Health Consequences of Religious and Philosophical Exemptions From Immunization Laws

Individual and Societal Risk of Measles

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Context All US states require proof of immunization for school entry. Exemptions are generally offered for medical, religious, or philosophical reasons, but the health consequences of claiming such exemptions are poorly documented.

Objectives To quantify the risk of contracting measles among individuals claiming religious and/or philosophical exemptions from immunization (exemptors) compared with vaccinated persons, and to examine the risk that exemptors pose to the nonexempt population.

Design, Setting, and Participants Population-based, retrospective cohort study of data from 1985 through 1992, collected by the Measles Surveillance System of the Centers for Disease Control and Prevention, as well as from annual state immunization program reports on prevalence of exemptors and vaccination coverage. The study group was restricted to individuals aged 5 to 19 years. To empirically determine and quantify community risk, a mathematical model was developed that examines the spread of measles through communities with varying proportions of exemptors and vaccinated children.

Main Outcome Measures Relative risk of contracting measles for exemptors vs vaccinated individuals based on cohort study data. Community risk of contracting measles derived from a mathematical model.

Results On average, exemptors were 35 times more likely to contract measles than were vaccinated persons (95% confidence interval, 34-37). Relative risk varied by age and year. Comparing the incidence among exemptors with that among vaccinated children and adolescents during the years 1985-1992 indicated that the 1989-1991 measles resurgence may have occurred 1 year earlier among exemptors. Mapping of exemptors by county in California indicated that exempt populations tended to be clustered in certain geographic regions. Depending on assumptions of the model about the degree of mixing between exemptors and nonexemptors, an increase or decrease in the number of exemptors would affect the incidence of measles in nonexempt populations. If the number of exemptors doubled, the incidence of measles infection in nonexempt individuals would increase by 5.5%, 18.6%, and 30.8%, respectively, for intergroup mixing ratios of 20%, 40%, and 60%.

Conclusions These data suggest the need for systematic review of vaccine-preventable incidents to examine the effect of exemptors, increased surveillance of the number of exemptors and cases among them, and research to determine the reasons why individuals claim exemptions.

JAMA. 1999;282:47-53 www.jama.com

Immunizations are among the most cost-effective and successful public health interventions. Due to the high contagion, morbidity, and mortality associated with most vaccine-preventable diseases (VPDs), and the safety, effectiveness, and potential financial savings offered by vaccines, all jurisdictions in the United States have introduced and actively enforce laws that require proof of immunization for school entrance.[1-3] Many of these laws were initially written specifically for smallpox and later amended to include other VPDs.[4] Although there are no federal laws mandating immunizations, the US Supreme Court has upheld the constitutionality of state vaccination laws. In 1905, the Court ruled in favor of a Massachusetts law; in 1922, the Court specifically addressed vaccination as a prerequisite for school attendance.[3] These federal rulings have served as precedents for state court rulings.

State immunization laws permit certain exemptions. As of January 1998, all states allow medical exemptions (eg, for individuals who are immunocompromised, have allergic reactions to vac-

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cine constituents, or have moderate or severe illness). To qualify for medical exemptions, parents or guardians must provide a letter or other documentation from a physician. Forty-eight states permit religious exemptions, and 15 states allow philosophical or personal exemptions.[5] Such exemptions are defined differently by each state. Texas requires that individuals claiming religious exemptions be a member of a recognized religious group that opposes all immunizations and submit a letter from a faith leader. By contrast, California offers personal beliefs exemptions, which require only a parental affidavit.

Persons who claim exemptions from immunizations for any reason may be at increased risk of contracting a VPD compared with immunized persons. In addition, persons who claim philosophical and/or religious exemptions (exemptors) may create some risk to the community because unvaccinated or undervaccinated persons may be a source of transmission. In contrast to medical exemptions, which are due to an intrinsic medical condition, religious and philosophical exemptions are voluntary choices. Exemptors also pose a social equity issue.[6] While vaccines cause fewer complications than VPDs, no vaccine is perfectly safe. For most VPDs, "herd immunity," an indirect protection for a community, may be established when a high enough proportion of the population is immunized to interrupt transmission.[3] High immunization levels therefore permit some unvaccinated individuals to reap benefits of immunization without facing risks.[6] The current success of immunization programs in achieving record-high levels of coverage and record-low levels of VPDs results in many parents being unfamiliar with VPDs. As a result, the desire of some parents to claim exemptions for their children may increase when vaccine coverage is high.[7] Since the actual impact of exemptors on disease occurrence has not been well studied, we analyzed risks of exemptors to themselves and to the communities in which they live.

