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Vaccine waning and mumps re-emergence in the United States

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Abstract

Following decades of declining mumps incidence amid widespread vaccination, the United States and other developed countries have experienced a resurgence in mumps cases over the last decade. Outbreaks affecting vaccinated individuals and communities with high vaccine coverage have prompted concerns about the effectiveness of the live attenuated vaccine currently in use. It is unclear if immune protection wanes, or if the vaccine protects inadequately against currently circulating mumps virus lineages. Synthesizing data from six studies of mumps vaccine effectiveness, we estimated that vaccine-derived immune protection against mumps wanes on average 27 (95% confidence interval: 16 to 51) years post-vaccination. After accounting for this waning, we found no evidence that the emergence of heterologous virus genotypes contributed to changes in vaccine effectiveness over time. A mathematical model of mumps transmission confirmed the central role of waning immunity to the vaccine in the re-emergence of mumps cases. Outbreaks from 2006 to the present among young adults, and outbreaks in the late 1980s and early 1990s among adolescents, aligned with peaks in mumps susceptibility of these age groups predicted to be due to loss of vaccine-derived protection. In contrast, evolution of mumps virus strains escaping immune pressure would be expected to cause a higher proportion of cases among children, not adolescents and young adults as observed. Routine use of a third vaccine dose at age 18 years, or booster dosing throughout adulthood, may be a strategy to prevent mumps re-emergence and should be assessed in clinical trials.

Introduction

Over the last decade, mumps outbreaks have thwarted the goal of eliminating indigenous or non-imported mumps virus transmission in the United States by the year 2010 (1, 2).

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Data and materials availability: Code for replicating analyses and figures is available at http://github.com/joelewnard/mumps.

Whereas over 90% of US-born children experienced mumps infections by age 20 in the pre-vaccine era (3), incidence declined substantially after licensure of a live attenuated vaccine (the Jeryl Lynn vaccine) in 1967, in particular after the 1977 recommendation for its routine use among infants as part of the measles-mumps-rubella (MMR) vaccine (2). Outbreaks among vaccinated middle school- and high school-aged children arose in the late 1980s, followed by sustained reductions in incidence after children were recommended to receive a second MMR dose at 4-6 years of age (4). However, an ongoing resurgence in mumps cases began with a series of outbreaks on university campuses in 2006 (2). An older age of infection (ages 18-29 years, compared to the pre-vaccine average of 5-9 years) has been a defining feature of these outbreaks (5), similar to recent occurrences in Canada, western Europe, and Asian countries with routine MMR vaccination (6–9).

These circumstances are troubling on two fronts. First, as many as 10% of mumps infections acquired after puberty may cause severe complications including orchitis, meningitis, and deafness, in contrast to a milder clinical course in children that typically involves fever and parotid gland swelling (10). Second, a majority of mumps cases in recent outbreaks have been reported among young adults who received two vaccine doses as recommended (11). This observation has prompted concerns about suboptimal performance of the Jeryl Lynn vaccine currently in use (12).

It is unclear whether recent outbreaks in vaccinated communities are due to the waning of vaccine-derived immunity or to the emergence of mumps virus strains escaping vaccine-driven immunological pressure. Distinguishing between these possibilities is critical to policymakers and members of the scientific and medical communities: at issue is whether the re-emergence of mumps can be prevented by modifying vaccine dosing schedules or if a new vaccine must instead be developed (12).

To this end, we sought to distinguish waning of vaccine-derived protection from long-term changes in vaccine effectiveness against circulating mumps strains using data from six epidemiological studies of mumps vaccine effectiveness performed over past decades in the United States and Europe (table S1). Pooling data from these studies, we tested whether the strength of vaccine-derived immune protection declines with time since receipt of the vaccine—a pattern that would suggest vaccine waning—and whether the degree of protection has changed over recent decades amid shifts in the circulating population of mumps virus lineages. We then measured the potential impact of the waning of vaccine-derived immunity on the susceptibility of the United States population to mumps over the decades since vaccine licensure, and used mathematical models to assess whether recent mumps virus transmission dynamics are more consistent with hypotheses of waning immunity or vaccine escape. Specifically, we compared expected age-specific incidence in stochastic simulations of mumps transmission within two hypothetical vaccinated populations. The first was subject to waning protection based on our estimates of the duration of vaccine-derived immunity; the second experienced durable protection but confronted mumps virus strains against which vaccination provided low degrees of protection. We used our findings to evaluate alternative vaccination policies aiming to enhance protection among adults.

Results

Evidence of waning immunity in studies of vaccine effectiveness

Uncertainty about the protective efficacy of the Jeryl Lynn mumps vaccine—ranging from 95% following a single dose in randomized controlled trials (13) to <50% 2-dose effectiveness during recent outbreaks (14)—has undermined efforts to gauge population immunity. This variation in estimates of effectiveness permitted us to evaluate several hypotheses about the reasons mumps cases have re-emerged among vaccinated persons (2, 12). Fitting a meta-regression model to data from prospective and retrospective cohort studies (table S1), we identified that the time elapsed since receipt of an individual's last vaccine dose accounted for 66.4% of unexplained variation in published vaccine effectiveness estimates (Fig. 1A-C). Applying our estimate of the vaccine waning rate to a model of exponentially-distributed durations of protection, we estimated that immunity persists, on average, 27.4 (95% confidence interval [CI]: 16.7 to 51.1) years after receipt of any dose. Among the 96.4% (CI 94.0 to 97.8%) of individuals expected to mount primary responses to mumps vaccination, we thus expected 25% may lose protection within 7.9 (CI 4.7 to 14.7) years, 50% within 19.0 (CI 11.2 to 35.4) years, and 75% within 38.0 (CI 22.4 to 70.8) years.

