenpox, such as:

- pregnant women
- people who have weakened immune systems – for example, from **HIV and AIDS** (https://www.nhs.uk/conditions/hiv-and-aids/) or through treatments such as **chemotherapy** (https://www.nhs.uk/conditions/chemotherapy/)

Read more about **who should have the chickenpox vaccination** (https://www.nhs.uk/conditions/vaccinations/when-is-chickenpox-vaccine-needed/).

Further information

- **Infectious illnesses in children** (https://www.nhs.uk/conditions/pregnancy-and-baby/infectious-illnesses-children/#close)
- **The NHS vaccination schedule** (https://www.nhs.uk/conditions/vaccinations/)
- **Skin rashes in babies** (https://www.nhs.uk/conditions/rashes-in-babies/#close)
- Video: **'I'm pregnant – should I worry about chickenpox?'** (https://www.nhs.uk/video/Pages/i-am-pregnant-should-I-worry-

Thank you, Madame Chair and Members. My name is Emily Fischer and I am an Environmental Engineer residing in Loveland, CO. I would like to speak about Section 1(e), page 3 lines 14-16, of the proposed bill, which states: Compared to other states, Colorado has a relatively lenient vaccine exemption process and one of the highest exemption rates for nonmedical reasons. Colorado's exemption rate currently sits at 2.6% and that number includes children who have received ALL but one of the recommended vaccinations or children who follow an alternative schedule. If a parent decides to delay even for a bit they are included in this number. If a parent decides they don't want to do the Chickenpox and only the Chickenpox vaccine they would be included in this number. Many other countries, like the U.K, do not vaccinate for Chickenpox. That entire country would be included in our exemption rate based on our exemption policy. They certainly wouldn't be able to get a medical exemption even with the reasoning stated in the National Health Service printout I just gave you. Colorado tops the Centers for Disease Control and Prevention's list of healthiest states in the country. According to the CDC, Mississippi has both the highest vaccine compliance rate, and the worst ranking for health in the nation. Mississippi also has the worst infant mortality rate in the nation. As seen on the CDC handout, our infant mortality is almost half of the rate in Mississippi. The other state with the strictest vaccine exemption process, West Virginia, is also in the bottom twelve for infant mortality. Please vote no on HB19-1312. Thank you.

2017 Colorado Statistics/Misrepresented Numbers

9,424 hospitalizations/ED visits due to "vaccine-preventable" diseases

9,116 were for **Flu**

(# tested for flu? # previously vaccinated for flu? # that had vaccine strains of flu? # that did NOT have vaccine strains flu? Lots of missing information here)

Flu shot **40%** effective in 2017

That leaves only **308** hospitalizations/ED visits for "vaccine-preventable" diseases (121 of those for chicken pox)

308 out of 1.2 million children under age 18 in Colorado =

.026%

Do not take these numbers at face value. Do not assume that 9,424 **unvaccinated** children were treated for "vaccine-preventable"diseases.

Children's Hospital Colorado

CONTAGIOUS COMMENTS

The Vaccine-Preventable Diseases Report

Jessica R. Cataldi MD, Carl Armon PhD, Marlee Barton MPH, Stephanie Wasserman MSPH, Elizabeth Abbott MPH, James K. Todd MD, Edwin J. Asturias MD

February 2019

- **In the News**: A case of measles in Denver
- **Statewide Summary:** The latest data on VPDs in Colorado and comparing our vaccination rates with other states
- **Mapping:** See where we have opportunities to improve immunization rates and Medicaid enrollment
- **Policy Perspective:** Why some Colorado parents continue to face barriers to accessing immunizations

In the News: What you need to know about measles in Denver

An adult living in Denver tested positive for measles on January 15 after returning from international travel. S/he visited several retail locations and an urgent care center in Stapleton before being hospitalized in Denver. It is unclear whether this person was vaccinated. State and local public health officials have contacted people who were directly exposed to this person and are monitoring for additional cases.

Symptoms of measles include fever, cough, runny nose and rash. Complications include pneumonia and encephalitis, or inflammation of the brain. One in four people sick with measles needs to be hospitalized and one in a thousand will die.[1] Young children, pregnant women and people with weakened immune systems are at higher risk of complications.

Measles is very contagious and even one case can lead to an outbreak, especially in places where vaccination rates are low. Because measles is so contagious, at least 95% of a community needs to be immunized to prevent the disease from spreading.[2,3] Across Colorado, 87-89%[4,5] of children 19-35 months of age have received at least one dose of MMR (the vaccine that protects against measles), which is below the threshold needed to reliably prevent an outbreak.

What can you do about measles?