METHODS

Cohort Study

Using a population-based, retrospective cohort study design, we quantified the risk of exemptors compared with vaccinated individuals in contracting measles. We identified measles cases among exemptors and vaccinated individuals from 1985 through 1992, using data derived from the Measles Surveillance System of the Centers for Disease Control and Prevention (CDC), Atlanta, Ga. This system receives weekly reports of confirmed measles cases from 53 reporting areas (50 states, New York City, Chicago, and the District of Columbia). The reports include county, age, whether the case was an international importation, vaccination status, and exemption status if unvaccinated.[8]

We restricted our study to school-aged children and adolescents (aged 5-19 years). We compared the relative risk of contracting measles of exemptors and vaccinated individuals. We estimated the number of exemptors using CDC annual, unpublished State Immunization Reports from 1990 through 1994. These reports provide the "percentage of enrollees with an exemption for 1 or more vaccines." Data submitted in the reports do not distinguish between religious, philosophical, and medical exemptors, so we contacted program managers to discern the types of exemptions. For states not able to identify type of exemptions (n = 34 [68%]), we used the overall percentages reported on state surveys, which include medical exemptions (mean average of medical exemptions in the 16 states for which it was possible to identify type of exemption was 0.16). For 1 state (Delaware), which did not report percentage of individuals claiming exemption for any year, we used the average percentage of exemptors for states that did report these data (0.66%). We applied the (mean) average for each state over these 5 years to the period 1985-1992. California provided county-specific data on the percentage of exemptors, which were used in developing the mathematical model.

We calculated the number of vaccinated individuals by assuming a 98% national vaccination coverage rate for school-aged children and adolescents, based on unpublished CDC school-survey data of yearly coverage by state and antigen. All states reported at least 98% vaccination coverage among school-aged youth for measles in the period 1985-1992. Sociodemographic variables were not available. We used age-specific population data from the Bureau of the Census to extrapolate the percentages into estimated numbers. Thus, we were able to estimate age-specific measles incidence and the relative risk of measles for exemptors compared with vaccinated persons.

Mathematical Model

To quantify the risk of contracting measles in communities that have contact with exemptors, we applied a mathematical model to the data from the cohort study (mathematical model available from the authors on request).[9] The model examines the spread of disease through a population consisting of different strata or groups. In our application, the model consists of 2 groups: school-aged exemptors and nonexemptors. It is assumed that youth within a given group mix randomly, but exemptors are more likely to be in contact with other exemptors, and nonexemptors are more likely to be in contact with other nonexemptors.

The extent to which youth are more likely to make contacts with others from the same group is determined by the intergroup mixing ratio, which may vary between 0 and 1. For example, if the mixing ratio is 0.6, then 60% of the contacts are made with children chosen at random from the entire community (including that child's own group), and the remaining 40% of a child's contacts are made with other children from the same group. When the intergroup mixing ratio is 1, there is random mixing between exemptors and nonexemptors, and when the mixing ratio is 0, there are no contacts between groups.

Another important parameter in the model is the transmission probability, which is the probability that a susceptible child becomes infected from a single infected child. This parameter may vary across communities because it depends on socioeconomic factors such as crowding. We assume that the vaccine reduces the transmission probability to each child by a given fraction, which is the vaccine efficacy. The vaccine efficacy in terms of transmission probabilities is defined as 1 minus the ratio of the transmission probability to a vaccinee and a nonvaccinee when both are exposed to a single infected person.[10] The estimate of this quantity depends on the assumption about the intergroup mixing ratio: for mixing ratios 0.6, 0.4, and 0.2, the estimated efficacy is 0.62, 0.42, and 0.22, respectively.

The vaccine efficacy in the model differs significantly from the traditional definition of vaccine efficacy, which estimates the measles vaccine to be about 90% to 95% efficacious.[1] Traditional vaccine efficacy is based on the overall attack rates for a vaccinee and a nonvaccinee during an outbreak. Efficacy also depends on the length of the epidemic period and on vaccine coverage. Estimation of efficacy also may be biased if vaccination is not random or if a vaccinee and a nonvaccinee do not have the same exposure to the infecting agent. Vaccine efficacy based on transmission probabilities, as in the model, standardizes exposure to a single contact with an infected person, so it does not depend on factors such as the vaccination strategy or coverage.[9] These 2 measures of vaccine efficacy can be quite different, even if there is no bias, especially if mixing is not random.