The gradual replacement of predominantly A-genotype mumps virus in the pre-vaccine era by mixed genotypes after vaccine introduction has also been suspected to contribute to diminished protection. However, we found no evidence for a decline in vaccine effectiveness over the years, 1965 to 2006, in particular after controlling for the effect of vaccine waning (Fig. 1D). Whereas we estimated a non-significant 1.29 (CI 0.70 to 2.37)-fold increase in the relative risk of infection given vaccination for each log year after 1964 in unadjusted analyses, this trend did not persist (adjusted relative risk=0.85; 95% CI 0.56 to 1.30) after controlling for longer time since vaccination among older age of subjects in later studies.

Moreover, we did not identify a difference in the duration of protection after a first dose of vaccine as compared to the duration of protection after a second dose (Fig. 1E). Whereas second doses were originally recommended to bolster immunity in case of failed "take" of the first dose, our findings suggested the second dose also restores immunity to the degree achieved prior to waning of the first dose, thus extending protection to older ages. Taken together, our findings support the central role of waning immune protection as a driver of variation in vaccine performance.

Changes in population susceptibility to mumps virus after vaccine introduction

To understand the epidemiologic context of mumps resurgence in older age groups, we assessed how waning vaccine-derived immunity and declining rates of natural transmission have impacted the susceptibility of the US population over the decades since vaccine introduction. We inferred the degree of immune protection as of 1967, when the vaccine was licensed, by fitting a mathematical model (table S2, fig. S1) to reproduce epidemiological dynamics in the pre-vaccine era at steady state (15). We estimated that the basic reproductive number (R_0) of mumps in the United States—the number of infections expected to result from an initial index case in a fully-susceptible population—was 4.79 prior to vaccine

rollout, in agreement with previous estimates of 3–7 for high-income settings in the twentieth century (16, 17). Allowing for loss of naturally acquired immunity did not improve model fit (15), consistent with longer-term persistence of high antibody titers after natural infection in comparison to vaccination in children (18).

The ongoing resurgence in mumps among young adults corresponded to cohort-specific changes in susceptibility resulting from vaccine waning and declining transmission over the decades since vaccine rollout (Fig. 2, fig S2). We estimated that 52.8% (CI 41.6% to 63.1%) of adults ages 20-24 years and 52.6% (CI 42.4% to 61.3%) of adults ages 25-29 years were susceptible to mumps virus infection in 2006 at the outset of the ongoing resurgence, in contrast to 33.8% (CI 30.4% to 37.6%) and 25.2% (CI 22.8% to 27.5%), respectively, as of 1990, and <10% in each age group before vaccine introduction. Susceptibility has also permeated older age groups amid the replacement of cohorts that experienced mumps as children. Whereas most individuals ages 65 and older had natural immunity as of 2016, we estimated that 29.2% (CI 24.7% to 32.3%) of those ages 40-64 years were at risk of infection.

In a further validation of model predictions, the emergence and disappearance of mumps outbreaks among adolescents during the late 1980s and early 1990s corresponded to a transient increase in predicted susceptibility at ages 10-19 years (Fig. 2). We estimated that susceptibility at ages 10-14 years peaked in 1991, when 45.8% (CI 39.3% to 52.4%) of children in this age group were at risk for infection, as well as 43.0% (CI 37.3% to 49.0%) of adolescents ages 15-19 years. These estimates reflect 2.85 (CI 2.65 to 3.30)-fold and 3.96 (CI 3.43 to 4.52)-fold increases in age-specific susceptibility, respectively, compared to the pre-vaccination era. Whereas breakthrough outbreaks beginning in the 1980s were hypothesized at that time to reflect inadequate responses of children to their first vaccine dose (19), our findings instead suggest that vaccine waning and declining natural exposure explain why adolescents were the population at highest risk for infection at that time.

We estimated that as of 2016, prevalence of susceptibility among children ages 10-14 years declined to 34.8% (CI 24.3 to 45.7%) due to the recommendation in 1989 for children to receive a second dose at ages 4-6 years (4). Whereas most adolescents experiencing cases during the initial resurgence had received one dose of vaccine in keeping with the recommendations at that time (20, 21), recent outbreaks have predominantly included individuals eligible to receive two doses (fig. S3). Thus, the increasing age of infection in the US more likely tracks with cases due to waning immunity after receipt of the second dose rather than a continuation of cases within a single, under-immunized cohort. These findings hold in sensitivity analyses assuming 1% and 2% annual declines in reporting effort (corresponding to 39% and 63% overall reductions in disease reporting by 2017) over the decades since vaccine introduction (fig. S4, fig. S5).

Predicted transmission dynamics under vaccine waning and viral escape

Our analyses have suggested that reduced vaccine effectiveness relates primarily to waning protection rather than the emergence of mumps virus genotypes escaping vaccine-driven immunity. However, our ability to compare these hypotheses using data from previous studies is limited by a lack of data about genotype-specific protection. To better understand

whether recent outbreaks are more consistent with vaccine waning or viral escape, we used a stochastic transmission model to compare expected epidemiologic dynamics under these scenarios in the year 2006, when the ongoing resurgence began. Using the approach taken above to update population immunity and transmission parameters in the absence of waning vaccine immunity (fig. S6, fig. S7), we simulated the spread of mumps virus strains against which the vaccine provided partial protection in a population of 1 million.

Under age-structured social mixing patterns that formerly caused mumps cases to center among school-aged children, waning of vaccine protection is a necessary mechanism to account for shifts in the age distribution of cases toward adolescence and young adulthood. We found that strains capable of vaccine escape would be expected to cause higher-than-observed incidence among younger children (Fig. 3A-E). In contrast to the median age of mumps cases of 22 years reported in 2006, the predicted median age of cases approached 14.2 years (CI 8.3 to 21.7) as strain-specific vaccine effectiveness declined to 0%. Although strains with lower ability to escape immune pressure may not concentrate to such an extent among children, we expected such strains to cause low incidence in a population unaffected by waning immunity (Fig. 3F). Model-predicted overall rates of mumps incidence exceeded reported rates at lower degrees of cross-protection. As compared to predictions under scenarios of viral escape, model-predicted dynamics under vaccine waning provided a closer match to reported overall and age-specific incidence, with an expected median age of 22.3 years (CI 17.7 to 26.3) among cases.

