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Identifying transmission routes of *Streptococcus pneumoniae* and sources of acquisitions in high transmission communities

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Abstract

Identifying the transmission sources and reservoirs of *Streptococcus pneumoniae* (SP) is a long-standing question for pneumococcal epidemiology, transmission dynamics, and vaccine policy. Here we use serotype to identify SP transmission and examine acquisitions (in the same household, local community, and county, or of unidentified origin) in a longitudinal cohort of children and adults from the Navajo Nation and the White Mountain Apache American Indian Tribes. We found that adults acquire SP relatively more in the household than other age groups, and children 2–8 years old typically acquire in their own or surrounding communities. Age-specific transmission probability matrices show that transmissions within household were mostly seen from older to younger siblings. Outside the household, children most often transmit to other children in the same age group, showing age-assortative mixing behavior. We find toddlers and older children to be most involved in SP transmission and acquisition, indicating their role as key drivers of SP epidemiology. Although infants have high carriage prevalence, they do not play a central role in transmission of SP compared with toddlers and older children. Our results are relevant to inform alternative pneumococcal conjugate vaccine dosing strategies and analytic efforts to inform optimization of vaccine programs, as well as assessing the transmission dynamics of pathogens transmitted by close contact in general.

Keywords: Infectious disease epidemiology, modelling, spread of disease, *Streptococcus pneumoniae* (pneumococcus), vaccine policy development.

INTRODUCTION

Identifying the transmission routes of *Streptococcus pneumoniae* (SP) among individuals of differing ages is a long-standing question in pneumococcal epidemiology and is relevant to vaccine disease prevention efforts [1]. Previous studies have hypothesized that toddlers are the infectious reservoir for the pneumococcus, typically acquiring SP at daycare and subsequently transmitting it to their siblings and parents [2]. However, recent work has suggested that infants may be reservoirs of infection themselves due to the long duration of nasopharyngeal (NP) SP colonization [3, 4]. Duration of SP carriage and contact patterns are factors that affect transmission and thus

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are important in mathematical modeling of pneumococcal transmission in populations and for designing optimal vaccine programs.

Here we analyze pneumococcal carriage data at the household and community level, collected in a series of detailed studies on the Navajo Nation and White Mountain Apache Tribal lands, after a decade of pneumococcal conjugate vaccine (PCV) use [5, 6]. We identify the potential routes of transmission between infants, toddlers, children, and their parents both inside and outside households, and their key drivers.

METHODS

NP colonization and prevalence

Data used in the current analysis have been described and analyzed elsewhere [5, 6]. Briefly, the data come from a prospective, longitudinal, observational cohort study of Navajo and White Mountain Apache families living on reservations in the southwest USA. Data were collected from March 2006 to March 2008. PCV was first used in these communities from 1997 to 2000 during a phase III, community randomized trial, and then was incorporated into the routine infant immunization schedule in late 2000. Parents were recruited at well-child or ill visits at Indian Health Service (IHS) clinics. Families were included if at least one parent was a member of the Navajo Nation or White Mountain Apache tribe, the family's home was on or near the Navajo Nation or White Mountain Apache Tribal lands, at least one child in the household was under 9 years old, and at least two persons in the household were willing to participate in the study for the 6-month time period. Enrolled families were visited monthly for a 6-month period (i.e. seven visits). NP swab samples and carriage risk factor questionnaires were collected at each visit. A total of 1074 individuals in 300 households were recruited in the study in five service units: Chinle, Fort Defiance, Gallup, Shiprock, and Whiteriver. Service units are regions across the Navajo Nation defined by the US Department of Health and Human Services. The service units span the Navajo Nation in North East Arizona and North West New Mexico. Each service unit is further divided into multiple communities. Therefore, household, community, and service units form the geographical hierarchy of this study, and we use this information to explore transmission at each level.