Our model provides equations that relate the disease attack rate (incidence) during an outbreak to the values of the transmission probabilities and intergroup mixing ratios. These equations are used to estimate the transmission probabilities from the observed attack rates among exemptors and nonexemptors and predict the expected attack rates based on changes in the number of exemptors.

To apply this model, we assumed that the population consists of 1000 communities. The distribution of the transmission probabilities over the communities was determined so that the overall numbers of expected cases in exemptors and nonexemptors were close to the observed frequencies. The ratio of transmission probabilities for exemptors and nonexemptors was also determined from the overall attack rates.

We developed the model to account for the clustering of exemptors as seen in national and California data. Five percent of the communities were assigned a rather high proportion of exemptors (5%); another 5% of the communities had no exemptors; and the proportion of exemptors in the remaining 90% of the communities was constant (0.21%), which was determined such that the overall proportion of exemptors was the same as in the entire population (0.44%).

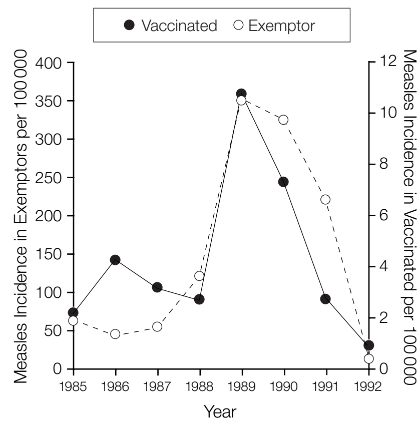
To empirically determine and quantify the impact of changes in the number of exemptors on the number of measles cases among nonexemptors, we explored various changes in the size of the exempt population: 50% decrease in the number of exemptors (ie, these individuals become vaccinated); and 50%, 100%, 200%, and 300% increases in the number of exemptors.

RESULTS

United States measles surveillance data indicate that exemptors were at a statistically significant increased risk of contracting measles vs vaccinated individuals for each age group and in every year (TABLE 1). On average, from 1985 through 1992, for persons aged 5 to 19 years, exemptors were 35 times more likely to contract measles than were vaccinated persons. The relative risk varied greatly by age group and by year, ranging from 4 times the risk of contracting measles for exemptors aged 15 to 19 years compared with vaccinated individuals in 1992, to 170 times the risk in 1988 for those aged 5 to 9 years . Cases among the vaccinated youth were more frequent in the older age categories. Cases among exemptors have a more uniform distribution across age categories (Table 1).

Comparing the incidence among school-aged exemptors with that among school-aged vaccinated children and adolescents during the years 1985 through 1992 indicates that the 1989-1991 measles resurgence may have occurred 1 year earlier among exemptors (FIGURE).

Figure. Timing of Measles Incidence in Exemptions Compared With Vaccinated Youth Aged 5 to 19 Years



Exemptor indicates individuals with religious and/or philosophical exemptions from mandatory school immunization laws; note varying scales between exemptor incidence and vaccinated incidence.

Mapping of exemptors by county was available for California, where school entry laws allow parents to elect personal belief exemptions from mandatory vaccinations for their children. Overall, approximately 0.5% of children enter kindergarten each year with such exemptions, a value that has remained relatively stable over the past 2 decades. However, the frequency of exemptors is not uniform in schools across the state. In 1995, in 84% of California's public and private schools with kindergartens, the proportion of children entering with exemptions was less than 1%. However, in 12% of schools, 1% to 4% of children entered with exemptions, and in 4% of schools, at least 5% of entrants were exempted. The proportion of exemptors is higher in the northern half of the state and is particularly high along the northern foothills of the Sierra Nevada Mountains and in some central and northern coastal areas.

Our mathematical model suggests that changes in the number of exemptors affects measles cases in the nonexempt population (TABLE 2). The mixing ratio largely determines the impact a particular increase or decrease of exemptors would have on the nonexempt population. For example, if the number of exemptors doubled, then the incidence of measles in the nonexempt population would increase by 5.5%, 18.6%, and 30.8% for intergroup mixing ratios of 20%, 40%, and 60%, respectively. The greater the increase in the number of exemptors, the more effect they have on the nonexempt population.