Potential impact of booster vaccination

If vaccine derived immunity wanes or confers shorter-lasting protection against genotypes currently in circulation as compared to those circulating in 1967, then administering additional vaccine doses may help control transmission by extending immune protection to older ages. Based on analyses of the effective reproductive number (R_E), or the number of new infectious cases emerging from a single infectious case under prevailing levels of immunity, we found that protection afforded by two vaccine doses alone is unlikely to support elimination of endemic mumps virus transmission from the US in the long term. If R_E stays below 1.0, then epidemics are unlikely to be sustained in the long term; as birth cohorts exposed to high rates of transmission in the 20th century are replaced by individuals whose protection comes only through vaccination, we expect R_E to approach 1.11 (CI 1.04 to 1.13) (Fig. 4). While administering a third vaccine dose by 18 years of age would not necessarily confer life-long protection based on our estimate of the time to loss of immunity, we nonetheless predict that this intervention could extend protection through young adulthood, thereby protecting age groups at risk in recent outbreaks. Low (56%) uptake of a third dose matching adult compliance with recommended tetanus-diptheria toxoid booster doses would be expected to sustain R_E around 0.88 (CI 0.83 to 0.91), based on transmission dynamics in the US as of 2016. Under a more optimistic scenario of 88% third-dose coverage—where third-dose uptake equates second-dose uptake among already-immunized individuals—we expect R_E to approach 0.77 (CI 0.72 to 0.79) as cohorts previously exposed to high transmission rates age out of the population.

Whereas we estimated most older adults are currently immune to mumps virus due to previous infection, our modeling suggested neither a two-dose nor three-dose vaccination program would be expected to protect over 50% of adults beyond the age of 40 years in the long term. This concern may motivate the use of routine booster doses in adulthood (Fig. 4). Based on our model, we expect that administering additional doses every 10 years or 20 years would lead to sustained protection in, at minimum, 68.0% (CI 58.5% to 77.6%) and 55.2% (CI 44.1% to 68.4%) of the population, respectively, under a scenario of 88% vaccine coverage; at the lower (56%) coverage level, we estimated protection among, at minimum, 59.0% (CI 48.2% to 71.2%) and 45.5% (CI 34.3% to 60.5%) of adults with dosing every 10 years or 20 years, respectively. Maintaining high prevalence of immunity in the population through repeated dosing may also help to contain emergence of new mumps virus strains (Fig. 4E). To sustain $R_E \geq 1$ under three-dose schedules, we estimated that an emerging strain would require, at minimum, 8.5% (CI 7.6% to 9.8%) to 15.7% (CI 11.9% to 20.3%) probability of causing infection in exposed persons otherwise protected by vaccination. Adding booster doses every 10 years increased this threshold probability to between 16.6% (CI 12.5% to 20.8%) and 22.9% (CI 16.4% to 29.7%) at varying degrees of vaccine coverage.

Discussion

Resurgent outbreaks centered among young adults have brought renewed attention to mumps following decades of progress toward its elimination from the US (2, 12). Understanding why cases have re-emerged is essential for determining how to contain the disease through vaccination. Our analyses show that vaccine derived immune protection wanes over time. We estimate the rate of waning and demonstrate that this waning immunity accounts for susceptibility in the age groups experiencing outbreaks over the decades since vaccine introduction in the US. In contrast, changes in the circulating genotypes of mumps virus over this same period have not been associated with reductions in vaccine effectiveness; moreover, our modeling suggests mumps virus strains escaping vaccine protection would be expected to cause disproportionate incidence among younger children, which has not been observed in most recent outbreaks. Guided by these outcomes, our model shows that routine use of a third vaccine dose around age 18 years, with or without regular dosing in adulthood, could help maintain immune protection in the population.

Distinguishing between the contributions of vaccine waning and the emergence of vaccine-escape virus strains to mumps resurgence helps inform whether new vaccines are needed to control transmission (22, 23). Our findings that vaccine effectiveness has not declined amid the replacement of genotype A mumps viruses (from which the Jeryl Lynn vaccine strain was derived), and that the age distribution of recent cases is inconsistent with expectations under vaccine escape, are in agreement with several lines of evidence that mumps vaccination protects broadly against heterologous strains (24). Neutralizing antibody responses to the Jeryl Lynn strain are effective *in vitro* against wild-type mumps virus strains responsible for recent outbreaks among vaccinated individuals (25, 26), and genetic distinctions have not been identified between strains isolated from vaccinated and unvaccinated mumps patients (27). High efficacy and effectiveness estimates for both the Jeryl Lynn (genotype A-derived) and Urabe (genotype B-derived) vaccines against clinical

illness caused by heterologous mumps genotypes further substantiate the notion of cross-neutralizing or monotypic immune responses (12).

Although the efficacy of a third dose has not been assessed in clinical trials, several observations suggest effectiveness of extended vaccine schedules. Whereas congregated US military populations resemble high-risk groups based on their age distribution and close-contact environments, no outbreaks have been reported in the military since a policy was adopted in 1991 of administering an MMR dose to incoming recruits, regardless of vaccination history (28). In addition, receiving a third dose was associated with protection in a recent observational study following a third-dose campaign undertaken in response to a university-campus outbreak (29), building on limited evidence from previous studies where third doses were only administered at the tail end of outbreaks (30–33). Trials demonstrating the clinical effectiveness of adult vaccine doses remain ideal to guide policy around the benefits of routine or reactive use of third doses, and may improve our understanding of immunological correlates of protection (34–36). Such trials—or further observational studies—will also play an important role in establishing the duration of protection after third or additional doses in adulthood. Modifying MMR vaccines to improve the magnitude or duration of immune responses against mumps virus may also improve protection. Notably, the mumps component of the vaccine induces lower-avidity antibody responses, and weaker specific memory B-cell proliferation, than the measles and rubella components (37, 38).