Parents

- Call your doctor if you think you or your child have symptoms: fever, rash, cough and runny nose
- Make sure you and your family are vaccinated- the MMR vaccine is 97% effective in preventing measles
- Check your childcare and school vaccination rates. Call or look online: https://www.cohealthdata.dphe.state.co.us/Data/Details/21

Health Care Providers

- Be sure patients traveling internationally are fully vaccinated, including MMR
- Contact CDPHE if you think a patient may have measles or have been exposed to someone with measles

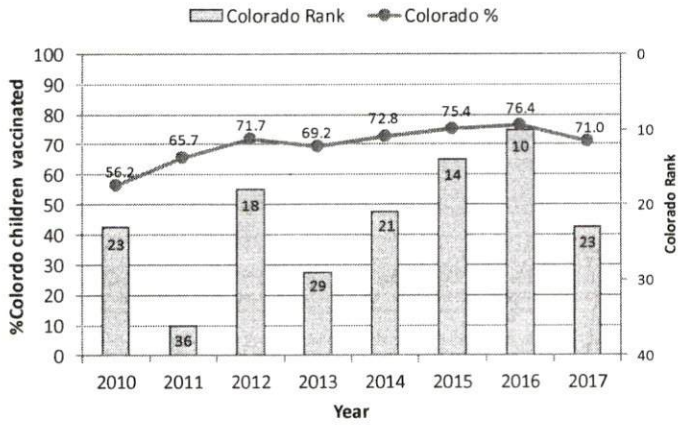
Between 2013 and 2017, Colorado had 1-2 reported cases of measles per year.[6] Public health teams respond to any case of measles by identifying people who may have been exposed and ensuring those people are protected against infection. Tri-County Health Department officials estimated the costs of responding to two separate measles cases in 2016 and 2017 at $18,000 and $49,000 respectively.[7]

Starting the new year with a measles case in Denver is concerning but not surprising based on increasing numbers of measles outbreaks across the country and around the world. The CDC reported 349 cases of measles in the US in 2018. At the beginning of 2019, an outbreak in the counties around New York City has grown to more than 200 cases and a newer outbreak of more than 40 people is ongoing in Oregon and southern Washington, an area with low vaccination rates. Many cases of measles in the US occur after someone returns from travel. In 2018, the World Health Organization (WHO) reported 60 million cases of measles in Europe and 17 million cases in the Americas. Most of the cases in Europe occurred in places with low immunization rates and the majority of cases in the Americas occurred in Brazil and Venezuela, in part due to weakening public health infrastructure.[8]

Statewide Summary: *Vaccination coverage had improved from 2013-2016, but NIS 2017 shows too many Colorado children are still incompletely protected.*

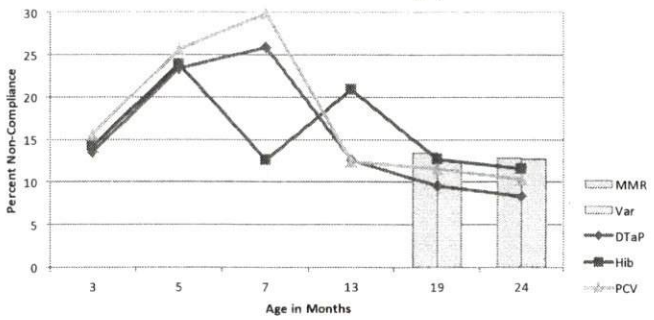
In the 2017 Centers for Disease Control and Prevention (CDC) National Immunization Survey (NIS), Colorado ranked 23rd among US States in vaccination rates for children 19-35 months of age (**Figure 1**, below).[4] This is a drop from being ranked 10th in 2016. More importantly, 29% of children in this age group had received fewer than the recommended number of doses of at least one of the vaccines required for enrolling in child care, leaving them vulnerable to many infectious diseases including measles, varicella, pertussis, and pneumococcal infection. Colorado's overall vaccination rate dropped to 71% in 2017 after having improved from 2013 through 2016. We still fall short of the Healthy People 2020 goal of 95% coverage for each of these vaccines in children 19-35 months of age.

Figure 1: NIS Vaccination Rates (4313314): US and Colorado (Source: NIS), 2010-2017



4313314: 4 doses of DTaP, 3 polio [IPV], 1 measles/mumps/rubella [MMR], 3 hepatitis-B, 3 *Haemophilus influenzae* type B [HiB], 1 varicella and 4 pneumococcal conjugate vaccine[PCV])

Figure 2: Colorado Vaccination Non-Compliance from 3 to 24 Months of Age, 2017



Number of vaccines required:						
DTaP	1	2	3	3	4	4
Hib	1	2	2	3	3	3
PCV	1	2	3	3	4	4
MMR					1	1
Var					1	1

http://pediatrics.aappublications.org/content/133/2/357

NIS data show that rates of non-compliance (not being up to date on recommended vaccinations) were highest among children 3-19 months (**Figure 2**, above). Like we have seen in years past, much of the gap in coverage for early childhood immunizations is seen in the same age group that experiences the highest burden of vaccine-preventable illness. In 2017, more than quarter of all infants in Colorado were behind on DTaP and PCV vaccinations at 7 months- an age when young children remain vulnerable to pertussis and pneumococcal disease. Coverage with MMR vaccine at 24 months of age was similar to 2016, but at 87% was still below the level required to protect a population against outbreaks of measles (~95%).[2,3]

Vaccine-preventable diseases caused over 9,000 hospitalizations and emergency department visits for Colorado children in 2017 and resulted in over $56 million in health care charges

Table 1 shows 2017 Colorado Hospital Association data for the number of cases of hospitalizations or emergency department (ED) visits associated with a vaccine-preventable disease (VPD) as well as the hospital-associated charges for these cases. Diagnoses of VPDs were identified using ICD-10 codes. Population estimates from the American Community Population Survey and the Colorado Health Institute were used to calculate incidence rates.