COMMENT

The control of VPDs by means of immunization requirements necessitates careful balance of individual rights and public good.[3,5] Policymakers must weigh the rights of individuals who wish to claim exemptions from immunizations against VPD risks that endanger the general public. Each US state has permitted some degree of exemptions for medical reasons or for religious and/or philosophical reasons.

Table 1. Relative Risk for Measles Among Individuals With Religious and/or Philosophical Exemptions Compared With Vaccinated Persons, United States, 1985-1992*

Age Groups, y	No. of Exemptor Cases	Exemptor Population	Exemptor Incidence per 100 000	No. of Vaccination Cases	Vaccinated Population	Vaccinated Incidence per 100 000	Relative Risk (95% Confidence Interval)†
				1985			
5-9	26	75 732	34.33	141	16 303 444	0.86	40 (27-61)
10-14	30	75 638	39.66	338	16 652 794	2.03	20 (14-29)
15-19	91	82 670	110.08	610	18 307 902	3.33	33 (27-41)
5-19	**147**	**234 040**	62.81	**1089**	**51 264 140**	2.12	30 (25-35)
				1986			
5-9	40	77 847	51.38	389	16 726 650	2.33	22 (16-31)
10-14	35	73 276	47.76	893	16 112 291	5.54	9 (6-12)
15-19	25	83 194	30.05	874	18 390 824	4.75	6 (4-10)
5-19	**100**	**234 317**	42.68	**2156**	**51 229 765**	4.21	10 (8-12)
				1987			
5-9	41	79 644	51.48	229	17 050 848	1.34	38 (28-54)
10-14	39	73 233	53.25	519	16 017 859	3.24	16 (12-23)
15-19	45	82 801	54.35	853	18 278 945	4.67	12 (9-16)
5-19	**125**	**235 678**	53.04	**1601**	**51 347 652**	3.12	17 (12-20)
				1988			
5-9	121	81 369	148.71	152	17 372 772	0.87	170 (134-216)
10-14	89	74 236	119.89	410	16 135 476	2.54	47 (38-60)
15-19	74	82 013	90.23	804	18 081 600	4.45	20 (16-26)
5-19	**284**	**237 618**	119.52	**1366**	**51 589 848**	2.65	45 (40-51)
				1989			
5-9	267	82 418	323.96	1020	17 526 411	5.82	56 (49-64)
10-14	288	76 125	378.33	1385	16 430 352	8.43	45 (40-51)
15-19	283	80 543	351.37	3119	17 726 632	17.59	20 (18-23)
5-19	**838**	**239 086**	350.50	**5524**	**51 683 395**	10.69	33 (31-35)
				1990			
5-9	287	83 706	342.87	1367	17 664 153	7.74	44 (39-50)
10-14	289	78 787	366.81	1032	16 816 683	6.14	60 (53-68)
15-19	204	79 269	257.35	1388	17 364 915	7.99	32 (28-37)
5-19	**780**	**241 762**	322.63	**3787**	**51 845 751**	7.30	44 (41-48)
				1991			
5-9	230	84 378	272.58	483	17 805 737	2.71	100 (86-118)
10-14	217	81 182	267.30	399	17 273 660	2.31	116 (98-137)
15-19	84	77 406	108.52	527	16 852 854	3.13	35 (28-44)
5-19	**531**	**242 966**	218.55	**1409**	**51 932 251**	2.71	81 (73-89)
				1992			
5-9	9	84 784	10.62	145	17 896 080	0.81	13 (7-27)
10-14	9	83 421	10.79	99	17 682 344	0.56	19 (10-39)
15-19	4	77 682	5.15	214	16 798 768	1.27	4 (2-12)
5-19	**22**	**245 887**	8.95	**458**	**52 377 192**	0.87	10 (7-16)

*Exemptors indicates persons with religious and/or philosophical exemptions from mandatory school immunization laws.
†Average relative risk for persons aged 5 to 19 years (1985-1992) was 35 (95% confidence interval, 34-37).

