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Commentary

Mumps to COVID-19: Vaccinated persons remain vulnerable when community uptake is low

Kristin K. Gaffney [a], M. Jana Broadhurst [b], David M. Brett-Major [c,*]

[a] College of Public Health, University of Nebraska Medical Center, Omaha, NE, USA
[b] Assistant Professor, Department of Pathology and Microbiology, College of Medicine, University of Nebraska Medical Center, Omaha, NE, Director, Nebraska Biocontainment Unit Clinical Laboratory; Director, Emerging Pathogens Laboratory, USA
[c] Professor, Department of Epidemiology, College of Public Health, University of Nebraska Medical Center, Omaha, NE, USA

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ABSTRACT

Vaccines against coronavirus disease 2019 (COVID-19) first became available in the United States and Europe outside clinical trials in December 2020, when administration began in high-priority populations such as healthcare workers and long-term care residents.[1] Since that time, global rollout progresses with wide variation in vaccination rates by country.[2] Depending upon product and SARS-CoV-2 variant, vaccine efficacies against infection range from approximately 70 to well over 90%, higher against severe disease. Well-resourced settings are starting to focus on booster doses among high risk persons, and locations with higher vaccination rates appear to have less COVID-19 patient and community impact. Yet, in every setting, primary vaccination to as many persons as possible remains incredibly important to effective pandemic risk management. Why this is the case, why even in settings with comparatively high vaccination rates and boosting we still should make the case that more primary vaccination matters can be answered by remembering mumps, and applying those lessons to promoting vaccine access.

1. Arkansas mumps outbreak 2016–2017

In 1967 the USA began vaccination against mumps virus, *Mumps orthorubulavirus,* to decrease complications such as meningitis, oophoritis, orchitis, pancreatitis, and deafness. [3] Ultimately, it was incorporated into the combination measles-mumps-rubella (MMR) vaccine, and later a second dose was recommended, and a third in outbreak settings. Since the early 2000′s, mumps outbreaks in the USA have occurred primarily in college or high-contact populations. [4].

As reported by Fields et al., on August 5, 2016, a Marshallese woman in Springdale, Arkansas, experienced onset of parotitis, the classic symptom of mumps infection. [5] She had no known history of mumps infection or vaccination. Within 26 days, over 50 cases were reported. By September 2017, nearly 3,000 confirmed and probable cases were recorded. [6].

Ultimately, more than half of cases were amongst school-aged children and adolescents (57% (1676/2954) age 5–17; overall median 15 years, IQR 10–26)). Also, more than half of cases were Marshallese (57%; a Pacific Islander ethnic group). [5] Serious complications were few with no significant difference between vaccinated and unvaccinated patients. [5] SH-genotyping confirmed that all 23 submitted samples were mumps genotype G. Broad community spread reached 37 of 75 counties, 130 schools, and over 300 workplaces and churches. Investigators collected vaccination status information for infected persons only, nonetheless revealing a disparity in coverage between adults and school age children (37 versus 92 percent). [Fig. 1.].

1.1. Unusual Age, Ethnicity, and spread for a mumps outbreak in the USA

In the Arkansas mumps outbreak, the unique population of infected persons by age and ethnicity merits consideration. While a majority of the mumps cases in this outbreak occurred among school-aged children (median 15 years), USA outbreaks overall from January 2016 to June 2017 recorded 9200 cases total with a median age of 21 years. [6,7,8] The Arkansas outbreak accounted for almost one-third of this total, suggesting an even greater difference by age between the Arkansas outbreak and others. [Table 1.].

Springdale, Arkansas, has a Marshallese population of approximately 12,000, the largest in the continental USA. [7] While only 7% of the Springdale population per the U.S. Census Bureau and

* Corresponding author at: 984395 Nebraska Medical Center, Omaha NE 68198-4395, USA.

E-mail addresses: kristin.gaffney@unmc.edu (K.K. Gaffney), jana.broadhurst@unmc.edu (M. Jana Broadhurst), david.brettmajor@unmc.edu (D.M. Brett-Major).