Influenza, pneumococcal disease and pertussis were the three most common reasons for hospitalization due to vaccine-preventable disease in Colorado children in 2017. Additionally, there were three deaths among Colorado children hospitalized for VPD- two with influenza (an infant and a toddler) and one with *H. influenzae* (a toddler).

As we have seen in recent years, the most common vaccine-preventable cause of hospitalization and ED visits was influenza, with 460 hospitalizations and 8,656 ED visits in Colorado children in 2017. Total hospital charges and ED charges for vaccine-preventable diseases were over $55 million, with over $42 million due to influenza alone. The second most common vaccine-preventable cause of hospitalization was pneumococcal disease, with 61 hospitalizations and total hospital/ED charges of almost $10 million. The next most common vaccine preventable cause of ED visits was varicella, with 120 ED visits and total hospital/ED charges of close to $1 million.

Table 1: Cases, rates, and charges for Colorado children 0-19 years of age with vaccine-preventable diseases, 2017.

Vaccine	Hospitalized Cases	Rate per 100,000	Hospital Charges	ED Cases	Rate per 100,000	ED Charges	Total Charges
Diphtheria	0	--	--	--	--	--	--
H. influenzae	8	0.56	$974,904	--	--	--	$974,904
Hepatitis A	3	0.21	$215,047	3	0.21	$33,850	$248,897
Hepatitis B	3	0.21	$92,473	3	0.21	$49,416	$141,889
Influenza	460	32.48	$20,107,457	8,656	611.12	$22,632,148	$42,739,605
Measles	0			3	0.21	$14,320	$14,320
Mumps	1	0.07	$15,743	11	0.78	$24,321	$40,064
Pertussis	12	0.85	$426,771	58	4.09	$132,862	$559,633
Pneumococcal disease	61	4.31	$9,673,258	6	0.42	$41,057	$9,714,315
Polio	0	--	--	--	--	--	--
Rubella	0	--	--	2	0.14	$3,968	$3,968
Tetanus	0	--	--	4	0.28	$65,847	$65,847
Varicella	10	0.71	$812,241	120	8.47	$185,187	$997,428
Total	558	39.40	$32,317,894	8,866	625.95	$23,182,976	$55,500,870

Most hospitalizations related to vaccine-preventable diseases occurred among infants and children under 5 (**Figure 3a**), while most ED visits occurred in children 5-19 years of age (**Figure 3b**).

Figure 3a: VPD hospitalizations of Colorado children in 2017 by age, including influenza (N = 555)

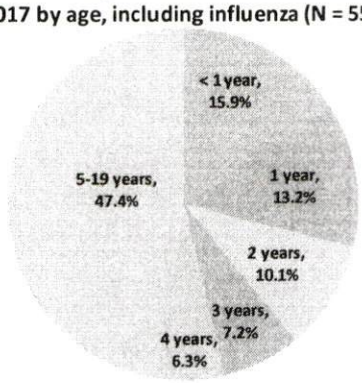
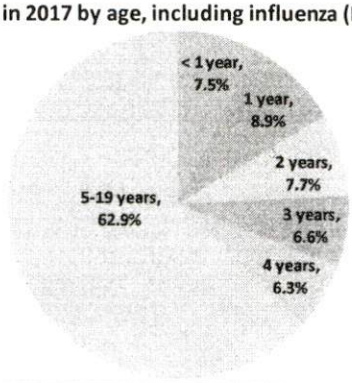


Figure 3b: VPD emergency department visits of Colorado children in 2017 by age, including influenza (N = 8,865)



Mapping Colorado Immunizations: *School District Immunization Rates and Health Care Access*

Marlee Barton, MPH, Colorado School of Public Health, University of Colorado

Comprehensive school district immunization data provides the opportunity to examine school immunization rates and health care access indicators at a local level. This data is available thanks to 2014 legislation (Colorado HB 14-1288) that requires schools and childcares to make immunization information publically available.

The 2016-2017 school immunization data collected by the Colorado Department of Public Health and Environment (CDPHE) was combined with 2015 insurance data from the Colorado Health Institute (CHI), clinic location data from the Vaccines for Children program (VFC, which provides vaccines for children with Medicaid), CDPHE health facilities data, and school demographic data from the Colorado Department of Education.