At low vaccination coverage and exemption levels, exemptors are unlikely to have a significant impact from a public health standpoint. Their impact is essentially a minor increase in the percentage of nonimmune or nonimmunized individuals, the great majority of whom are unvaccinated for other reasons. When vaccination coverage levels are high, herd immunity results in low incidence of VPDs, and reports of vaccine adverse events compared with disease incidence are more visible.[11] For diseases that are transmitted from person to person (and are therefore affected by herd immunity, eg, poliomyelitis, measles, pertussis, rubella, diphtheria, and varicella), individual and societal risk-benefit calculations may diverge.[6] The individual (or parents) wishing to minimize individual risk may decide to avoid vaccination by claiming an exemption, relying on the fact that others are vaccinated to provide protection.

Society's motives in vaccination, however, are to protect both individuals and their neighbors.[6] If a large number of individuals choose exemption, a "tragedy of the commons" may result,[12] with reductions in vaccination coverage and ensuing resurgence of VPDs. In several countries in the 1970s and 1980s, concerns about alleged or suspected adverse effects led to decreases in pertussis immunization resulting in a major resurgence in the incidence of pertussis.[13] Such outbreaks highlight the continued relevance of state vaccination laws as long as VPDs have not been eradicated globally.

The effort to increase availability of philosophical exemptions to vaccinations may reflect this divergence in perceived risk-benefit.[5] Unfortunately, VPDs other than poliomyelitis are unlikely to be eradicated globally in the near future.[14] Consequently, high immunization levels against these VPDs will need to be maintained. Thus, in settings like the United States, where levels of reported VPDs are low and reported adverse events following immunization are relatively prominent,[15] debate over appropriateness of exemptions to mandatory immunizations is likely to continue.

There have been many reports of VPD outbreaks that started primarily in exempt individuals and then spread to vaccinated persons.[5] For example, a 1996 measles outbreak in Utah exemplified the effect that clusters of exemptors can have on the community. Statewide, 118 cases occurred, with 107 in Washington County.[16] Compared with the percentage of exemptors nationally (0.44%), Utah has almost 3 times the national average (1.2%), while Washington County has more than 7 times the national average (3.7%). Of the Washington County cases, 48 (45%) were among exemptors. The outbreak lasted 6 generations. Two (66.7%) of the 3 cases in the first generation were exemptors, as were 17 (53%) of 32 cases in the second generation, and 15 (60%) of 25 cases in the third generation. The substantial percentage of exemptors in this outbreak, as well as the concentration of cases among exemptors in the beginning of the outbreak, suggests that they played a major role in transmission (Rebecca Ward, community health specialist, Utah Immunization Program, oral and written communications, September 1997 through September 1998). Such reports confirm the biological plausibility of outbreaks starting in susceptible, unvaccinated individuals and then spreading to vaccinated children and adolescents who are inadequately protected due to vaccine failure.

While individual outbreaks of measles,[17,18] pertussis,[19] rubella,[20] and poliomyelitis[21,22] in unvaccinated religious communities have been reported, data are lacking to quantify the risk of acquiring a VPD among exemptors vs the general population and the risk that exemptors may pose to the nonexempt public. Our study estimates that from 1985 through 1992, school-aged children and adolescents claiming exemptions in the United States were 35 times more likely to contract measles than vaccinated youth. Surveillance data suggest that increases in VPD incidence among exemptors may be a sentinel effect for a potential outbreak among the general population. We also developed a mathematical model that permits quantification of the risk relationship between exemptor and nonexemptor communities, depending on the relative increase or decrease of exemptors and the degree of mixing between the 2 communities.

We chose to use 1985-1992 measles data for this study because this was the most complete data set to which we had ready access. The data examined in this study include the 1989-1991 measles resurgence, the largest outbreak since 1977. In 1990 alone, 26 672 cases of measles and the largest annual number of measles deaths (n = 89) since 1971 were reported.[23] The resurgence has been attributed to poor coverage rates among children younger than 5 years in urban areas and certain minority groups.[24] We focused on school-aged children and adolescents because approximately 80% of measles cases during these years were among in-

Table 2. Change in Number of Measles Cases Among Vaccinated Youth Due to a Decrease or Increase in the Number of Religious and/or Philosophical Exemptions From Immunization Requirements*

Change in No. of Exemptors	Intergroup Mixing Ratio†		
	60%	40%	20%
50% Decrease	12.3% Less cases	8.7% Less cases	3.1% Less cases
50% Increase	15% More cases	9.5% More cases	3.1% More cases
100% Increase	30.8% More cases	18.6% More cases	5.5% More cases
200% Increase	66.8% More cases	36.9% More cases	10.5% More cases
300% Increase	108.4% More cases	55.7% More cases	15.2% More cases