NP specimens were obtained with Dacron swabs, using methods described elsewhere, and stored in 1 ml of skim milk, tryptone, glucose, and glycerin (STGG) transport medium [7]. A 100 µl aliquot of each NP specimen in STGG was inoculated onto trypticase soy agar with 5% sheep blood and gentamicin (Becton Dickinson); pneumococci were isolated and identified in the Centers for Disease Control and Prevention (CDC) Respiratory Diseases Branch Streptococcus Laboratory, using methods described elsewhere [8]. Serotypes were identified from a single colony using the Quellung reaction. Polymerase chain reaction [8] or a Quellung reaction with specific factor sera [9] was used to distinguish 6A from 6C among carriage isolates originally identified as 6A.

Definitions and statistical methods

An acquisition event was defined as NP colonization in an individual who was not colonized at the previous visit, was colonized with other serotypes at the preceding visits, or was colonized with the same serotype at visits before the immediately preceding one. We attempted to find the source of transmission by searching NP colonization of other individuals carrying the same serotype at the previous visit at expanding radii: within household, outside household but within the same community, outside community but within the same service unit, then across all service units. Serotypes not seen in any of the four levels of hierarchy were classified as new importation events. If multiple individuals in the same area were identified as transmission sources, we consider them as equal contributions and count them as sources. For each new acquisition, the household, community, service unit, and exact ages of both transmitter and transmitee were available.

We calculated the percent of pneumococcus acquisition (transmission events) at each geographic level, and estimate the source of the serotypes of different age groups: 0–10 months (infants), 10 months to 2 years (toddlers), yearly until 5 years, 5–8 years, and >15 years (Fig. 1). The lower two age strata were chosen to address the specific roles of infants with limited mobility *vs.* young children (see Supplementary Fig. S1) and older children and adults were combined for parsimony. As each child was followed with monthly visits within a 6-month period, when normalizing across multiple visits, we estimated a child's age to be approximately the age at third visit.

Transmission events were defined by identification of identical serotypes present in two individuals over two consecutive study visits. We begin looking for identical serotypes in other members of the household; if none are found, we look in the same community, then in

the same service unit, then in a different service unit. If no potential sources are found, we consider it an importation. To compare transmission across age groups, we calculated age-specific transmission probability matrices at each geographic level. We wished to estimate the per-pair probability of transmission, and thus calculated the number of transmission events by the number of potential contacts between two age groups. Assuming a given geographic level has n divisions and the population of each division k is N_k (with individuals of age i in community k denoted as $N_{k,i}$), the age-specific transmission probability r_{ij} between age group i and j was calculated based on total number of acquisitions between the two age groups A_{ij} (where $A_{i,j}$ is the total number of transmissions from age i to age j, with $A_{i,j} \neq A_{j,i}$) divided by the maximal possible number of pairs of individuals between the two age groups C_{ij}, i.e. $r_{ij} = (A_{ij}/C_{ij})$. The pairs of individuals at each geographic level C_{ij} is calculated as follows:

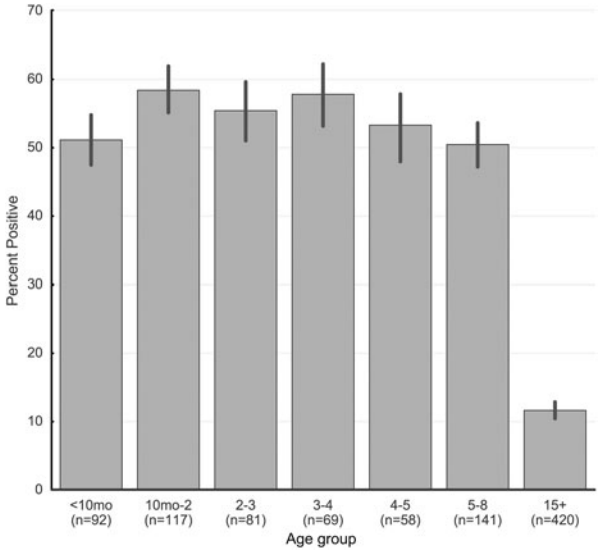

Fig. 1. Percentage of subjects with positive NP carriage of SP by age in all seven visits, with 95% confidence intervals.