Indicators of High Immunization Rates

- Prevalence of Free-or-Reduced Lunch (PR 1.25, CI 1.09-1.43)
- Prevalence of Medicaid (PR 1.29, CI 0.09-1.75)

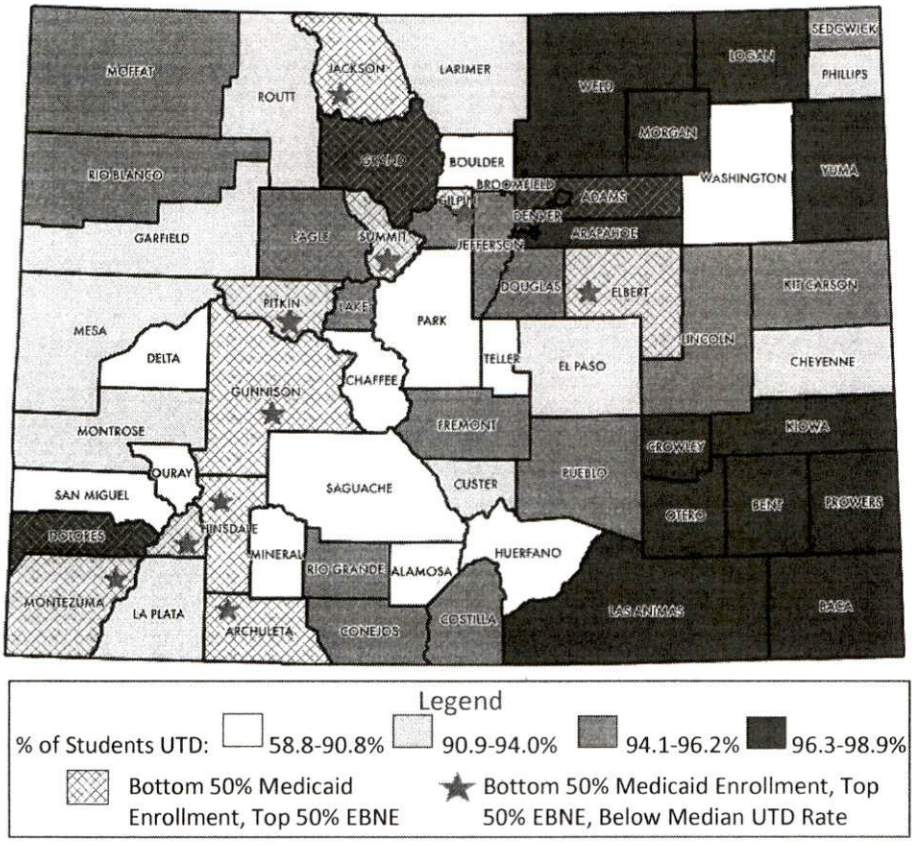
Indicators of Low Immunization Rates

- Prevalence of Student Mobility (PR 0.51, CI 0.33-0.80)
- Prevalence of Private Insurance (PR 0.88, CI 0.77-1.04)

Adjusted prevalence ratios showed that districts with more students enrolled in Medicaid or with more students eligible for free-or-reduced lunch were more likely to have ≥95% of their K-12 students up-to-date (UTD) with the school-required immunizations. This analysis also showed that districts with more students enrolled in private insurance or with more mobile students (those who begin and finish the school year in different districts) were less likely to have ≥95% of students UTD. Neither presence of VFC providers nor public health facilities within a district impacted the UTD status of students.

After seeing the link between Medicaid enrollment and school district immunization rates, we looked at county-level CDPHE immunization data for the 2017-2018 school year and 2015 insurance data from CHI. Every county in Colorado has children who are eligible for Medicaid but not currently enrolled (eligible but not enrolled or EBNE). There is a cluster of counties in the southwest corner of Colorado where there are more children who are EBNE and a similar cluster of counties in the same location with low Medicaid enrollment.

Map 1: Counties with High EBNE & Low Medicaid Prevalence (2015) Shown with UTD Immunization status (2017-2018)



Map 1 includes county immunization rates and highlights counties that fall above the median prevalence of EBNE children (2.7%) and below the median prevalence of Medicaid enrollment as places where there may be the greatest opportunity to increase Medicaid enrollment.

Again, several of these counties cluster in southwest Colorado and many also have lower immunization rates. Across Colorado, 19 counties fit the highlighted profile (high EBNE with low Medicaid enrollment). Of those counties, 10 fall below the median immunization rate for Colorado (94%) and are marked with stars on **Map 1**. The initial analysis demonstrated that Medicaid enrollment is associated with higher immunization rates.

There may be opportunities to increase immunization rates in certain counties by increasing Medicaid enrollment where there are more children who are eligible but not enrolled; especially in the southwest corner of the state.

Communities across Colorado have unique patterns of immunization coverage and require diverse approaches to strengthen vaccine uptake. These findings highlight the power of local data to identify immunization and health access trends at the county and school-district level.

