The United Kingdom and United States have recently experienced large outbreaks of mumps, which raises concerns about vaccine effectiveness. The effectiveness of the mumps component of the measles, mumps, rubella (MMR) vaccine was estimated using the screening method. In England from January 2004 through March 2005, 312 cases of mumps were reported in children eligible to have received 2 doses of MMR vaccine. Of these children, 52 (16.7%) had received 1 dose of MMR vaccine, and 97 (31.1%) had received 2 doses. Vaccine effectiveness was 88% (95% confidence interval [CI] 83%–91%) for 1 dose and 95% (95% CI 93%–96%) for 2 doses. The effectiveness of 1 dose declined from 96% (95% CI 81%–99%) in 2-year-olds to 66% (95% CI 30%–83%) in 11- to 12-year-olds, and the effectiveness of 2 doses declined from 99% (95% CI 97%–99.5%) in 5- to 6-year-olds to 86% (95% CI 74%–93%) in 11- to 12-year-olds (p<0.001 for 1 or 2 doses). Waning immunity may contribute to mumps outbreaks in older vaccinated populations.

In October 1988, immunization against mumps was introduced in the United Kingdom as a single dose of measles, mumps, rubella (MMR) vaccine offered to all children 12–15 months of age (1). Reports of disease declined 79% in the first year, from 20,713 in 1989 to 4,277 in 1990. In 1996, a second dose of MMR was introduced at school entry (2). From 1990 through 2003, the number of reported cases declined from 95% (95% CI 97%–99.5%) in 5- to 6-year-olds to 86% (95% CI 74%–93%) in 11- to 12-year-olds (p<0.001 for 1 or 2 doses). Waning immunity may contribute to mumps outbreaks in older vaccinated populations.

During 2005–2006, a large outbreak of mumps involving >2,500 possible cases from 11 states was reported in the United States (7). The reemergence of mumps in countries that had high levels of vaccine coverage for many years raises questions about the effectiveness of the mumps component of the MMR vaccine and the possible contribution of waning immunity.

In early clinical trials, the efficacy of a single dose of mumps vaccine was >95%, but estimates of the effectiveness in field evaluations have been 62%–85% (8–18). The possibility of waning immunity has been suggested in several studies but not conclusively demonstrated (11–13,19). The UK outbreak offered the opportunity to evaluate the effectiveness of 1 or 2 doses of MMR vaccine and to investigate the presence of waning immunity by using routinely collected data.

**Methods**

We reviewed clinically reported mumps cases in England from January 1, 2004, through March 31, 2005, that were confirmed by oral fluid mumps-specific immunoglobulin M testing within 6 weeks of symptom onset (20). Only case-patients eligible to have received 2 doses of MMR vaccine through the routine program (i.e., those born after 1992) were included. Case-patients 3–5 years of age were excluded because children receive the second dose of MMR between these ages and, therefore, reliable population coverage data are not available for comparison. Pos-
sible vaccine-associated cases (i.e., symptom onset within
6 weeks after vaccination) were also excluded. Vaccination
histories were obtained from physician records or child
health computerized recordkeeping systems.

Quarterly population vaccine coverage data for chil-
dren 2 and 5 years of age were obtained from the Cover of
Vaccination Evaluated Rapidly program (21,22). Because
of changes in health service boundaries and child health
computerized recordkeeping systems, data for a small
number of areas were missing for some quarterly periods. In
addition, 5-year coverage data have been shown to underesti-
mate the true coverage in some areas (23). To compensate
for this, coverage data were adjusted. Missing values were
estimated using linear interpolation from the values sub-
mitted in previous and subsequent quarters. When cover-
age of first-dose MMR for the same birth cohort was lower
at 5 than at 2 years of age, the coverage at 5 years of age
was assumed to be 3% higher than the value at 2 years of
age (based on data from a sentinel surveillance scheme)
(22). The adjusted data were used to approximate popula-
tion coverage for school-year cohorts (born from October
1 through September 30 of the following year) to allow for
similar levels of exposure within school years. Coverage
data at 5 years of age for children born in 2000 were not
yet available, so values were estimated from the previous
cohort and data from the first 2 quarters. Coverage data
were divided into 2 categories, within and outside London,
because coverage estimates are lower in London but fairly
similar in the rest of the country (24).