Several limitations of the analysis should be considered. Our use of aggregated rather than individual-level data from vaccine effectiveness studies contributed to an imprecise estimate of the time to loss of immunity, in turn limiting the precision of our estimates of population susceptibility. Individual-level data from post-licensure vaccine studies could support better inferences about the magnitude and duration of vaccine protection, thus aiding policy decisions. Identifying immunological correlates of protection from such datasets would also aid evaluations of alternative vaccination schedules and measurements of population immunity. Second, we lack data on genotype-specific incidence that could help us infer differential protection of the Jeryl Lynn vaccine against circulating strains. Epidemiological studies of outbreaks caused by distinct virus lineages, and in populations exposed to different circulating mumps viruses, can better characterize genotype specificity in the strength or duration of vaccine protection. Last, our analysis addresses mumps epidemiology in the United States, where prevalence of immunity within particular birth cohorts may differ in relation to settings that introduced routine mumps vaccination later or use different vaccine schedules. The burden of cases and prevalence of immunity across ages or birth cohorts should be considered as a basis to guide vaccination policy within specific countries.

Analyzing nationally-aggregated incidence datasets also limited our ability to investigate how geographic or socioeconomic differences in vaccine uptake and contact rates contribute to the dynamics of focal outbreaks, as might occur in close-contact settings such as university dormitories (40). However, our inferences about vaccine waning and the changing age distribution of mumps cases offer insight into why mumps resurgence has been possible throughout geographically and socioeconomically distinct communities. In this regard, the widespread re-emergence of mumps in vaccine-compliant communities stands in stark

contrast to the focal re-emergence of measles in communities with low vaccine coverage (11).

Changes in the epidemiology of mumps have implications for disease surveillance. Diminished clinical awareness of mumps, expectations that it appears in pediatric rather than adult populations, and protection against symptoms in vaccinated individuals (41) may limit routine detection of cases, and thus bias disease reporting. Indeed, serological surveys have provided evidence of higher-than-reported rates of mumps virus infection in the US prior to 2006 (28, 42). The tendency to identify outbreak-associated cases through contact tracing may also favor detection of cases in university campuses and other closely-connected populations, underscoring the importance of epidemiological surveillance to identify infections occurring in the community.

The ongoing resurgence in mumps among young adults has undermined previous enthusiasm about near-term elimination of this disease from the US (1). Our analysis suggests that vaccinated individuals lose protection against infection on average 27 years after receipt of their last dose, and that this rate of vaccine waning explains susceptibility in adolescent and young-adult cohorts at the time of post-licensure outbreaks in these age groups. Re-emergence of mumps among older, previously-vaccinated individuals whose immunity has waned parallels recent experience with varicella outbreaks affecting immunized communities as a result of waning vaccine-derived protection (43). As demonstrated in mumps epidemiology, immunity in previously infected cohorts may buffer transmission and delay breakthrough epidemics from occurring until decades after vaccine introduction. We expect population susceptibility to mumps to continue increasing as transient vaccine-derived immunity supersedes previous infection as the main determinant of mumps susceptibility in the US population. These observations indicate the need for either innovative clinical trial designs to measure the benefit of extending vaccine dosing schedules or new vaccines to address the problem of waning vaccine-induced protection (44).

Materials and Methods

Study design

Our study comprises four parts. First, we conducted a meta-analysis of six studies on mumps vaccine effectiveness in the US and Europe to assess hypotheses of waning protection and diminished effectiveness against currently circulating strains. We next applied estimates of the waning rate to infer changes over time in the susceptibility of the US population, accounting for vaccine uptake and incidence of natural infection. We integrated a system of differential equations forward from initial conditions, defined from the pre-vaccination endemic equilibrium (as inferred over the years 1960-1964), by back-calculating transmission rates from reported mumps incidence. We next modeled expected transmission dynamics under scenarios of vaccine waning and viral escape, and estimated long-term impacts of adult vaccination schedules on population susceptibility. Full technical details pertaining to our analyses are presented in the Supplementary Materials and Methods; a brief summary is provided here.

Meta-analysis of vaccine effectiveness studies

We performed a systematic review of prospective and retrospective cohort studies calculating effectiveness of the Jeryl Lynn-strain mumps vaccine via a PubMed search and citation tracking. Details of the studies used to infer vaccine effectiveness are listed in table S1. We used an inverse variance-weighted meta-regression model, accounting for study-level heterogeneity, to measure unadjusted and multivariate-adjusted associations of the following variables with study-level estimates of the relative risk of infection associated with vaccination:

1. Time since receipt of the last vaccine dose, indicating waning vaccine immunity;
2. Time from 1964 (when the Jeryl Lynn vaccine was developed) to the year of mumps exposure, indicating long-term changes in vaccine effectiveness associated with changes in circulating genotypes; and
3. Vaccine doses received, with an interaction term for time since last dose to test for differential waning of first and second doses.

Regression model summary statistics indicated the proportion of variance explained by these covariates. We used our estimate of the association between instantaneous risk of infection and time since vaccination to fit an exponential distribution to the duration of vaccine derived immune protection, and used this fitted distribution as the basis for further modeling.