References

1. Hamborsky J, Kroger A, Wolfe C. *Epidemiology and Prevention of Vaccine-preventable Diseases: The Pink Book: Course Textbook.* Public Health Foundation; 2015.
2. De Serres G, Gay NJ, Farrington CP. Epidemiology of transmissible diseases after elimination. *Am J Epidemiol.* 2000;151(11):1039-1048; discussion 1049-1052.
3. Thompson KM. Evolution and Use of Dynamic Transmission Models for Measles and Rubella Risk and Policy Analysis. *Risk Anal.* 2016;36(7):1383-1403.
4. CDC National Center for Immunization and Respiratory Diseases ISD. National Immmunization Survey 2017. 2018; https://www.cdc.gov/vaccines/imz-managers/nis/datasets.html. Accessed December 30, 2018.
5. CDPHE. CIIS county level rates. https://www.colorado.gov/pacific/cdphe/ciiscountylevel. Accessed January 24, 2019.
6. CDPHE. Colorado reportable disease data. https://www.colorado.gov/pacific/cdphe/colorado-reportable-disease-data. Accessed January 23, 2019.
7. Marx GE, Chase J, Jasperse J, et al. Public Health Economic Burden Associated with Two Single Measles Case Investigations - Colorado, 2016-2017. *MMWR Morb Mortal Wkly Rep.* 2017;66(46):1272-1275.
8. WHO. Regional summary of reported measles cases. Measles and Rubella Surveillance Data. https://www.who.int/immunization/monitoring_surveillance/burden/vpd/surveillance_type/active/measles_monthlydata/en/. Accessed January 26, 2019.

Policy Perspective: *Addressing the barriers to vaccination that some Colorado families face*

Stephanie Wasserman, MSPH, Colorado Children's Immunization Coalition

Colorado parents who refuse or delay vaccinating their children are a growing concern for our state because this trend leaves pockets of under- and unvaccinated kids in our schools, childcares and communities, making us all vulnerable to outbreaks of vaccine-preventable diseases. However, many families in Colorado want to vaccinate but continue to face barriers to accessing services. For these Coloradans, low immunization rates reflect ongoing challenges in insurance coverage, geography and other issues. While the Affordable Care Act (ACA) has increased the number of insured Coloradans covered on private health insurance or through Medicaid, many are still not able to easily and conveniently access immunization services and are missing out on the public health benefits and protections of vaccines. For example, fewer than 600 Colorado health care sites (including community health centers, pediatric and family practices, hospitals, Indian Health Service, local public health agencies, rural health centers, school-based health centers and youth services) participate in the Vaccines for Children (VFC) program, the federal program that allows healthcare providers to administer free vaccines to uninsured, Medicaid-eligible, and Alaska Native or American Indian children. One Colorado county (Gilpin) lacks a single healthcare provider site that participates in the VFC program. Another seven rural counties (Custer, Dolores, Elbert, Jackson, Mineral, Pitkin and San Juan), offer only a single location where VFC vaccine is available. Of these seven sites, more than half are small, rural local public health agencies, many staffed with a single public health nurse providing immunizations at limited times, or by appointment only. This means that some families are expected to travel many miles to get vaccinated at times that may not be feasible or convenient for them. Transportation challenges, inability to take time off of work, childcare issues and other barriers result in missed opportunities to vaccinate and lower immunization rates. Colorado must do more to provide funding, capacity and resources to support core public health infrastructure, especially in rural communities, and to encourage increased participation among health care providers in the VFC program.

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Seasonal Influenza Vaccine Effectiveness, 2004-2018

CDC conducts studies to measure the benefits of seasonal flu vaccination each flu season to help determine how well flu vaccines are working. These vaccine effectiveness (VE) studies regularly assess and confirm the value of flu vaccination as a public health intervention. Study results of vaccine effectiveness can vary based on study design, outcome(s) measured, population studied and the season in which the flu vaccine was studied.

CDC has been working with researchers at universities and hospitals since the 2003-2004 flu season to estimate how well flu vaccine works through observational studies using medically attended laboratory-confirmed flu as the outcome. This is the U.S. Flu Vaccine Effectiveness (VE) Network. The U.S. Flu VE Network currently consists of five study sites across the United States that measure the flu vaccine's effectiveness at preventing outpatient medical visits due to laboratory-confirmed influenza. CDC's observational studies at U.S. Flu VE Network sites measure outpatient visits* for laboratory-confirmed influenza infections using a highly accurate lab test called rRT-PCR to verify the outcome. These studies compare the odds of vaccination among outpatients with acute respiratory illness and laboratory-confirmed influenza infection to the odds of vaccination among outpatients with acute respiratory illness who test negative for influenza infection.

The overall, adjusted vaccine effectiveness estimates for influenza seasons from 2004-2018 are noted in the chart below. (Estimates are typically adjusted for study site, age, sex, underlying medical conditions, and days from illness onset to enrollment.)

On This Page

Info on Flu Vaccine Effectiveness

CDC conducts studies to measure the benefits of seasonal flu vaccination each flu season to help determine how well flu vaccines are working.

