
Evaluation of a Two-Dose Measles, Mumps, and Rubella Vaccination Schedule in a Cohort of College Athletes

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Others who made this study possible were Mr. Richard O'Neill, EDCP, MD DHMH, who recognized and referred research opportunities at UMBC, Ms. Sue Silberman and Mr. Al Ritter, Laboratories Administration, MD DHMH, who performed the enzyme-linked immunosorbant assays, and Ms. Helen Mihialovici of the UMBC Student Health Center, who managed student health records.

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Synopsis

Despite high vaccination levels, measles outbreaks continue to occur among vaccinated adults. In response, new guidelines call for two doses of measles vaccine. To determine seroprevalance and response to vaccination in seronegative persons, we tested serums from 256 college athletes at a Maryland State college by enzyme-linked immunosorbant assay, vaccinated seronegatives, then re-tested vaccinees. High school records were obtained for persons seronegative to measles.

Of 256 students, 53 (21 percent) were seronegative to measles alone, 13 (5 percent) were seronegative to rubella alone, and 5 (2 percent) were seronegative to both. Among those seronegative to measles, 86 percent had previously received a dose of measles vaccine. After vaccination, 37 persons initially seronegative to measles and 9 seronegative to rubella were 97 percent and 100 percent seropositive, respectively. The high measles seroconversion rate suggests that the two-dose vaccine schedule should effectively control campus measles outbreaks and, if given as measles-mumps-rubella vaccine, will also improve immunity to rubella and mumps.

IN 1983, when case counts of measles in the United States had reached a nadir of 1,497, it appeared that measles elimination was at hand (1,2). However, by 1989, case counts were 18,193, a twelvefold increase that has continued, with 27,786 cases reported for 1990. Likewise, in the United States the incidence of rubella had steadily declined since introduction of the vaccine. A low of 225 cases was reported in 1988 and only 2 indigenous cases of congenital rubella syndrome were reported in 1989. However, in 1990 there has been a relative resurgence of rubella outbreaks, especially among adults in prisons, universities, and religious communities with prohibitions against vaccination. Measles epidemics have occurred among mostly unvaccinated preschool-age children and among mostly vaccinated school-age children

and young adults (3). High levels of vaccination of this older group have been well documented (4-6).

In response to the increasing number of measles cases among persons vaccinated with one dose of measles containing antigen, both the Immunization Practices Advisory Committee (ACIP) (7) and the American Academy of Pediatrics (AAP) (8) have recommended two-dose schedules of measles-containing antigen, given as measles-mumps-rubella (MMR) vaccine, to persons born after 1956. The purpose of the new two-dose MMR schedule is to produce immunity in previously vaccinated susceptibles. Finland (9) and Sweden (10,11) have used two-dose schedules since the early 1980s.

College students have figured prominently in the resurgence of measles. From 1980 through 1989, 6 percent of all reported measles cases were transmit-

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ted in college settings. Of all cases among college students that occurred between 1986 and 1989, 51 percent had received one dose of measles vaccine in accordance with the guidelines effective at that time (12). The susceptibility rate for college students was estimated to be 5 percent to 15 percent in 1985 (13).

The policy of one Maryland State college is to require self-reported vaccine histories of all matriculated students. In autumn 1989, intercollegiate athletes were additionally required to be tested by enzyme-linked immunosorbant assays (ELISA) for measles and rubella antibodies. The measles ELISA assay detects antibodies that are specific indicators of measles protection (14,15). Athletes found to be seronegative to either antigen were vaccinated using MMR. We sought to assess the rate of seronegativity in this population of athletes and to evaluate the response to vaccination among those found to be seronegative. Since self-reported vaccine histories were available, we also sought to identify which histories might predict seronegativity.

Methods

In August and September 1989, all intercollegiate athletes at the college were required to submit blood samples before participating in college athletics. The samples were tested by the Laboratories Administration, Maryland Department of Health and Mental Hygiene, using ELISA for total measles antibody (A) and total rubella antibody (B). In accordance with the manufacturers' instructions, samples with index values of 1.00 or more were considered seropositive for measles or rubella. Persons seronegative to either or both antigens were requested to come to the campus health unit for vaccination; at least two letters were sent and three telephone calls made to each student before he or she was considered lost to followup. Seronegative students were vaccinated (C) and again tested by

ELISA (A and B) between 3 weeks and 1 year after vaccination. No measles or rubella disease was reported from the college during the study period.