Modeling population immunity and mumps virus transmission

We used a system of ordinary differential equations to describe changes in the population of susceptible and protected persons, partitioned into those who had and had not received mumps vaccines. Updating the model to address the contributions of vaccination and vaccine waning to population immunity, we back-calculated changes in natural immunity in the population based on the relation

$$\Lambda(i,t) \propto \lambda(i,t)\left[\pi_U S(i,t) + \pi_V F(i,t)\right]$$

between reported incidence rates (Λ) in age group i and year t and the force of infection to which individuals were exposed (λ), the populations of susceptible unvaccinated (S) and vaccinated (F) persons, and the probabilities (π_U and π_V, respectively) for these individuals to experience symptoms if infected. As described in the Supporting Information, this approach allowed us to account for changes over time in transmission patterns leading to time-varying estimates of the basic reproductive number. Susceptible vaccinated persons (F) comprised those failing to mount an immune response immediately following vaccination (primary vaccine failure) as well as those whose initial protection had waned (secondary vaccine failure). Model parameter values and their sources are listed in table S2. Age-specific incidence reports were collated from nationwide surveillance (45); our model accounted for age-structured mixing among individuals partitioned across age 10 classes (0-11 months, 1-4 years, 5-9 years, 10-14 years, 15-19 years, 20-24 years, 25-29 years, 30-39 years, 40-64 years, and ≥65 years). Members of the i^{th} age class encountered the force of infection

$$\lambda(i) \propto \sum_{j=1}^{10} C_{(S)}(i,j)\frac{I(j)}{N(j)}$$

cumulatively through interactions with infectious individuals (I) distributed across all j age classes; the matrix $C_{(S)}$ conveyed age-specific mixing patterns. We inferred starting-time age-specific prevalence of immunity in the US population (as of 1967) by fitting a mathematical model of mumps transmission to recapitulate age-specific incidence in the pre-vaccine era at steady state. To compare predicted incidence during an introduced outbreak against observations from the year 2006, we implemented stochastic realizations of extended versions of the model under scenarios where we assumed waning of immunity or circulation of strains with differential risk of infecting persons protected by vaccination. We assessed which scenario was more consistent with epidemiological observations based on model-predicted age-specific and overall incidence rates, as well as the predicted median age of infection.

Assessing extended-dose strategies

We compared the long-term performance of different vaccination schedules including the addition of a third dose by age 18 years and the use of routine boosters at 10-year or 20-year intervals through adulthood. We calculated the prevalence of age-specific immune protection achieved under these strategies and resulting values of the effective reproductive number (R_E), describing the number of cases an infectious individual would be expected to cause under prevailing conditions. We also calculated the minimum probability of immune escape a novel mumps virus strain would need to invade a population protected under these different strategies, defined as the minimum probability of infecting a vaccinated, protected individual upon exposure such that $R_E \geq 1$.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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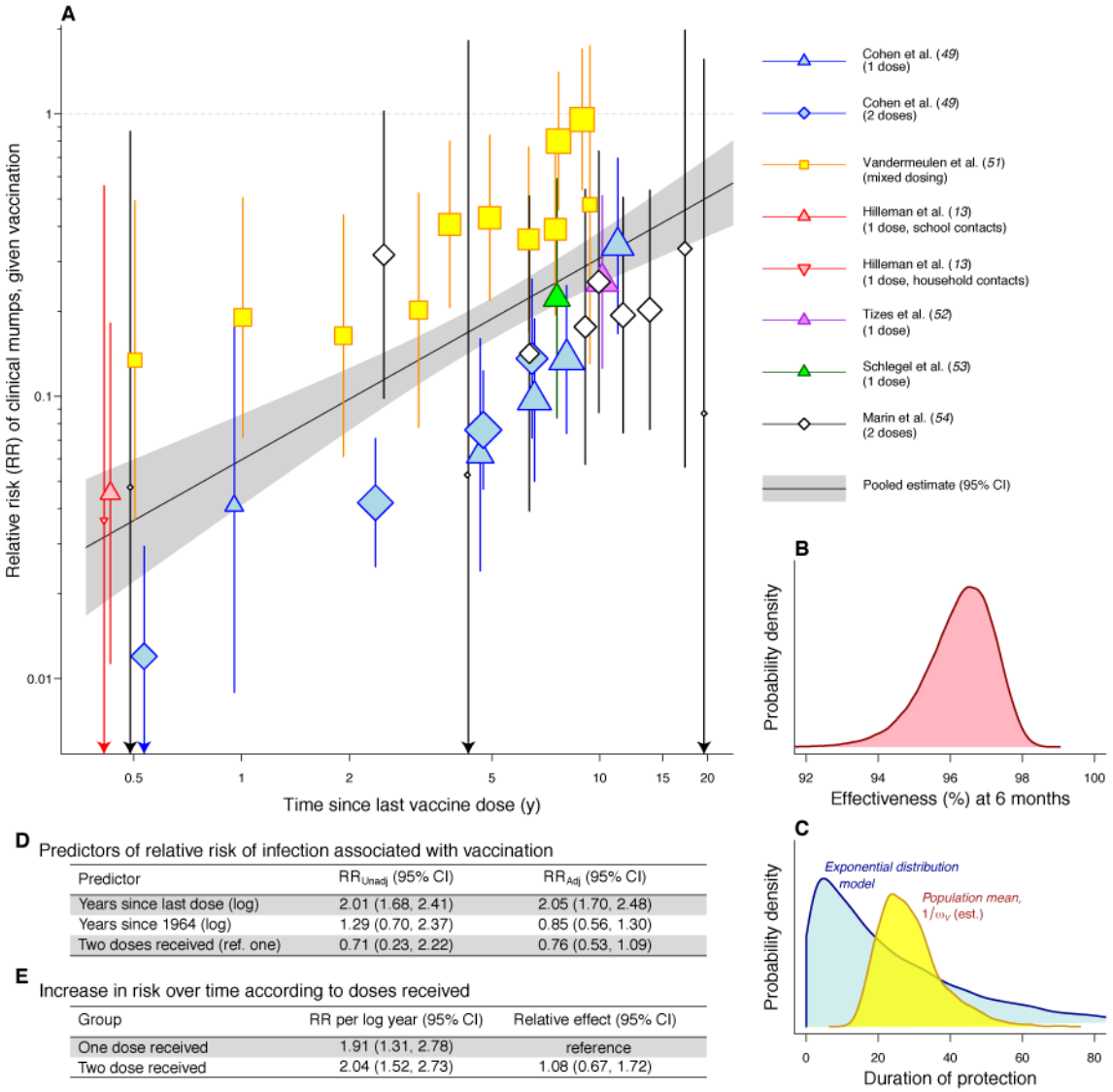
One Sentence Summary

The estimated waning rate of vaccine-conferred immunity against mumps predicts changes in the ages of mumps cases seen over the past five decades.