More ›

Table. Adjusted vaccine effectiveness estimates for influenza seasons from 2004-2018

Influenza Season†	Reference	Study Site(s)	No. of Patients‡	Adjusted Overall VE (%)	95% CI
2004-05	Belongia 2009 (http://www.ncbi.nlm.nih.gov/pubmed/19086915)	WI	762	10	-36, 40
2005-06	Belongia 2009 (http://www.ncbi.nlm.nih.gov/pubmed/19086915)	WI	346	21	-52, 59
2006-07	Belongia 2009 (http://www.ncbi.nlm.nih.gov/pubmed/19086915)	WI	871	52	22 ,70
2007-08	Belongia 2011 (https://www.ncbi.nlm.nih.gov/pubmed/21767593)	WI	1914	37	22, 49
2008-09	Unpublished	WI, MI, NY, TN	6713	41	30, 50
2009-10	Griffin 2011 (https://www.ncbi.nlm.nih.gov/pubmed/21857999)	WI, MI, NY, TN	6757	56	23, 75

2010-11	Treanor 2011 (https://www.ncbi.nlm.nih.gov/pubmed/22843783)	WI, MI, NY, TN	4757	60	53, 66
2011-12	Ohmit 2014 (https://www.ncbi.nlm.nih.gov/pubmed/24235265)	WI, MI, PA, TX, WA	4771	47	36, 56
2012-13	McLean 2014 (https://www.ncbi.nlm.nih.gov/pubmed/25406334)	WI, MI, PA, TX, WA	6452	49	43, 55
2013-14	Gaglani 2016 (https://www.ncbi.nlm.nih.gov/pubmed/26743842)	WI, MI, PA, TX, WA	5999	52	44, 59
2014-15	Zimmerman 2016 (https://academic.oup.com/cid/article/63/12/1564/2282808/2014-2015-Influenza-Vaccine-Effectiveness-in-the)	WI, MI, PA, TX, WA	9311	19	10, 27
2015-16	Jackson 2017 (https://www.ncbi.nlm.nih.gov/pubmed/28792867)	WI, MI, PA, TX, WA	6879	48	41, 55
2016-17	Unpublished final estimates.	WI, MI, PA, TX, WA	7410	40	32, 46
2017-18	Rolfes 2019 (https://academic.oup.com/cid/advance-article/doi/10.1093/cid/ciz075/5305915)	WI, MI, PA, TX, WA	8,436	38	31, 43
2018-19*	Doyle 2019	WI, MI, PA, TX, WA	3,254	47*	34, 57

* Vaccine effectiveness estimates for 2018-2019 are preliminary estimates and will be updated with final estimates at the end of the 2018-2019 U.S. influenza season.

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Figure. Effectiveness of Seasonal Flu Vaccines from the 2004-2018 Flu Seasons

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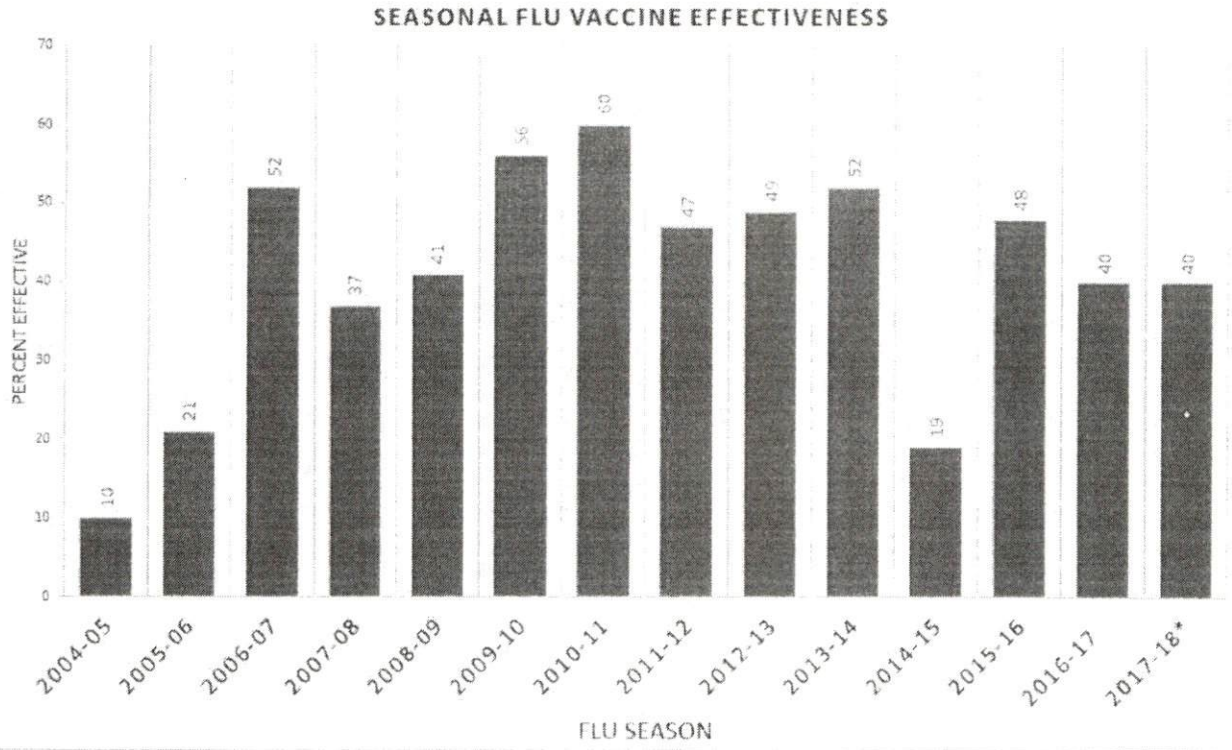