$$C_{ij}^{\text{household}} = \begin{cases} \Sigma_{k=1}^{n^{\text{household}}} N_{k,i}N_{k,j} & \text{if } i \neq j \\ \Sigma_{k=1}^{n^{\text{household}}} N_{k,i}(N_{k,j}-1)/2 & \text{if } i = j \end{cases}$$

$$C_{ij}^{\text{community}} = \begin{cases} \Sigma_{k=1}^{n^{\text{community}}} N_{k,i}N_{k,j} - C_{ij}^{\text{household}} & \text{if } i \neq j \\ \Sigma_{k=1}^{n^{\text{community}}} N_{k,i}(N_{k,j}-1)/2 - C_{ij}^{\text{household}} & \text{if } i = j \end{cases}$$

$$C_{ij}^{\text{site}} = \begin{cases} \Sigma_{k=1}^{n^{\text{site}}} N_{k,i}N_{k,j} - C_{ij}^{\text{household}} - C_{ij}^{\text{community}} & \text{if } i \neq j \\ \Sigma_{k=1}^{n^{\text{site}}} N_{k,i}(N_{k,j}-1)/2 - C_{ij}^{\text{household}} - C_{ij}^{\text{community}} & \text{if } i = j \end{cases}.$$

Note $C_{ij} = C_{ji}$, and that $A_{i,j}$ can be considered the total unique serotypes shared from age i to age j. Proportion tests were used to compare differences in proportion of acquisition events between age groups across households or sites, and binomial proportion confidence intervals were calculated to assess uncertainty in the estimated transmission probabilities and to test statistical significance of the estimates. The number of 'successful trials' was the number of potential acquisition events between age groups (A_{ij}) and the 'number of trials' was the total potential number of contacts by age group (C_{ij}). We note the confidence intervals were calculated under the assumption that observations of carriage in the same individual and across individuals were independent.

RESULTS

Over the study period, 6399 NP specimens were collected from 999 individuals (Table 1 shows the age distribution of study subjects) who completed the study; SP was isolated from 2294 NP specimens. Figure 1 shows the percentage of subjects with NP carriage of SP by age strata. As reported in previous findings [5], children under 5 years of age have a high prevalence (over 50%) of pneumococcal carriage. Infants under 10 months of age have similar prevalence as in other age categories, in accordance with other high pneumococcal burden settings [10–12]. The overall carriage prevalence is similar to that of the pre- and early PCV7 eras in these communities [13].

A total of 1235 SP acquisition events were identified – an average of 1·24 per person (Table 1). The highest probability of acquisition was seen in those between 2 and 8 years of age, with an average of two acquisitions per person over the 6-month period. The probability of acquisition was similar for all child age groups, ranging from 1·47 per person in those under 10 months of age to 2·04 per person for those 2–3 years of age. Both the carriage prevalence (10·8%) and new acquisition events in adults

Table 1. *Summary of pneumococcal acquisition*

	All	Under 10 months	10 months to 2 years	2–3 years
Total study population	999	92	117	81
Total acquisitions	1235 (1·24/person)	135 (1·47/person)	209 (1·79/person)	165 (2·04/person)
Percent of acquisitions within household (95% CI)	24% (21·7–26·5)	23% (16·2–31)	28·2% (22·2–34·9)	23% (16·8–30·2)
Percent of acquisitions in same community	27·4% (25–30)	32·6% (24·8–41·2)	32·1% (25·8–38·8)	35·2% (27·9–43)
Percent of acquisitions in same service unit	36·8% (34·1–39·6)	31·1% (23·4–39·6)	32·1% (25·8–38·8)	31·5% (24·5–39·2)
Percent of acquisitions from other service units	9·2% (7·7–11)	11·1% (6·4–17·7)	5·7% (3–9·8)	9·1% (5·2–14·6)
Percent of acquisitions from importation	2·4% (1·6–3·4)	2·2% (0·5–6·4)	1·9% (0·5–4·8)	1·2% (0·1–4·3)
	3–4 years	4–5 years	5–8 years	15+ years
Total study population	69	58	141	420
Total acquisitions	133 (1·93/person)	115 (1·98/person)	276 (1·96/person)	177 (0·42/person)
Percent of acquisitions within household (95% CI)	27·1% (19·7–35·5)	20·9% (13·9–29·4)	15·9% (11·8–20·8)	34·5% (27·5–42)
Percent of acquisitions in same community	25·6% (18·4–33·8)	19·1% (12·4–27·5)	25·7% (20·7–31·3)	20·9% (15·2–27·6)
Percent of acquisitions in same service unit	37·6% (29·3–46·4)	44·3% (35·1–53·9)	43·8% (37·9–49·9)	36·2% (29·1–43·7)
Percent of acquisitions from other service units	6·8% (3·1–12·5)	10·4% (5·5–17·5)	12·7% (9–17·2)	6·8% (3·6–11·5)
Percent of acquisitions from importation	3% (0·8–7·5)	5·2% (1·9–11)	1·8% (0·6–4·2)	1·7% (0·4–4·9)