D Predictors of relative risk of infection associated with vaccination

Predictor	RR_{Unadj} (95% CI)	RR_{Adj} (95% CI)
Years since last dose (log)	2.01 (1.68, 2.41)	2.05 (1.70, 2.48)
Years since 1964 (log)	1.29 (0.70, 2.37)	0.85 (0.56, 1.30)
Two doses received (ref. one)	0.71 (0.23, 2.22)	0.76 (0.53, 1.09)

E Increase in risk over time according to doses received

Group	RR per log year (95% CI)	Relative effect (95% CI)
One dose received	1.91 (1.31, 2.78)	reference
Two dose received	2.04 (1.52, 2.73)	1.08 (0.67, 1.72)

Fig. 1. Synthesis of prospective and retrospective cohort studies estimating the relative risk of clinical mumps in vaccinated and unvaccinated individuals

We illustrate the results of our meta-analysis of studies of mumps vaccine effectiveness, from which we estimated rates of vaccine waning. (**A**) Shown here is how estimates of vaccine effectiveness (defined as one minus the relative risk of experiencing mumps for a vaccinated individual, relative to an unvaccinated individual) differ across the six studies analyzed here. Time since last dose accounts for 66.4% of residual variation in estimates after accounting for random sources of between-study heterogeneity. Points representing study-level estimates are scaled in size to reflect differences in sample size. Lines signify 95% confidence intervals and are truncated where they exceed the plotted range (arrowheads). (**B**) At 6 months after vaccine receipt (the earliest time point assessed in primary studies), we estimate 96.4% (94.0 to 97.8%) of recipients are protected; we apply this as our estimate of the probability of vaccine “take”. (**C**) A parsimonious model of exponentially distributed durations of protection predicts loss of protection after, on average,

$\frac{1}{\omega_V}$ = 27.4 years (95%CI: 16.7-51.1), as indicated by the yellow plotted area. The blue plotted area illustrates the distribution of times to loss of protection for vaccinated individuals, generated by pooling exponential distributions parameterized using estimates of ω_V. (**D**) Contrary to the hypothesis of reduced effectiveness against diverse mumps genotypes currently in circulation, we did not identify evidence of a decline in vaccine effectiveness over time, whereas evidence of waning vaccine-derived immunity persisted in a model adjusting for calendar year. Unadjusted estimates of the relative risk (RR) of clinical mumps given vaccination—and estimates adjusted for time since vaccination, years since 1964, and doses received—are calculated via meta-regression using incidence data from the original studies (13, 49, 51–54). (**E**) Using this meta-regression framework, we identified no difference in the waning rate (as defined by the inverse of the association between time since vaccination and relative risk of mumps given vaccination; see Materials and Methods) after receipt of a first or second dose (95% CI: 33% decrease to 72% increase in the relative risk of mumps given vaccination per log-year since vaccination; p>0.1).