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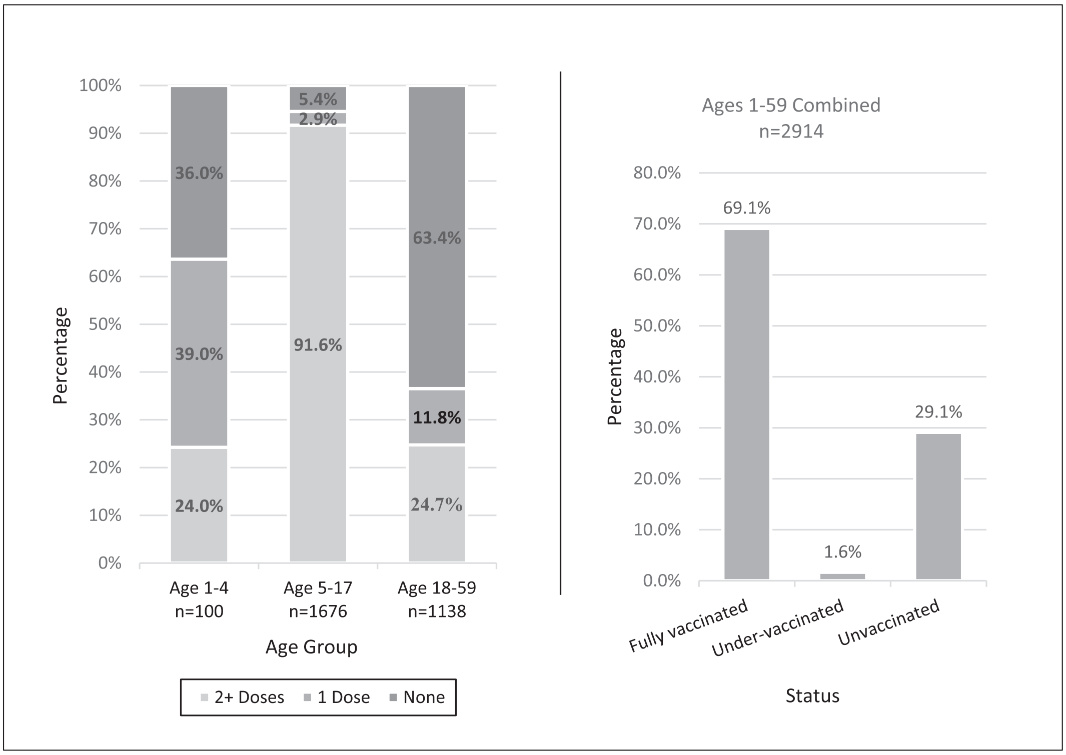

Fig. 1. Measles mumps rubella (MMR) vaccination status of infected persons in the Arkansas mumps outbreak by age group and number of doses, and overall by comparison to Advisory Committee on Immunization Practices recommendations, August 2016–July 2017. Infected persons were classified as unvaccinated when vaccination could not be confirmed. Vaccine status analysis excluded 37 persons for whom vaccine was not recommended, and 3 for whom age information was missing. Adapted and derived from tabular data from Fields et al. [5].

Table 1
Contrast between Arkansas, Colorado, and aggregate USA mumps outbreaks, 2016–2017 [16].

	United States	Arkansas	Colorado
Timeframe	Jan 2016 – Jun 2017	Aug 2016 – Jul 2017	Nov 2016 – Mar 2017
Outbreaks	150	1	1
Cases	9200	2954	47
Median age	21 years (IQR 19–22)	15 years (IQR 10–26)	20 years (IQR 12–27)
Marshallese		57% (1692/2954)	98% (46/47)
Vaccination	45% unknown/<2 doses (4185/9200)	30% unconfirmed/none (892/2954)	72% unconfirmed (34/47)
Geography		37 counties	2 counties
Maximum weekly cases		272	8
Cumulative at 12th week		859	24

Abbreviation: IQR, interquartile range.

0.4% of the state population, this group constituted 57% of outbreak cases. In the primary outbreak report, Fields et al. described high-density living, frequent social gatherings, low health literacy, low socioeconomic status, and oft-delayed medical care experienced in the Marshallese community. [6] Some adults in the population also may have been impacted immunologically due to nuclear testing prior to their emigration to the continental USA. Insufficient immune response to vaccination was possible.

The Arkansas outbreak also exhibited intense spread suggesting a short incubation period or high reproductive rate. A Colorado outbreak in a smaller Marshallese population during the same time period, with potentially lower community engagement, displayed a much lower intensity (Table 1). This was despite that Arkansas had higher 2-dose MMR vaccination coverage for kindergarten than Colorado for the 2016–17 school year (92 vs. 87 per cent). [8] The difference in outbreak intensity was further demonstrated by a shorter interval between successive cases in Arkansas, 8–10 rather than 18 days. [9].

1.2. The impact of community case rate pressure

Our analysis here of the Arkansas and contemporary mumps outbreaks suggests that pressure from household and community exposure resulted in breakthrough cases in a highly vaccinated school-age subpopulation despite use of a highly successful vaccine. The vaccinated sub-group was well mixed in the unvaccinated population. School age children have high levels of household interaction with younger and older family members. This differs than outbreaks in college settings or close-knit groups less integrated with the larger population, potentially limiting spread. When disease rates were low, the school-age population was adequately protected through vaccination; however, when disease rates increased, exposure opportunities increased, and vaccine-induced immunity was inadequate in some persons. This effect has been observed elsewhere, as recently reported by Bennett et al. related to reduced rotavirus vaccine effectiveness when disease burden is high. [10] While variability in immune response to receiving the vaccine, waning vaccine immunity, and some variance among mumps viruses within strains also may have contributed to high case rates. Increased exposure pressure and the presence of viral variants can work together to propagate a viral threat. For instance, a United Kingdom study of household transmission of SARS-CoV-2 Delta variant demonstrated attenuated but substantial onward transmission among vaccinated persons, despite also showing that vaccinated persons had faster viral load decline (by 1 log per day) and so should be less efficient at introducing virus to others. [11].