Table shows the breakdown of SP acquisition by geography, within age strata. Binomial confidence intervals are presented. We note that we are omitting 21 8–15 year olds who contributed 35 transmission events from the detailed table.

(0·42 per person) were low. Previous analyses of these data explored the role of children for introducing, transmitting, and sustaining pneumococcal strains in the household. We now extend those analyses to address in more detail the age-specific roles of individuals, and the geographic level of strain transmission and introduction in the community.

Figure 2 shows the proportion of the acquisitions by source for each age group. Adult acquisitions originated from within the household more commonly than they did from the study population as a whole (34·5% *vs.* 24%, $P = 0{\cdot}02$) or than from the 5 to 8 years old group (18·6 percent units greater, $P < 0{\cdot}0001$). Children in the 5–8 years age group were significantly more likely to acquire SP in their own service unit than the other age groups (9 percent units greater, $P = 0{\cdot}001$). In general, importation events (events with no identified source) were rare, ranging from 1·7% of novel acquisitions in those above 15 years of age to 5·2% in those 4–5 years of age.

The patterns of potential transmission routes varied greatly by age group. Figure 3 shows the numbers of potential contacts (C_{ij}) within households, community and site by age group. Few households have more than one child in a defined age strata (the diagonal of the matrix), and there are relatively higher numbers of contacts between toddlers and infants (3–4 years old to 2–3 and 2–3 to 10 months to 2 years). Similarly, within the community, 2–3 year olds contact 10 months to 2 years frequently and 10 months to 2 years contact 0–10 months frequently.

Figure 4 shows the proportion of potential contacts in an age-pair (i.e., 3–4 to 2–3 year olds) that resulted in SP transmission. Examining these proportions reveals several patterns: first, those community members >15 years old are involved in much less transmission than those in younger age groups, both within household and community. Second, within household, transmission is dominated by older to younger siblings with the highest probabilities of infection from 4–5 to 3–4 years. Third, children under 8, especially older children, preferentially transmit to people of the same age within the same community and site. This assortative mixing behavior with age is consistent with findings from contact pattern studies [14], and is likely due to children interacting within childcare or classroom settings.

Transmission of SP from colonized mother to infant is a likely source of early colonization. In this study, the mother–infant transmissions are rarely seen for both inside and outside households (Fig. 4), similar to other studies [15, 16]. Within the household