Prior to registration, all students were required by the college to complete a medical form which included their history of vaccination against measles, rubella, and other vaccine preventable diseases. Provider verification was not required, but reference to provider records was encouraged. These college records were reviewed and dates of reported vaccination were recorded. Chi-square and one-tailed Fishers exact tests were used to evaluate statistical significance.

To validate self-reported vaccination histories, high school vaccination records were sought for all athletes seronegative to measles. High school records were compared for agreement on doses and age at delivery of measles vaccine. A previous study in Maryland had shown high levels of agreement between high school and provider records. Eliminated from comparison for agreement were those seronegative persons who attended high schools that routinely shredded vaccine records upon graduation.

Results

The 256 athletes had a median age of 19 years (range 16–27 years) and 62 percent were male; 90 percent were Maryland residents. All 256 athletes were tested for measles antibodies. Of these, 58 (23 percent, 95 percent confidence intervals (CI) 18 to 28 percent) were seronegative.

Neither age nor sex was associated with seronegativity to measles. Of the 58 persons seronegative to measles, 9 had attended high schools that routinely shredded vaccination records upon graduation. Of the remaining 49 persons, 42 (86 percent) had high school records indicating that at least one dose of measles vaccine had been given after 12 months of age. Of the 58 seronegative athletes, 55 (95 percent) were then vaccinated with MMR. Of these 55, 37 (67 percent) had second serologies performed. Upon re-testing, 36 (97 percent) of these were seropositive.

Similarly, these 256 athletes were serotested for rubella antibody. Eighteen (7 percent, 95 percent CI 5 to 11 percent) were seronegative. Five (28 percent) of these 18 were also seronegative for measles. Neither age nor sex was associated with seronegativity to rubella. Seventeen (94 percent) of the 18 were vaccinated with MMR. The one person lost to followup was also seronegative to measles. Of these 17, second serologies were obtained for 9

Table 1. Measles serostatus of athletes' self-reported history of measles vaccine, University of Maryland, August–September 1989

Number of doses and age at vaccination	Total			Last vaccine dose before Jan. 1, 1980			Last vaccine dose after Jan. 1, 1980		
	Number	Seronegative		Number	Seronegative		Number	Seronegative	
		Number	Percent		Number	Percent		Number	Percent
None.....	32	5	16
One dose at younger than 12 months..	9	4	44	9	4	44
One dose at 12–14 months	63	17	27	63	17	27
One dose at 15 months or older	116	25	22	92	23	25	24	2	8
Two doses at 12 months or older	36	7	19	11	4	36	25	3	12
Total	256	58	23	175	48	27	49	5	10

Table 2. Vaccine history of athletes with seronegative measles status

Reported doses of vaccine and age at vaccination	Number seronegative	Vaccine status in high school records
None.....	5	3 records not shredded; 1 given vaccine after 12 months, 1 at 12–14 months, 1 at 15 months or older.
One dose at younger than 12 months....	4	4 records not shredded; 1 agreed for younger than 12 months, 1 at 12–14 months, 2 not available.
One dose at 12–14 months	17	15 records not shredded; 12 agreed for 12–14 months, 2 documented at 15 months, 1 not available.
One dose at 15 months or later	25	20 records not shredded; 16 agreed for 15 months or later, 2 documented at 12–14 months, 1 documented 2 doses, 1 not available.
Two doses after 12 months	7	7 records not shredded; 2 agreed for 2 doses, 1 documented 1 dose at 12–14 months, 3 documented 1 dose at 15 months, 1 not available.

(53 percent) athletes. All nine were seropositive for rubella antibodies on re-testing.

Overall, 71 (28 percent) persons were initially seronegative to either measles or rubella. Three seronegative persons were lost to followup and one failed to seroconvert, leaving at least four (1.6 percent) athletes seronegative to either measles or rubella or both at the end of this program.

Table 1 shows the distribution of self-reported vaccination histories and serologic results. Comparisons of agreement between the self-reported histories and the high school records of seronegative students are shown in table 2. Of the 49 measles-seronegative students with unshredded high school records, 31 (63 percent) had school records that exactly agreed as to the number of doses and age at measles vaccination reported by the athlete. Among the 35 seronegative persons reporting only one dose given at or after 12 months of age, 80 percent agreed.