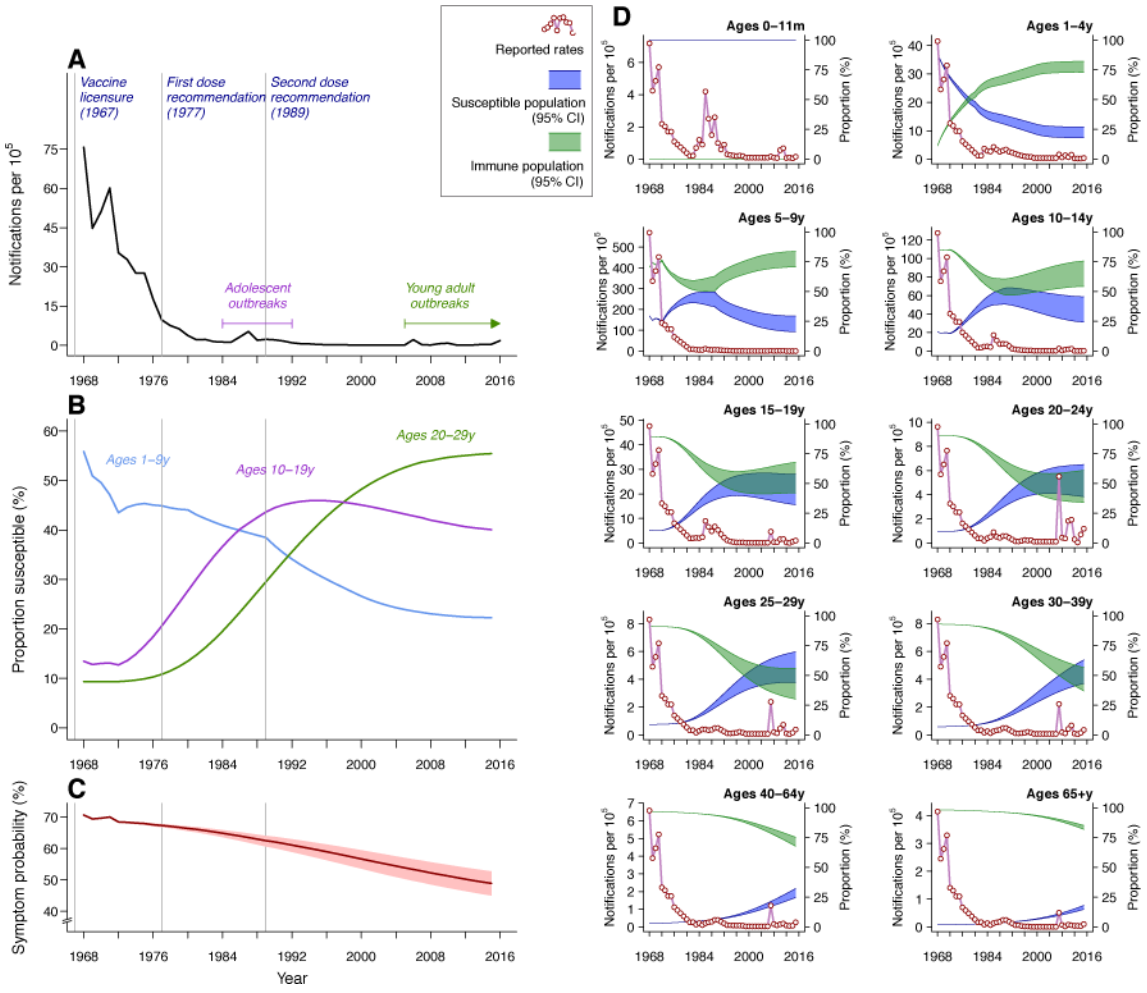


Fig. 2. Mumps incidence and estimates of population susceptibility over time

Here we illustrate changes in the proportion of the population, by age, predicted to be susceptible to mumps based on the estimated waning rate of vaccine-derived immune protection and the incidence of mumps infection in the population. (**A**) Overall rates of reported cases declined following vaccine licensure in 1967, punctuated by outbreaks primarily among adolescents from 1984-1992 and recent outbreaks (2006 onward) centered among young adults. These outbreaks have corresponded with (**B**) peaks in the model-inferred proportion of individuals susceptible to mumps infection at ages 10-19 and 20-29 years of age, respectively and (**C**) reductions in the proportion of infections that cause symptoms and are reported due to vaccine protection against symptoms. (**D**) Changes in the proportion of individuals susceptible to infection across different ages are plotted against case notification rates.

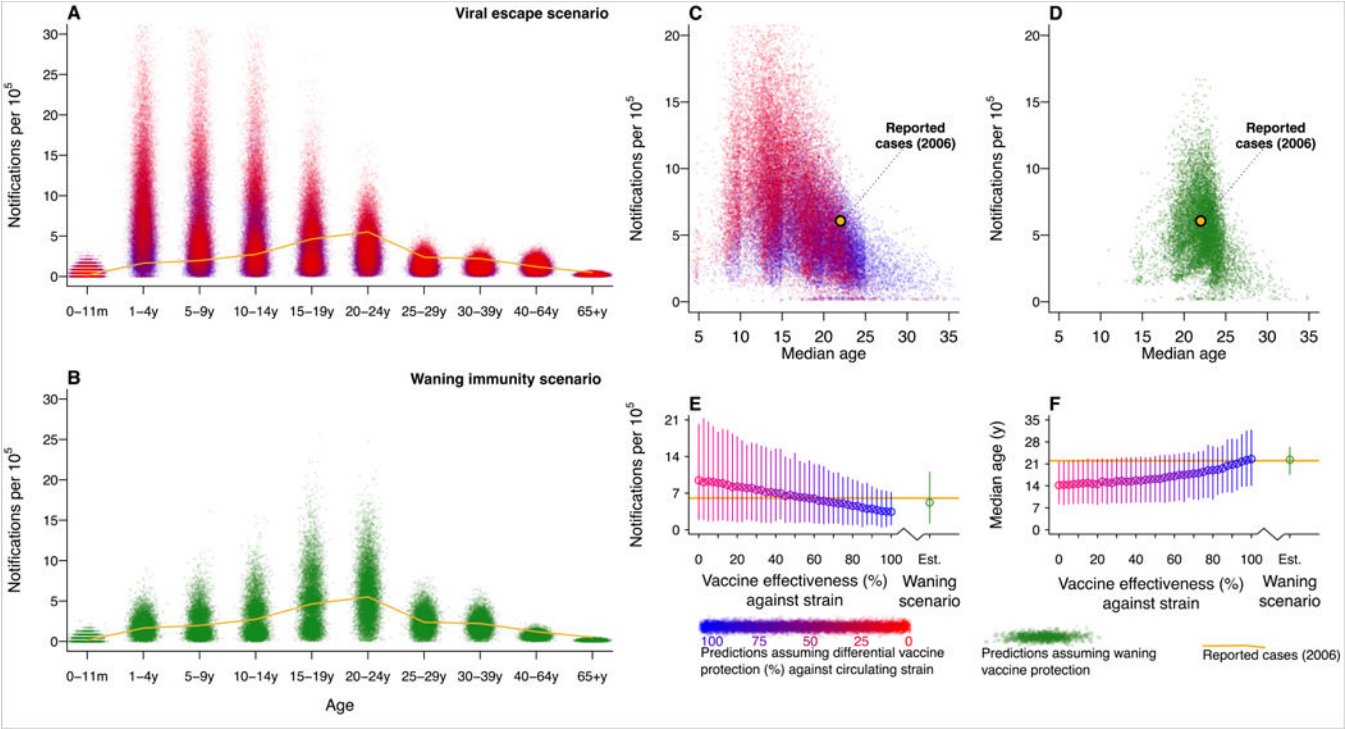


Fig. 3. Anticipated transmission dynamics under scenarios of vaccine escape and vaccine waning

Here we use a stochastic simulation model to predict the epidemiology of mumps outbreaks under the scenario of mumps virus escaping vaccine-induced immune pressure and the scenario of waning vaccine-derived immunity (**A**) A stochastic model of an emerging vaccine-escape strain of mumps virus in a vaccinated population predicts excess incidence in young age groups, in keeping with their higher historical burden of mumps. (**B**) In contrast, the fit of a model incorporating waning vaccine-derived immunity matches the observed age distribution. (**C**) Higher overall incidence rates and (**D**) a younger age distribution of cases are predicted when immune responses to the vaccine offer minimal cross-protection against the circulating strain, as compared to the fit of the model with waning vaccine immunity. (**E**) Whereas the model with a viral-escape strain can reproduce the age distribution of cases at low degrees of immunological mismatch, (**F**) lower-than-reported incidence is expected under this scenario, again in contrast to the fit of a model with waning vaccine immunity. Lines in (**E**) and (**F**) signify 95% confidence intervals.