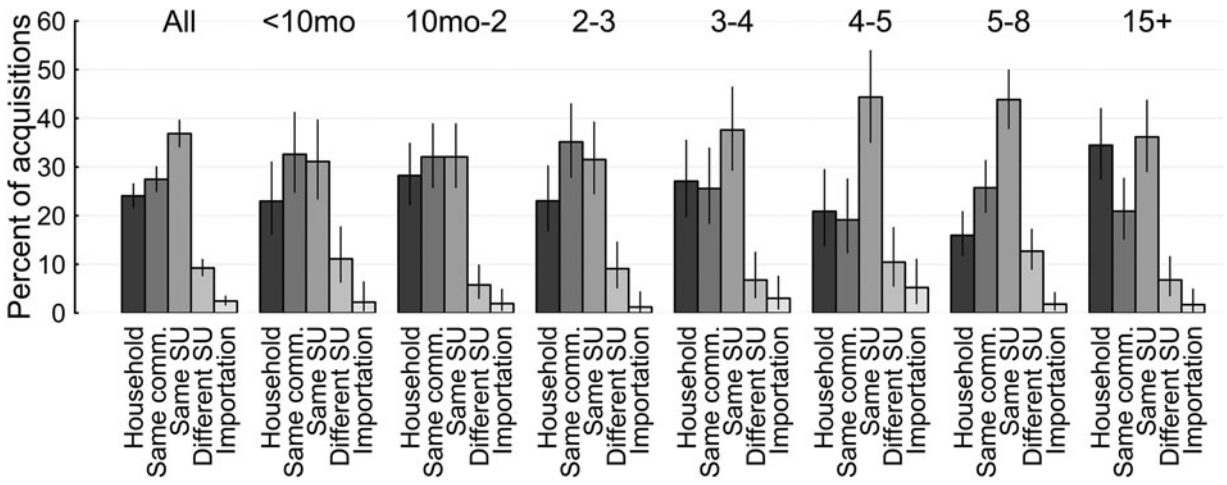

Fig. 2. Acquisition sources by age group. Figure shows the percentage of SP acquired within an individual's household, their community, their service unit (SU), another SU, or with no discernible source. Binomial confidence intervals are plotted as whiskers.