2. Implications for COVID-19 risk management

The core message of this analysis is that community-level risk does not get separated between sub-groups that are vaccinated and sub-groups that are not vaccinated. Everyone is at risk when the entire community does not participate in achieving high vaccination rates in concert with other mitigative measures. Even when perceiving social silos—e.g., "I live and work among people who think and act just like me and so I am at low risk because I do not mingle with people who do not think like me"—ultimately, transmission and so pandemic risk becomes shared.

Initially, immunization programs against SARS-CoV-2 were rolled out first to high-risk populations. This may have led to maximum vaccine impact in those groups being hindered while community disease burden was high and immunity low. Continued SARS-CoV-2 variant rise compounds this problem as epitope escape, large-scale community transmission, and waning initial vaccine immunity work together to promote persistent propagation in the pandemic. This is most recently being observed with SARS-CoV-2 Omicron variant which as of the writing of this article is replacing Delta variant in some quarters. [12] Highly vaccinated high-risk subpopulations such as healthcare workers or teachers who continue to be exposed to high levels of disease occupationally and personally may still be susceptible to infection under the pressure of high background infection rates. Uneven global rollout exacerbates these issues. High background infection rates may create enough pressure through increased exposure time to cause disease breakthrough in a greater than expected proportion of the vaccinated population. Consequently, caution should be applied when assessing population-level vaccine impacts in this context. As subsequent doses of current or variant-adapted vaccines are offered, these considerations will continue to matter in managing the pandemic.

Understanding local and individual context is essential when addressing low uptake. Low background immunity due to poor vaccine uptake may occur for a number of reasons. Low health literacy and limited engagement with healthcare in some cultural contexts may contribute, as noted in the Arkansas mumps outbreak. Vaccine access continues to be a problem for COVID-19 in many regions globally due to supply and distribution inequities. [2] Hopefully, increasing safety and efficacy data as well as the mounting narratives promoting additional vaccine doses in some contexts will assist readiness to accept primary vaccination.

How much vaccination is enough to matter to a community is a difficult question to answer. Like R_0, vaccine effectiveness estimates shift in outbreak versus persistent risk scenarios and in different contexts. An industry-sponsored cohort study in a large U.S. health system estimated the vaccine effectiveness of mRNA-1273 against infection at over 87% across a period with increasing Delta variant cases, [13] yet even U.S. states where vaccine uptake has been over 70% have been experiencing persistent COVID-19 caseloads large enough to cause health system stress, albeit lower than their neighbors. [14] Mumps vaccine effectiveness estimates in settings with lower background case pressure are comparable. [15] In the pandemic setting, this emphasizes the need for multi-modal risk mitigation strategies (e.g., vaccine is necessary but not sufficient), and suggests that vaccination targets should approach what is sought for MMR, over 9 in 10 persons. However, this is speculative and taking lessons from Arkansas, if vaccine uptake is well distributed across the entire population, lower use of vaccine may be required to have a quelling effect on the pandemic.

In the mumps outbreak investigation, total cases may have been underestimated subject to limitations of testing and contact tracing also increasing misclassification bias, also a factor for COVID-19. Another challenge was correctly classifying vaccination status of adults, for whom records were not consistently available. [6] However, if the true rates were higher, this only emphasizes the need to recognize vaccination as a critical tool while appreciating that it must be broadly implied, and should not feed a preventative misconception about the importance of other risk mitigation measures. When case rates are high, multi-modal risk mitigation is indicated, and public health messaging should promote vaccination as part of a comprehensive strategy. The potential cascading influence from unvaccinated pockets should be discussed in risk communication. Registering COVID-19 vaccinations will be important to evaluating vaccine effectiveness but may meet some resistance due to privacy concerns. Another limitation in this analysis was the lack of publicly available individual or cluster level case data. More granular data may have led to different conclusions regarding transmission and infection trends. Local level data on COVID-19 vaccination, case status, and incidence rates will be helpful to monitor vaccine performance.

The Arkansas mumps outbreak of 2016–2017 provides a case study of a highly vaccinated sub-population vulnerable to disease when the rest of the community has low levels of immunity and a high background infection rate, and where the highly vaccinated group has high levels of interaction with the general population through household or community mixing. Our secondary analysis demonstrates ways in which the mumps outbreak's lessons have application to the current COVID-19 vaccination environment, and may be important considerations for policy makers and public health leaders. Even as vaccination coverage increases with improved access and acceptance, reducing the background rate of infection through mitigation activities remains important to protecting vaccinated as well as unvaccinated populations.

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