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Belongia EA, Kieke BA, Donahue JG, et al. Effectiveness of inactivated influenza vaccines varied substantially with antigenic match from the 2004-2005 season to the 2006-2007 season. J Infect Dis. 2009 Jan 15;199(2):159-67. doi:10.1086/595861. PubMed PMID: 19086915. (http://www.ncbi.nlm.nih.gov/pubmed/19086915)

Belongia EA, Kieke BA, Donahue JG,et al. Influenza vaccine effectiveness in Wisconsin during the 2007-08 season: comparison of interim and final results. Vaccine. 2011 Sep 2;29(38):6558-63. doi: 10.1016/j.vaccine.2011.07.002. Epub 2011 Jul 19. PubMed PMID: 21767593. (http://www.ncbi.nlm.nih.gov/pubmed/21767593)

Flannery B, Clippard J, Zimmerman RK, Norwalk MP, Jackson ML, Jackson LA, Monto AS, Petrie JG, McLean HQ, Belongia EA, Gaglani M, Berman L, Foust A, Sessions W, Thaker SN, Spencer S, Fry AM. Early Estimates of Seasonal Influenza Vaccine Effectiveness – United States, January 2015. MMWR Morb Mortal Wkly Rep. 2015 Jan 13;64(1);10-15. (https://www.cdc.gov/mmwr/preview/mmwrhtml/mm6401a4.htm)

Griffin MR, Monto AS, Belongia EA, et al. Effectiveness of non-adjuvanted pandemic influenza A vaccines for preventing pandemic influenza acute respiratory illness visits in 4 U.S. communities. PLoS One. 2011;6(8):e23085. doi: 10.1371/journal.pone.0023085. Epub 2011 Aug 12. PubMed PMID: 21857999. (http://www.ncbi.nlm.nih.gov/pubmed/21857999)

McLean HQ, Thompson MG, Sundaram ME, Kieke BA, Gaglani M, Murthy K, Piedra PA, Zimmerman RK, Nowalk MP, Raviotta JM, Jackson ML, Jackson L, Ohmit SE, Petrie JG, Monto AS, Meece JK, Thaker SN, Clippard JR, Spencer SM, Fry AM, Belongia EA. Influenza Vaccine Effectiveness in the United States During 2012-2013: Variable Protection by Age and Virus Type. J Infect Dis. 2014 Nov 18. pii: jiu647. [Epub ahead of print] PubMed PMID: 25406334. (http://jid.oxfordjournals.org/content/early/2014/12/16/infdis.jiu647.long)

Ohmit SE, Thompson MG, Petrie JG, et al. Influenza vaccine effectiveness in the 2011-2012 season: protection against each circulating virus and the effect of prior vaccination on estimates. Clin Infect Dis. 2014 Feb;58(3):319-27. doi: 10.1093/cid/cit736. Epub 2013 Nov 13. (http://www.ncbi.nlm.nih.gov/pubmed/24235265)

Treanor JJ, Talbot HK, Ohmit SE, et al. Effectiveness of seasonal influenza vaccines in the United States during a season with circulation of all three vaccine strains. CID 2012; 55(7):951-959. Epub 2012 Jul 25. PubMed PMID: 22843783. (http://www.ncbi.nlm.nih.gov/pubmed/22843783)

Jackson ML, Chung JR, Jackson LA, Phillips CH, Benoit J, Monto AS, Martin ET, Belongia EA, McLean HQ, Gaglani M, Murthy K, Zimmerman R, Nowalk MP, Fry AM, Flannery B. N Engl J Med. 2017 Aug 10;377(6):534-543. doi: 10.1056/NEJMoa1700153. PMID: 2879286 (https://www.ncbi.nlm.nih.gov/pubmed/28792867)

* From 2004-05 through 2010-11, the Network also enrolled inpatients.

† Vaccine effectiveness (VE) estimates for the 2008-2009 flu season have not yet been published.

‡ Number of patients used in VE calculation.