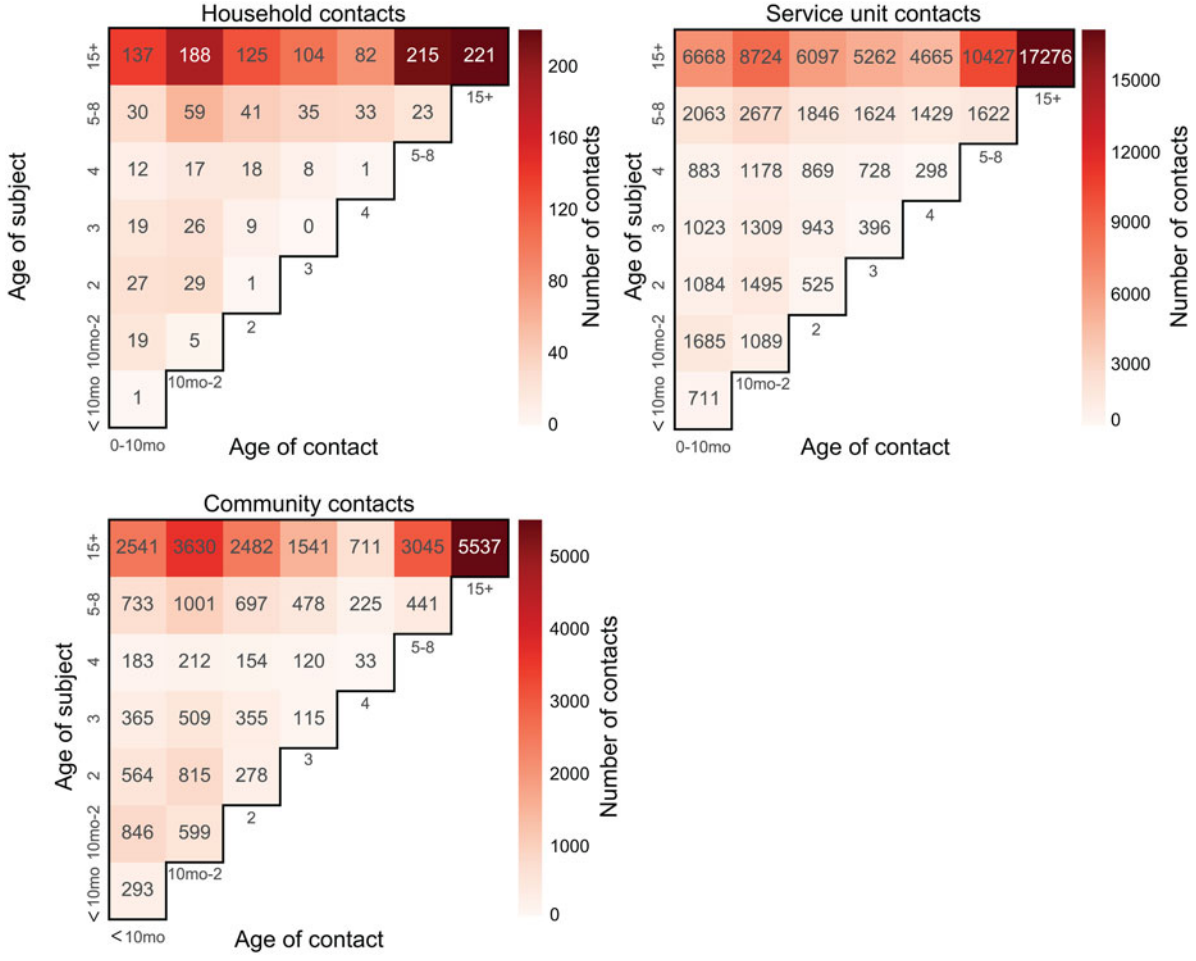

Fig. 3. Number of contacts across age groups. Figure shows the number of potential contacts between age groups within the household, community, and service unit.