*Table based on 1985-1992 national measles data for persons aged 5 to 19 years. Exemptors indicates persons with religious and/or philosophical exemptions from mandatory school immunizations laws.
†Indicates the percentage of contacts made randomly in the entire community (including child's own group); the remaining contacts are made with other children from the same group.

dividuals younger than 19 years.[25] Furthermore, exemptions are granted when immunization laws are enforced—usually at day care or school entrance. If not medically exempt, the choice is either to become immunized or become an exemptor. The relative risk between exemptors and vaccinated persons quantifies the consequences of this choice.

We developed a mathematical model based on the known characteristics of exemptors that emerged from the CDC State Immunization Reports and California data. Exemptors tend to cluster within local and state boundaries, thereby increasing the effect that they may have on the rest of the population in comparison with a dispersed pattern. For example, a state may have a relatively low percentage of exemptors overall, while a community in that state may have a substantially higher percentage of exemptors. Our model accounts for this by dividing the population into 1000 communities with varying percentages of exemptors. The mixing ratio accounts for individual choices in social settings. Although there may be a relatively small number of exemptors in the state or county, there could be a significant clustering of exemptors in a given individual's social sphere (eg, school, social organizations, and religious community). It is impossible to quantify a mixing ratio on a national level, but personal preferences in social settings suggest that this fluctuates as accounted for in our model.

Our study findings should be interpreted with the following caveats. Cases of measles among exemptors may have been underreported to the Measles Surveillance System because they are more likely to occur in communities with "alternative" health care beliefs, or overreported because measles vaccination was not recorded in the child's immunization history. Furthermore, there may have been inaccuracies in determining the numbers of exemptors because these data were based on state reports from 1990 through 1994. If there was a substantial change in the percentage of exemptors in any state during these years compared with 1985 through 1989, the earlier estimations may be inaccurate. The number of religious and/or philosophical exemptors may have been overestimated because medical exemptions were included in 34 states for which it was not possible to distinguish between type of exemption.

There are also limitations in the age-specific analysis. Vaccination coverage was estimated using state reports for kindergarten through grade 12. It is possible that immunization coverage was higher for the younger students because the primary point of enforcement is typically at first entry to school and strict enforcement of laws began in the late 1970s.[5] This could account for differences in the age distribution of measles cases among exemptors and vaccinated children. These differences also could be explained by the possibility of waning immunity among vaccinated children or environmental exposure (ie, older children may be more likely to have environmental exposure to measles because of age-related differences in social settings and numbers of contacts). It is also possible that some individuals claimed an exemption for a specific vaccine, but not for other vaccines. If this were the case, the child would be counted in the denominator of the exemptor incidence, despite possible immunization for measles.

Unfortunately, surveillance data prior to 1985 or after 1992 are not available to determine if the earlier increase in incidence among exemptors compared with vaccinated children observed in the Figure has a general sentinel effect or an ecologic aberrance unique to these years. However, such an effect is consistent with the known higher susceptibility rate in exemptors.

Throughout this study, exemptors are defined as individuals claiming religious and/or philosophical exemptions offered by individual states. While this definition is functional for an epidemiologic study, it may not be for policy issues because each state defines exemptions differently. Some states require an unequivocal statement from a religious leader that immunization conflicts with the person's religious belief. This type of requirement for an exemption essentially assesses the strength of conviction of the individual applying for an exemption, similar to Selective Service boards assessing exemptions from military draft. Other states grant exemption based on a form signed by parents, indicating that immunizations are against the individual's personal belief. In these states, efforts may not be made to assess strength of conviction.

Further research is needed to better quantify the magnitude of the risks that exemptors pose to nonexemptors. For example, systematic review of the role of exemptors in facilitating transmission in recent and future VPD outbreaks may be useful. Public health surveillance for VPDs should routinely monitor exemption status among new VPD cases. Methods to help identify potential increases in the number or clustering of exemptors before VPD outbreaks occur may be needed. Having determined that exemptors are a risk factor for contracting a VPD, it is important to discover the underlying reasons why individuals are claiming exemptions. Interventions should be developed and implemented to counter misunderstanding of the relative risks and benefits of immunization at both the individual and societal level.