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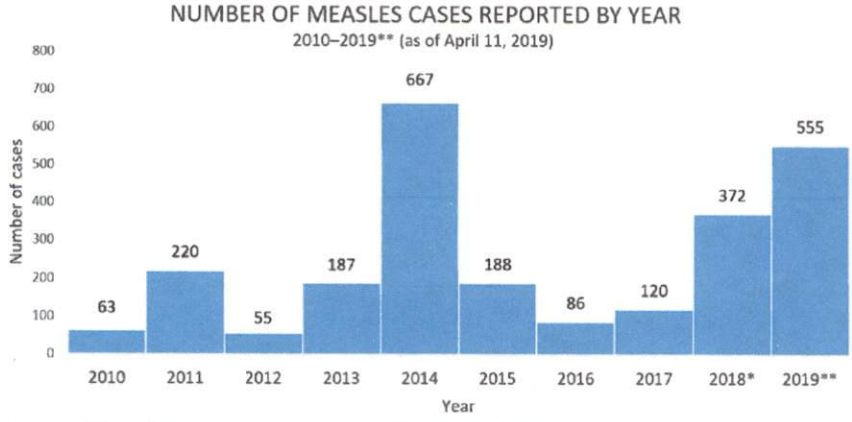
Measles Cases and Outbreaks

Measles Cases in 2019

From January 1 to April 11, 2019, 555** individual cases of measles have been confirmed in 20 states. This is the second-greatest number of cases reported in the U.S. since measles was eliminated in 2000.

The states that have reported cases to CDC are Arizona, California, Colorado, Connecticut, Florida, Georgia, Illinois, Indiana, Kentucky, Maryland, Massachusetts, Michigan, Missouri, Nevada, New Hampshire, New Jersey, New York, Oregon, Texas, and Washington.



*Cases as of December 29, 2018. Case count is preliminary and subject to change.

Cases as of April 11, 2019. Case count is preliminary and subject to change. **Data are updated every Monday.

Measles Outbreaks Reported to CDC

Measles outbreaks (defined as 3 or more cases) are currently ongoing in 2019 in the following jurisdictions:

- New York State, Rockland County (http://rocklandgov.com/departments/health/measles-information/)
- New York City (https://www1.nyc.gov/site/doh/health/health-topics/measles.page)
- Washington (https://www.doh.wa.gov/YouandYourFamily/IllnessandDisease/Measles/MeaslesOutbreak)
- New Jersey (https://www.state.nj.us/health/cd/topics/measles.shtml)
- California, Butte County (https://www.cdph.ca.gov/Programs/CID/DCDC/Pages/Immunization/measles.aspx)
- Michigan (http://www.michigan.gov/measlesoutbreak)

These outbreaks are linked to travelers who brought measles back from other countries such as Israel, Ukraine, and the Philippines, where large measles outbreaks are occurring. Make sure you are vaccinated against measles (https://www.cdc.gov/measles/travelers.html) before traveling internationally.

Spread of Measles

The majority of people who got measles were unvaccinated.

Measles is still common in many parts of the world including some countries in Europe, Asia, the Pacific, and Africa.

Travelers with measles continue to bring the disease into the U.S.

Measles can spread when it reaches a community in the U.S. where groups of people are unvaccinated.

Measles Outbreaks

In a given year, more measles cases can occur for any of the following reasons:

- an increase in the number of travelers who get measles abroad and bring it into the U.S., and/or
- further spread of measles in U.S. communities with pockets of unvaccinated people.

Reasons for an increase in cases some years:

- 2018: The U.S. experienced 17 outbreaks in 2018. Three outbreaks in New York State, New York City, and New Jersey, respectively, contributed to most of the cases. Cases in those states occurred primarily among unvaccinated people in Orthodox Jewish communities. These outbreaks were associated with travelers who brought measles back from Israel, where a large outbreak is occurring. Eighty-two people brought measles to the U.S. from other countries in 2018. This is the greatest number of imported cases since measles was eliminated from the U.S. in 2000.
- 2017: A 75-case outbreak was reported in Minnesota in a Somali-American community with poor vaccination coverage.
- 2015: The United States experienced a large (147 cases), multi-state measles outbreak linked to an amusement park in California. The outbreak likely started from a traveler who became infected overseas with measles, then visited the amusement park while infectious; however, no source was identified. Analysis by CDC scientists showed that the measles virus type in this outbreak (B3) was identical to the virus type that caused the large measles outbreak in the Philippines in 2014.
- 2014: The U.S. experienced 23 measles outbreaks in 2014, including one large outbreak of 383 cases, occurring primarily among unvaccinated Amish communities in Ohio. Many of the cases in the U.S. in 2014 were associated with cases brought in from the Philippines, which experienced a large measles outbreak.
- 2013: The U.S. experienced 11 outbreaks in 2013, three of which had more than 20 cases, including an outbreak with 58 cases. For more information see Measles — United States, January 1-August 24, 2013.
- 2011: In 2011, more than 30 countries in the WHO European Region reported an increase in measles, and France was experiencing a large outbreak. These led to a large number of importations (80) that year. Most of the cases that were brought to the U.S. in 2011 came from France. For more information see Measles — United States, January-May 20, 2011.
- 2008: The increase in cases in 2008 was the result of spread in communities with groups of unvaccinated people. The U.S. experienced several outbreaks in 2008 including three large outbreaks. For more information see Update: Measles — United States, January–July 2008.

See also: The Surveillance Manual chapter on measles that describes case investigation, outbreak investigation, and outbreak control for additional information.

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