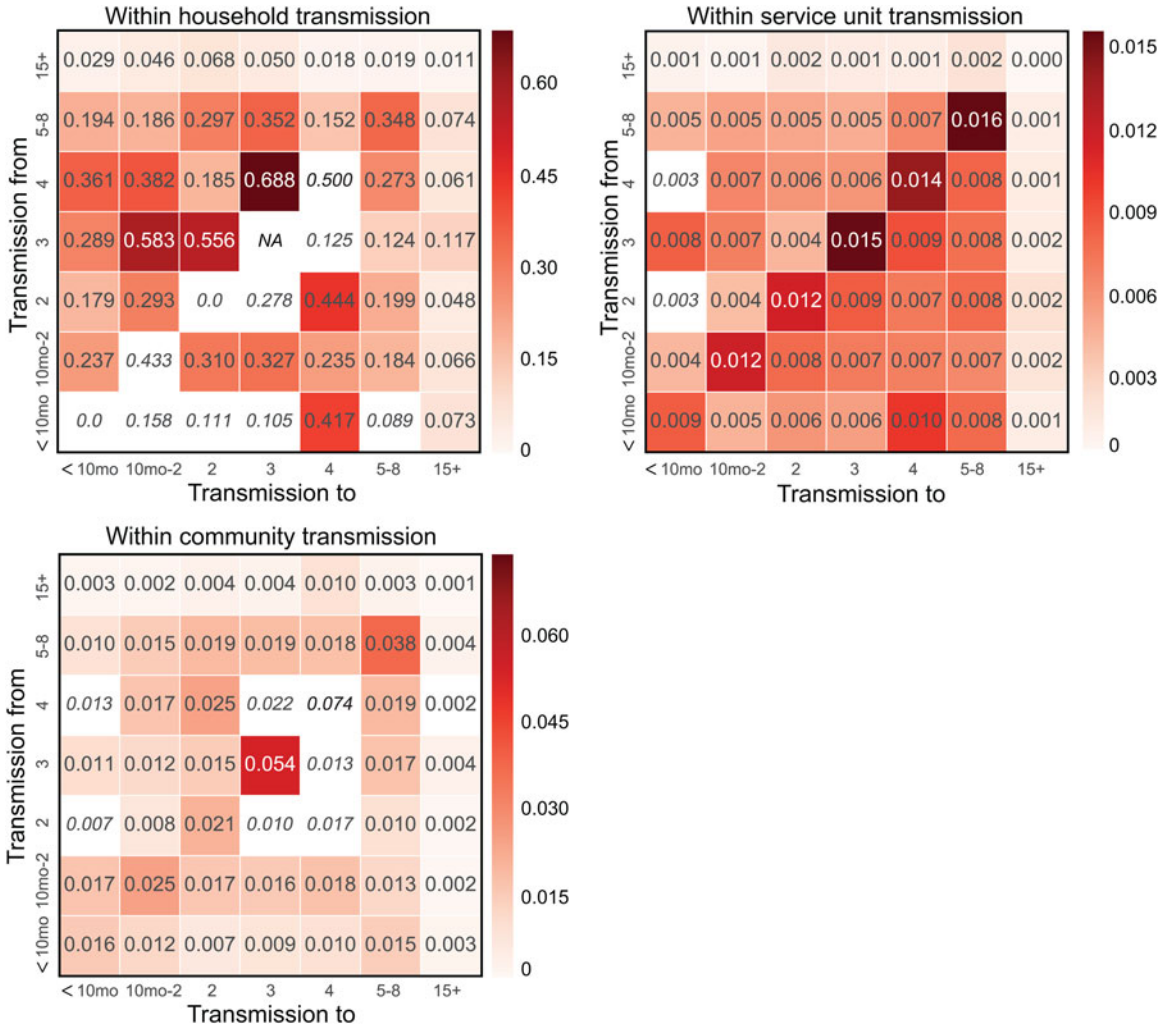

Fig. 4. Proportion of contacts that result in SP transmission between ages. Figure shows the transmission probabilities of SP by age groups from individuals on the Y-axis to individuals on the X-axis within the household, community, or service unit (multiple communities). Transmission probabilities are calculated as the proportion of potential contacts in an age pair (i.e. 3–4 to 2–3 year olds) that resulted in transmission. Transmission events that were not statistically significant are plotted in small italics.

also, transmission from infant to mother is more frequent than mother to infant, also consistent with other studies [17].

DISCUSSION

Our study infers sources of SP transmission across ages and local geographies. We find markedly different transmission routes and sources of SP by age group. For infants under 10 months, despite having a high prevalence of SP colonization, the direction of transmission is most likely from older siblings rather than other infants or parents. In general, we were confident in the possible sources of acquisition, especially at the household or community level, because in most acquisition events, a single source was identified (see Supplementary Fig. S2).

Previous analyses using the same data echo this, suggesting that older children are more likely to introduce SP into the household and transmit to younger children and adults [6]. Based on the above findings, we further breakdown the age groups and indirectly identify the transmission events and sources of SP colonization. We find that the sources of infection vary greatly across age and local geography (i.e. within household, community, or service unit). These results have important implications for understanding potential reservoirs of SP, revising PCV vaccination schedules [1], mathematical modeling of SP transmission dynamics, the potential interaction of SP and other co-infecting pathogens [18, 19], and perhaps most

importantly, for drawing conclusions about the critical community size necessary for SP persistence [20, 21], which is a critical feature for understanding what vaccine programs need to achieve to accrue the greatest impact from these life-saving vaccines.

While contact transmission studies are difficult to conduct due to a myriad of logistical and ethical reasons [14], previous studies have not indicated toddlers as important in respiratory transmission [22–24], nor have identified specific per-pair transmission probabilities by 1 year age groups. The canonical contact tracing study – the Polymod study – suggests older children attending daycare and preschool have higher numbers of contacts (as compared with those under 4 years old) and thus are primary drivers of transmission [14]. If toddlers are one of the primary drivers of transmission, as suggested here or as shown in other studies of acquisition in high carriage prevalence areas [25, 26], future studies and vaccination efforts should target these groups to eliminate reservoirs of SP.

Of specific importance is the question of whether PCV schedules providing a reduced number of doses would be effective in maintaining suppression of carriage and disease achieved through PCV schedules with a greater number of doses [1]. Consideration has been given to a '1 + 1' schedule in which one dose of PCV is administered early in infancy and a booster is administered at 9–12 months of age. Depending on the effectiveness of a single priming PCV dose for preventing carriage of SP – an open question in pneumococcal biology – high transmission in children who fail to receive a booster or receive it at a delayed age could drive ongoing transmission of vaccine-type SP, resulting in persistence of disease. Future work should evaluate the effects of one dose of PCV on carriage in the first year of life, as well as assessing the timing of the booster dose and its potential ramifications on transmission in young age groups.