As shown in table 1, seronegativity among those reporting one dose of measles vaccine decreased with increasing age at vaccination (44 percent for those vaccinated before 12 months, 27 percent for those vaccinated between 12 and 14 months, and 22

percent for those vaccinated at 15 months or older), with a trend toward statistical significance (chi-square test for trend = 2.25, $P=.13$). Among the 116 persons who reported one dose of measles vaccine after 15 months, the 92 persons reporting vaccination before 1980 were more likely to be seronegative for measles than the 24 persons reporting vaccination since that date (25 percent versus 8 percent, $P=.08$).

The 222 persons who reported receiving at least one dose of rubella containing antigen on or after their first birthday were not less likely to be seronegative than the 34 persons who did not (7 percent versus 6 percent, $P=.56$). Among these same 222 persons, the 183 persons vaccinated before 1980 had a higher seronegative rate than the 39 persons vaccinated in 1980 or later (8 percent versus 3 percent), but this difference was not statistically significant ($P=.19$).

Discussion

This study has documented a high seronegativity rate to measles and rubella among a cohort of college athletes, demonstrated that more than 95

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percent of seronegative persons became seropositive after receipt of a dose of MMR, and confirmed reported effects of age and date of measles vaccination.

The overall measles seronegativity rate (23 percent) was higher than that previously reported in studies that used the same assay (16-18). Although the populations in those studies were of comparable ages, they were an earlier birth cohort and were hospital employees, thus they may have had greater exposure to wild measles virus.

High school records confirmed the self-reported vaccine histories of the students in our study and established that the seronegative persons had been well vaccinated. These athletes were healthy, young, middle-class adults with States of residence not different from other students at the school. Our seronegativity rate may not reflect true susceptibility: while a positive ELISA connotes protection (4), ELISAs may be insensitive to protective antibodies detected by the plaque neutralization assay (PNA) (19). In contrast to PNAs, ELISAs for measles antibodies are inexpensive and widely used to identify possibly susceptible persons. To understand better the public health significance of ELISA seronegativity, PNA studies of serums negative by ELISA are needed.

One dose of MMR vaccine caused seroconversion in 97 percent of persons seronegative to measles and 100 percent of those seronegative to rubella. Because immunoglobulin (IgM) titers were not measured after vaccination, we were not able to define whether the high initial seronegative rate was due to primary vaccine failure or waning immunity.

Self-reported earlier age at vaccination and vaccination before 1980 were both associated with seronegativity to measles. This finding is consistent with epidemiologic studies showing increased risk of disease among those vaccinated at an earlier age (20) and those vaccinated before 1980 (21). Still, comparison with high school records showed that a

substantial portion (15 percent) of self-reported records were miscoded, confirming that self-reported histories are not ideal for studies of vaccine effects. This conclusion was reemphasized by the unexpected finding of 19 percent seronegativity among 36 persons self-reporting two doses of vaccine; only 2 of the 7 seronegative persons had high school histories that agreed.

Extending high school record reviews to the seropositives might have better quantified these effects, but we chose to follow up only those self-reports which we had the most reason to doubt (the seronegatives). While limiting the scope of this study to dimensions within the reach of a campus health unit limited the precision of available data, it probably enhanced the feasibility of replication.

Self-reported vaccination histories are widely used as entrance requirements by colleges. While the large majority of self-reports of one dose of measles vaccine among seronegatives agreed with high school records, self-reports of two doses did not consistently agree. This difference may have resulted from a failure to update high school records. Receipt of an additional dose given during high school or prior to matriculation should be documented on the high school record or in the permanent immunization record.

The ACIP, AAP, and American College Health Association have all recommended that new college entrants be required to document two doses of live measles vaccine after the first birthday, physician diagnosed measles, or laboratory evidence of measles immunity (12). In this small cohort of college athletes, antibody screening and locating the seronegative persons for vaccination was a feasible, though time consuming strategy. For larger cohorts of students, such a program probably would not be feasible. In this cohort, giving a dose of MMR to all those without a reported history of two doses after their first birthday would have been easier to administer and would have led to approximately the same seropositive rate.

Regardless of the cause of seronegativity, the high rate of seroconversion in this study suggests that, if followed, the two-dose measles vaccine schedule can be an effective means of limiting the number and size of campus outbreaks of measles. Additionally, when given as MMR, this schedule will increase protection against rubella for seronegative college women of childbearing age (thus affording protection against congenital rubella syndrome) and, though not tested in this cohort, is expected to increase immunity to mumps.

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Equipment

- A. Measlestat, Whittaker M. A., Bioproducts, Walkersville, MD.
- B. Rubella ELISA, Wampole Laboratories, Cranbury, NJ.
- C. MMR-II, Merck, Sharp and Dohme, Rahway, NJ.