Statistical Analysis
Vaccine effectiveness was calculated from the propor-
tion of confirmed mumps cases vaccinated (PCV) and the
proportion of the population vaccinated (PPV) using the
following formula (25):

\[
\text{Vaccine effectiveness} = \frac{1 - (\text{PCV}(1 - \text{PPV}))}{(1 - \text{PCV})\text{PPV}}
\]

The data were grouped by school year, age, sex, and
area of residence (within or outside London) and were ana-
yzed by using logistic regression with an offset (incorpo-
rating expected PPV by area and birth cohort) for vaccine
coverage. When estimating vaccine effectiveness for 1
dose, those who had received 2 doses were excluded from
the calculation of PPV. Similarly, those with only 1 dose
were included when estimating vaccine effectiveness for 2
doses. To estimate overall effectiveness, a model includ-
ing only a constant was fitted. Effectiveness in different sub-
groups was estimated from univariable models. If >1 vari-
able was statistically significant on univariable analysis,
multivariable analysis was performed.

Data from computerized child health systems, used
for scheduling and recording vaccinations given, have
consistently been shown to underestimate vaccine cover-
age (26,27). Sensitivity analyses explored the effects of
possible underestimation of vaccine coverage by repeat-
ing calculations assuming that PPV was 1%, 2%, and 5%
higher than that reported. Vaccine effectiveness estimates
were also calculated using the unadjusted coverage data to
examine the effect of data cleaning.

Estimating coverage in older children from a measure-
ment at 5 years of age could lead to an underestimate of
effectiveness if there were a subsequent increase in cov-
verage. Therefore, we obtained data on children vaccinated
with MMR after 5 years of age from the child health com-
puter system in the former South Thames region in 2000.
Analyses explored the effect of an increase in coverage of
0.04%–0.4% per year of age after 5 years of age. The pro-
portion of persons predicted to be susceptible to mumps,
by age in England in 2005, was calculated by multiplying
age-specific estimates of vaccine effectiveness by annual
birth cohort coverage data.

Results

Vaccine Effectiveness
We found 312 confirmed cases of mumps that were eli-
gible for inclusion. Vaccination history was obtained for all
case-patients. The proportion of unvaccinated case-patients
decreased with increasing age and was higher in younger
birth cohorts (Table 1). The proportion of vaccinated case-
patients did not differ according to area of residence or sex.

Age at first dose of MMR vaccine ranged from 10
months to 5 years 9 months and at second dose from 16
months to 6 years. Of those who had received MMR, >90%
received the first dose at 12–24 months of age and the sec-
ond dose at 3–5 years of age.

Adjusted population vaccine coverage declined during
the study period (Table 2). Outside London, the percentage
of children who received 1 dose of MMR by their second
birthday declined from 92.7% to 82.7% from the 1993 to
the 2002 birth cohort. The percentage who received 2 dos-
es by their fifth birthday was more stable, declining from
78.1% to 76.4% from 1993 to 2000. In London, estimates
of coverage were lower and also declined over time.

Overall estimates of vaccine effectiveness were 87.8%
(95% confidence interval [CI] 83.1%–91.1%) for 1 dose
and 94.6% (95% CI 92.9%–95.9%) for 2 doses. There
was no statistically significant variation in vaccine effec-
tiveness for 1 or 2 doses by area of residence (p = 0.3 for
1 dose, p = 0.7 for 2 doses) or sex (p = 0.7 for 1 dose,
p = 0.2 for 2 doses). Vaccine effectiveness decreased with
increasing age for those who received either 1 or 2 doses
(p<0.001) (Table 3). Vaccine effectiveness also varied with
birth cohort (p = 0.02 for 1 dose, p = 0.003 for 2 doses). As
birth cohort and age were correlated, it was not possible
to separate the effects of age group and birth cohort for 1-dose effectiveness; the effect of birth cohort on 2-dose effectiveness was lost when adjusted for age. Application of our estimates of vaccine effectiveness to UK coverage data (Figure 1) predicts that >20% of children 11–12 years of age are not protected against mumps.