Funding/Support: This work was supported in part by National Institute of Allergy and Infectious Diseases grant R01-AI32042.

Acknowledgment: We thank the following individuals for their contributions to this study: Stephen Redd, MD, and Susan Redd from the National Immunization Program, Centers for Disease Control and Prevention, Atlanta, Ga, for their cooperation and assistance in obtaining data from the Measles Surveillance System; Dennis O'Mara, National Immunization Program, Centers for Disease Control and Prevention, for his assistance in working with state immunization program managers; state immunization program managers, Loring Dales, MD, and Rebecca Ward for their time and assistance in providing important data; William Pann, MPH and Stella Chuke, MPH, for their contributions in mainframe statistical programming; Alan Hinman, MD, Task Force for Child Survival and Development, Walter Orenstein, MD, National Immunization Program, and Robert F. Breiman, MD, Stephen Sepe, MPH, and Jane Zanca, National Vaccine Program Office, for their insightful critique of the study; and the *JAMA* reviewers for their insightful critique of the final manuscript.

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> There's nothing really difficult if you only begin—some people contemplate a task until it looms so big, it seems impossible, but I just begin and it gets done somehow. There would be no coral islands if the first bug sat down and began to wonder how the job was to be done.
>
> —John Shaw Billings (1838-1913)

response protective effect, and patients with MS have lower levels of uric acid than controls.[4,5] To further assess this possible inverse relationship between nitric oxide and uric acid, we performed a circadian analysis of these 2 substances in a series of subjects without a history of either MS or gout.

Methods. In 1979, 11 healthy male volunteers, then aged 32 to 57 years, were selected from a military reserve unit on the basis of good venous access. In 1979, and again in 1988, 1993, and 1998, blood was obtained at 3-hour intervals over a 24-hour period, and the uric acid concentration of each sample was measured. Nitric oxide levels were also measured in the 1998 samples. Five of the subjects developed type 2 diabetes during the study period, but no other chronic diseases were reported. Data were analyzed for circadian characteristics by population multicomponent analysis.[6]

Results. The mean uric acid levels at the 4 successive measurement years were 0.40 mmol/L (95% confidence interval [CI], 0.33-0.46 mmol/L), 0.40 mmol/L (95% CI, 0.36-0.43 mmol/L), 0.39 mmol/L (95% CI, 0.33-0.45 mmol/L), and 0.38 mmol/L (95% CI, 0.35-0.42 mmol/L), respectively. This stability of uric acid over time allowed us to pool the values for the analysis. A significant circadian rhythm was obtained for a harmonic model with 2 components (with periods of 24 hours and 8 hours) for both uric acid ($P<.001$) and nitric oxide ($P=.004$). The timing of uric acid peak and nitric oxide trough concentrations is virtually cosynchronous, at 5:08 and 5:32, respectively (FIGURE).

Comment. The temporally reciprocal relationship between uric acid and nitric oxide in these men suggests that their concentrations are physiologically related. This observation supports previous results of the protective effects of uric acid in nitric oxide–mediated diseases, such as MS.

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CORRECTIONS

Inaccurate Statement: In the Original Contribution entitled "Health Consequences of Religious and Philosophical Exemptions From Immunization Laws: Individual and Societal Risk of Measles" published in the July 7, 1999, issue of THE JOURNAL (1999;282:47-53), there was an inaccurate statement on page 48 that reads, "Texas requires that individuals claiming religious exemptions be a member of a recognized religious group that opposes all immunizations and submit a letter from a faith leader." It should read, "Texas law requires that individuals claiming religious exemptions submit an affidavit signed by the parent or guardian stating that the immunization 'conflicts with the tenets and practices of a recognized religious organization of which the applicant is an adherent or member.'" There is no requirement that the affidavit be signed by a faith leader or that exemption be for all vaccinations.

Incorrect Wording: In the Original Contribution entitled "Prognostic Value of 24-Hour Blood Pressure in Pregnancy" published in the October 20, 1999, issue of THE JOURNAL (1999;282:1447-1452), the footnotes to two of the tables were worded incorrectly. On page 1448, in Table 1, and on page 1449, in Table 2, the second footnote (†) should read, "*P* value is comparison between normotensive, white coat hypertensive, and true hypertensive groups for all characteristics."