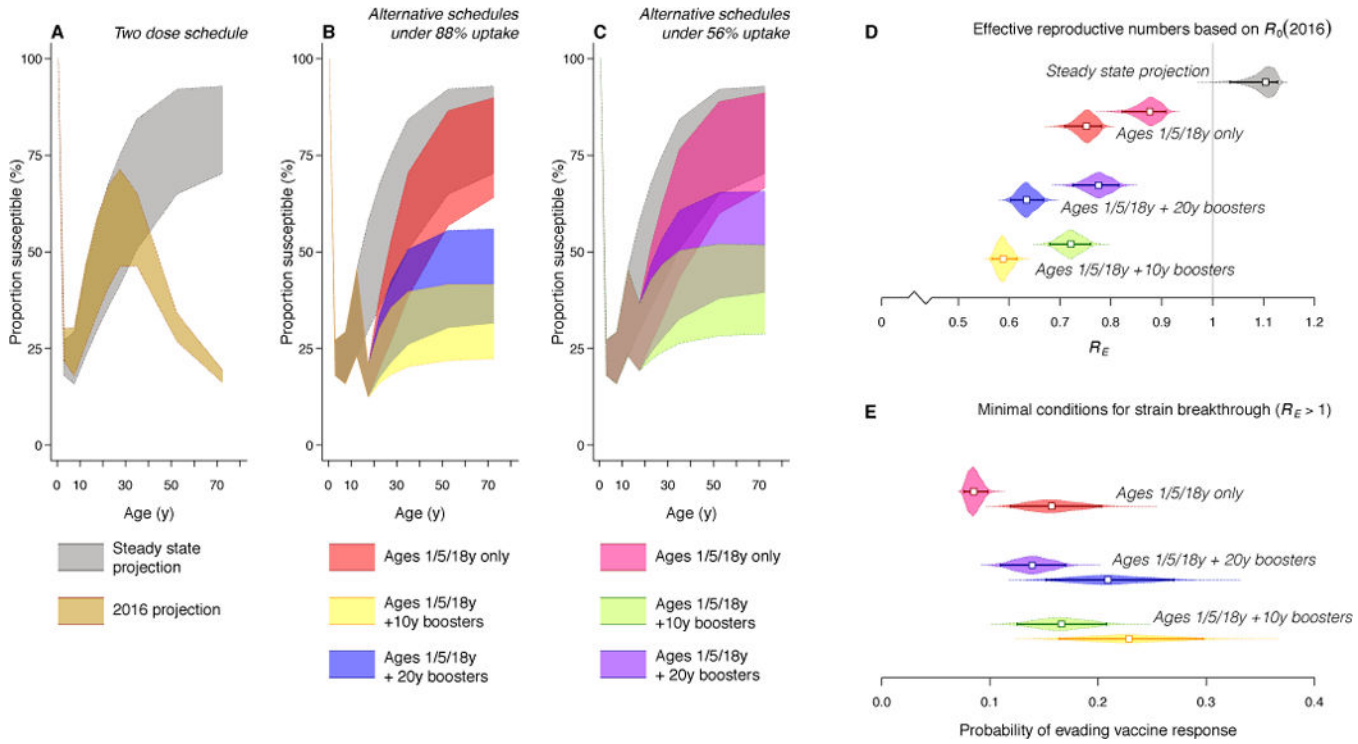


Fig. 4. Age-specific immunity and transmission dynamics under two- and three-dose vaccine schedules

Waning vaccine-derived protection in the population raises the question of how additional vaccine doses would impact mumps transmission. To address this question, we evaluated several scenarios. **(A)** Cohorts over 40 years of age as of 2016 were exposed to endemic transmission prior to and shortly after vaccine rollout and likely retain life-long protection. However, a population protected only by 2-dose vaccination would be expected to experience high prevalence of susceptibility over age 20 years. (**B** and **C**) Our modeling suggests the duration of protection can be extended through young adulthood by adding a third dose around age 18, whereas routine booster doses every 10 years or 20 years would be expected to sustain longer-term protection. Lines and shaded areas delineate median estimates and 95% confidence intervals, respectively. (**D**) Under transmission dynamics estimated as of 2016, protection in young adult age groups achieved through the use of a third vaccine dose is expected to reduce the effective reproductive number (R_E) below 1. We however predict R_E to approach 1.10 under the two-dose schedule as cohorts that experienced high rates of mumps infection age out of the population; larger reductions in R_E are sustained at higher coverage and with more frequent dosing. Colors are the same as in panels A-C. (**E**) In turn, these extensions of protection provide a stronger barrier against emergence of strains escaping vaccine immunity. A new strain with 8.5% (CI 7.6% to 9.8%) probability of evading vaccine-induced immunity and infecting a vaccine-protected individual would be expected to succeed under a three-dose schedule with low coverage. We however estimate that a novel strain would require 22.9% (CI 16.4% to 29.7%) probability of infecting such an individual to emerge in a population with 88% uptake of the third dose

and 10-year boosters. Lines denote 95% confidence intervals and shaded areas represent distributions around R_E estimates.