**Sensitivity Analysis**

Estimates of vaccine effectiveness using raw coverage data were 86.5% (95% CI 81.5%–90.3%) for 1 dose and 96.8% (95% CI 95.6%–97.7%) for 2 doses. Estimates of vaccine effectiveness increased from 87.8% to 90.8% for 1 dose and from 94.6% to 99.3% for 2 doses, for an increase in PPV of 1%–5% (Table 4).

Age at first MMR vaccination was available for 148,525 children registered on the South Thames child health computer system. In each birth cohort, 3–45 children per year received the first MMR dose at >5 years of age, most between 5 and 6 years of age. On average, an additional 0.04% (95% CI 0.036%–0.045%) of children received MMR vaccine per year of age after their fifth birthday. In the sensitivity analysis (Figure 2), a fixed increase in coverage per year of age did not abolish the statistically significant decline in vaccine effectiveness until coverage increased by at least 0.4% per year, 10× greater than that estimated from children in the South Thames region.
Discussion

Our estimate of 87.8% effectiveness for 1-dose mumps vaccine is lower than efficacy estimates from clinical trials (8,9) but higher than those from most published field evaluations (10–14). Lower estimates in field studies could result from problems with vaccine storage or administration, errors in case definition (i.e., clinical instead of laboratory-confirmed cases) or ascertainment, inaccurate determination of vaccination status, and bias from conducting studies during outbreaks (10,28,29). Because clinical trials have relatively short follow-up periods, waning immunity may also produce lower observed effectiveness in field evaluations. We observed a decline in protection with increasing age, which suggests that waning immunity may occur. After 2 doses, the magnitude of this decline is small, and effectiveness remains above >85% even 6–7 years after the second vaccination.

Research on whether protection from mumps vaccine declines with time since vaccination is contradictory. In 2 US outbreaks, children vaccinated >5 (12) or >3 (19) years before each outbreak were at higher risk for mumps. In 2 other US outbreaks, no evidence was found for increased infection rate with time since vaccination (11,16). A study from Belgium found increasing risk for disease with time since vaccination (13). In the presence of natural boosting, neutralizing antibodies have been demonstrated up to 12 years after vaccination (30). However, duration of antibody persistence in a high-coverage setting where mumps circulation has declined is not known. In Finland, a decline in mumps antibody titers was demonstrated in vaccinated children (31), and the proportion of children seropositive for mumps antibodies some years after MMR vaccination was lower than expected in Sweden and the United Kingdom (32,33).

Our estimates may be affected by several biases. Unvaccinated children may mix with other unvaccinated children and exposure may be more common than in vaccinated children, which would lead to an overestimation of vaccine effectiveness. Because most cases occurred in age groups not eligible for vaccination, however, it is likely that exposure to mumps was fairly uniform.

In addition, those who do not access healthcare for vaccination may be less likely to seek care for mumps disease. Consequently, these cases may be less likely to be reported, which would lead to an underestimation of vaccine effectiveness. The availability of free universal primary care, however, means that persons with mumps should not have difficulty accessing medical care in the United Kingdom. Studies during local outbreaks may also underestimate vaccine effectiveness, as a chance cluster of cases is more likely to be reported (29). The 2004–2005 outbreak of mumps was a national outbreak affecting all regions of the United Kingdom and is therefore unlikely to be subject to this bias (6).