A useful tool for investigating novel PCV schedules is mathematical modeling of SP transmission. Biologically realistic models can be constructed with various age groups and used to test potential long-term outcomes of reduced-dose schedules. Importantly, these models can be used to inform the design of field-based studies, allowing them to focus firmly on the variables that are most likely to result in a change in vaccine performance. In this way, the vaccine development process gains efficiency and confidence that we have answered the critical questions and can act on the results for program design. Key to the accurate characterization of these models is the pathogen transmission rates between age groups. The results presented here will be useful to modelers wishing to capture SP, and potentially other respiratory pathogen transmission dynamics. Perhaps most importantly, they will provide an additional benchmark for sensitivity analyses when examining the underlying assumptions present in a mathematical model.

There are several potential drivers for the differences observed in transmission probability across age groups. Differences in the prevalence of carriage across age groups (though as seen in Fig. 1 the prevalence is nearly identical across ages), differences in infectiousness (in terms of transmitting carriage to others) across the age groups, and differences in susceptibility across age groups could all explain between age variability and should be explored in further detail.

We found that over 80% of SP transmissions occurred within the same service unit, suggesting SP is likely self-persisting within these service units. Importantly, the population of the Navajo Nation and White Mountain Apache reservation totals 173 667 and 13 409 in the US 2010 Census (15 167 and 1693 children under 5; 15 391 and 1336 for children between 5 and 10 years old, respectively), suggesting that the population size for SP to persist — the so-called critical community size for transmission – might be small, and that vaccine coverage across communities should be not only high but also uniform. Heterogeneous coverage might create pockets of persistence leading to difficulty in clearing the remaining SP vaccine types.

Another open question in pneumococcal epidemiology is the extent of, and mode of action of, interaction between SP and other respiratory pathogens, such as influenza or respiratory syncytial virus (RSV) [18, 21]. Our study did not examine transmission of other pathogens, and thus we cannot determine if the younger aged transmission of SP is related to coinfection. On the one hand, perhaps coinfection with influenza or RSV enhances bacterial shedding of SP and thus increases transmission. On the other, reduced influenza or RSV incidence in older children may reduce SP shedding and thus transmission. Quantification of the effects of SP and other respiratory pathogens on transmission remains a relevant avenue for further research.

Our study has several limitations. First, we do not have genetic sequences of SP isolates from this study; a full set of characterizations would have allowed us to confirm directionality of transmission. However, the diversity of pneumococcal serotypes present in the

study population as well as the chronological order of the infections strongly suggests the order of infections. Looking at the number of identified sources per subject with new acquisitions at different levels, we could track back to a single source of infection mostly at the household level, which gives a more confident representation of transmission (see Supplementary Fig. S2); but because there are multiple potential transmission sources outside the household and because we consider them contributors with equal probability, the uncertainty in who-infected-whom begins to increase at the community and service unit level. Given as the absolute numbers of potential contacts increases as we move to community and service unit levels, we may be seeing serotype matches by chance, thus overestimating the transmission probabilities in these levels. Nonetheless, it is still indicative of transmission.

Second, the findings from any high pneumococcal transmission setting study, like this one, may not be representative of the transmission dynamics from low prevalence settings. The relatively high prevalence of SP in the study setting may affect the transmission dynamics across age groups. However, we believe our results will be applicable to other settings of similar socio-demographic characteristics (e.g. use of daycare) insofar as those drive pneumococcal transmission dynamics. Third, due to the enrollment criteria (infants, children, and their parents), we do not have colonization data on children between 9 and 15 years of age. Future studies should investigate their role in transmitting SP, which may be considerable in households with large numbers of children. Fourth, false-negative NP swabs or undetected multiple colonizations will obscure the estimates of the probabilities of transmission resulting in both over- or underestimation, depending on in whom (transmitter or receiver) the sample was missing or misclassified.

Despite these limitations, our study demonstrates the differences in location of SP acquisition across age groups and highlights the key role of toddlers and older children in transmission of SP, especially toddlers (10 months to 3 years old) – a group previously considered to be less important in the overall transmission of the pneumococcus. Future work can use these results to investigate reservoirs of SP as well as to estimate herd effects under different PCV dosing schedules.

SUPPLEMENTARY MATERIAL

The supplementary material for this article can be found at https://doi.org/10.1017/S095026881700125X.

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DECLARATION OF INTEREST

No conflicts of interest.

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