The screening method relies on accurate estimates of population vaccine coverage (25). Estimates of vaccine effectiveness were similar using raw and adjusted coverage values, which suggests that our adjustments had not introduced any major bias. Sensitivity analyses that explore the effects of underestimation of vaccine coverage demonstrate that overall effectiveness could be as high as 90% for 1 dose, but this would require true coverage to be ≥5% higher than recorded.

If mumps cases had occurred before the period of our investigation, a false impression of waning immunity could have resulted because these cases would have affected proportionately more unvaccinated than vaccinated children (34). Immunity develops in children who have had mumps, so unvaccinated children would be preferentially removed from the population at risk. Therefore, with increasing age, the proportion of mumps cases diagnosed in vaccinated children would increase. From 1990 through 2003, however, UK mumps incidence was extremely low, so past infection is unlikely to be responsible for the observed decline in vaccine effectiveness with increasing age.

The possible effect of migration to and from the United Kingdom on these estimates is difficult to assess. Of immigrants to the United Kingdom, ≈80% arrive from...
monwealth countries or the European Union each year, and approximately 40,000 are children <15 years of age (35). Some of these countries do not use routine mumps vaccine; therefore, our estimates of vaccine coverage in older children may be too high. This would lead to an apparent increase in effectiveness with age, rather than the effect observed.

The use of vaccine coverage at the fifth birthday assumes that no further mumps vaccines are given after this age. If coverage gradually increased after this age, effectiveness would be underestimated for older age groups. Children 5–12 years of age, however, have generally not been targeted by MMR catch-up campaigns, and the target payment incentive in primary care does not apply after 6 years of age (36). From the South Thames data, most MMR given after the fifth birthday is given to children 5–6 years of age, and the numbers vaccinated are too low to produce the observed decline in effectiveness. We therefore conclude that an increase in coverage after 5 years of age is unlikely to fully explain the decline.

No evidence has shown that vaccine quality and handling changed over time. All cohorts >6 years of age were only eligible for MMR-II (Sanofi Pasteur MSD, Berkshire, UK) for the first dose, so a change in product cannot be responsible for the decline in first-dose effectiveness after this age. Priorix (GlaxoSmithKline, Uxbridge, UK) became available in 1998, but as population coverage by vaccine manufacturer is not available, we are unable to show any differences between vaccines.

According to this study, <80% of children 11–12 years of age are protected against mumps, less than the suggested threshold of 90%–92% to interrupt transmission (37). The true proportion of those with immunity may now be higher than this because many unvaccinated persons will have acquired natural infection and vaccinated persons may have been boosted by exposure during the outbreak.

Our estimates of vaccine effectiveness suggest that the mumps component of MMR provides excellent protection through routine administration in the United Kingdom. The observation of waning immunity is, however, a cause for concern because the proportion of susceptible adolescents may increase, which could lead to future outbreaks in this age group. Because most recent cases have occurred in persons too old to have been vaccinated, the contribution of waning immunity to the current UK outbreak is small (6). To minimize the risk of future outbreaks, MMR vaccine coverage with both doses must be improved and maintained.

Dr Cohen is a clinical microbiologist/epidemiologist, Epidemiology Unit, National Institute for Communicable Diseases, National Health Laboratory Service, Johannesburg, South Africa. Her research interests include vaccine-preventable diseases, surveillance, HIV, and opportunistic infections.

References

Mumps Vaccine Effectiveness, England


26. Ramsay M, White J, Crowcroft N. MMR uptake data are unlikely to be subject to manipulation. BMJ. 2002;324:1394.


Address for correspondence: Cheryl Cohen, National Institute for Communicable Diseases, Private Bag X4, Sandringham, 2131, Johannesburg, South Africa; email: cherylc@nicd.ac.za

NEW

Job Postings and Conference Announcements

For information on how to publish your job and conference announcements in Emerging Infectious Diseases, please contact the CDC Foundation (http://www.cdcfoundation.org), 50 Hurt Plaza, Suite 765, Atlanta, GA 30303, USA. Phone (404) 653-0790. Fax: (404) 653-0330.