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Stable dynamics of pneumococcal carriage over a decade in the pre-PCV era

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ABSTRACT

Streptococcus pneumoniae (SP) nasopharyngeal carriage studies are important to understand SP circulation prior to implementation of vaccination programs. It is generally not known how stable these carriage rates are over time.

Carriage studies were conducted in Southern Israel during a decade preceding Pneumococcal Conjugate Vaccine (PCV) introduction. We estimated total and vaccine-type SP carriage at 6 months of age to be stable at 35% (95% CI: 26, 44) and 19% (95% CI: 15, 24), respectively in Jewish and 70% (95% CI, 62, 77) and 41% (95% CI: 38, 45) in Bedouin populations.

The stability of carriage rates in two disparate populations over 10 years suggests a single survey may be sufficient to characterize pneumococcal carriage pre-PCV.

1. Introduction

Globally, pneumococcal conjugate vaccine (PCV) has been effective at reducing incidence of pneumococcal pneumonia and invasive pneumococcal disease (IPD) [1], largely through reductions in *Streptococcus pneumoniae* (SP) carriage and transmission [2]. Typically, two proxy metrics for measuring changes in SP transmission are changes in infant SP carriage prevalence and acquisition of SP carriage episodes. Quantifying reductions is complicated by limited prevalence and acquisition data prior to introduction of PCV in a given setting. There may be few carriage surveys pre-PCV and these may have been done a number of years prior to the introducing PCV [3]. Under these circumstances, quantifying carriage reduction (and therefore vaccine impact) will depend upon assumptions about pre-PCV time trends in infant carriage and whether these are stable over time. Whether explicit or implicit, qualifying impact of PCVs on pneumococcal carriage (overall, VT or NVT) relies typically on the assumption that carriage prevalence is stable near an equilibrium level prior to vaccine introduction [4].

Southern Israel constitutes a unique setting to study historical infant carriage dynamics as it is one of few places in which there were numerous infant carriage studies spanning the decade prior to PCV introduction in 2009 as well as the decade after introduction [5–9]. In the present work, we use this unique collection of data to assess the validity of the assumption of stability in pre-PCV dynamics. We do this through analysis of both cross-sectional carriage and carriage acquisition, focusing on both Jewish and Bedouin communities present in Southern Israel. These two distinct ethnic populations differ significantly with regard to pneumococcal carriage and disease.

2. Methods

2.1. Setting

In southern Israel (the Negev region), the Jewish and Bedouin populations, differing in their socioeconomic conditions and lifestyles, live side by side. However, both have access to the same medical services. The Jewish population is mainly urban, whereas the Bedouin population, formerly desert nomads, is in transition to a western lifestyle [10]. Contact between children of the two populations is rare. The Bedouin population lives in scattered clusters and Bedouin townships, while the Jewish population lives mostly in cities and the rest live in Jewish townships and villages. Children of the two populations do not frequent the same day-care facilities or schools and do not have common social life.

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The Bedouin population is characterized by overcrowding, lower education level, larger family size and lower income than the Jewish populations [10]. In 2004, the crude birth-rate was 55.3 vs 21.0 per 1000 in the Bedouin and Jewish population, respectively [11]. During the period 2004–2016, the annual mean births was 7732 Bedouins children and 8160 Jewish children. The mean family size (±SD) among the Bedouin population was 8.2 ± 0.9 persons vs only 3.2 ± 0.1 among the Jewish population) [12]. The average monthly family income was two-fold higher in the Jewish population [11]. Hospitalization rates for respiratory and other infectious diseases were higher among Bedouins [13].

Pneumococcal nasopharyngeal carriage is usually higher among Bedouin infants than among Jewish infants and maternally-derived pneumococcal anti-polysaccharide antibodies are often higher in young Bedouin infants [6]. All children in the area are born in one hospital, where they also receive all emergency and inpatient services. Vaccines are given in public sector Mother and Child Health Centers for a token annual family membership fee. All children in Israel are entitled to medical insurance free of charge.

2.2. Carriage studies

From 1997 to 2008, prior to PCV introduction in the population, there were a total of 9 infant nasopharyngeal (NP) SP carriage studies among Jewish children and 8 studies among the Bedouin children in Southern Israel. Summaries of the relevant data collected in each study are provided in SM Table S1, and studies denoted as either cross sectional population studies or longitudinal acquisition studies [5–9].

2.3. Cross sectional analysis

Cross sectional total and vaccine-type (VT) SP carriage prevalence was analyzed for children under 2 years of age using random effects logistic regression with a (log transformed) age fixed effect and a random intercept for the study population [14]. Models were constructed separately for Bedouin and Jewish population groups. Antibiotic use prior to NP swabbing was reported in only 4 of the 9 studies and therefore was not included in the final analysis for the sake of parsimony. Previous antibiotic usage was not a criteria for inclusion into the studies, therefore it is assumed that the study populations are unbiased samples with respect to health status and antibiotic usage. Effects of sex were not found to be significant, in agreement with other childhood NP carriage studies [15]; therefore this covariate was not included in the final analysis. A time dependent covariate was also initially included to adjust for secular trends. Inclusion of this covariate in the analysis of overall carriage was not found to be statistically significant and did not result in a better fit to the data as indicated by a substantially higher value of Bayesian Information Criterion (BIC). Therefore, this covariate was not included in the final model. For comparison, estimated parameters for the model and BIC values are given in SM Table S2. Parameter estimates for the final models including p values for fixed effects are given in SM Table S3.

Ninety-five percent confidence intervals for carriage prevalence were computed via bootstrap simulation for fixed and random effects. Computations were performed in R version-3.3 with logistic regressions performed within the lme4 [14] package and bootstrap simulations performed using *the predictInterval* function included in the merTools package [16] for multi-level models.

2.4. Longitudinal analysis

Carriage acquisition for the 1997 and 2007 longitudinal studies was analyzed through Kaplan-Meier survival analysis. The impact of number of siblings as well as seasonality on acquisition was investigated through the use of a Cox proportional hazards model with a sinusoidal seasonal covariate [17]. Validity of the proportional hazards assumption was established by testing the association of the scaled Schoenfeld residuals with time. For parsimony in comparisons between acquisition curves in different studies with similar observation schedules, we took time of acquisition to be the time of swab collection as opposed to inferring the time of acquisition within the interval from [17] the last-negative to first positive swab. This implies that absolute quantification of seasonal timing (as opposed to magnitude of effect) will be biased towards later dates by at most the interval between swabs (2–4 months).

3. Results and discussion

3.1. Cross sectional data analysis: estimating age-dependent carriage prevalence in infants

Fig. 1 shows the estimated total pneumococcal carriage prevalence and VT carriage at 6 months of age, in and VT generated from the random intercepts log-age adjusted logistic regression models.

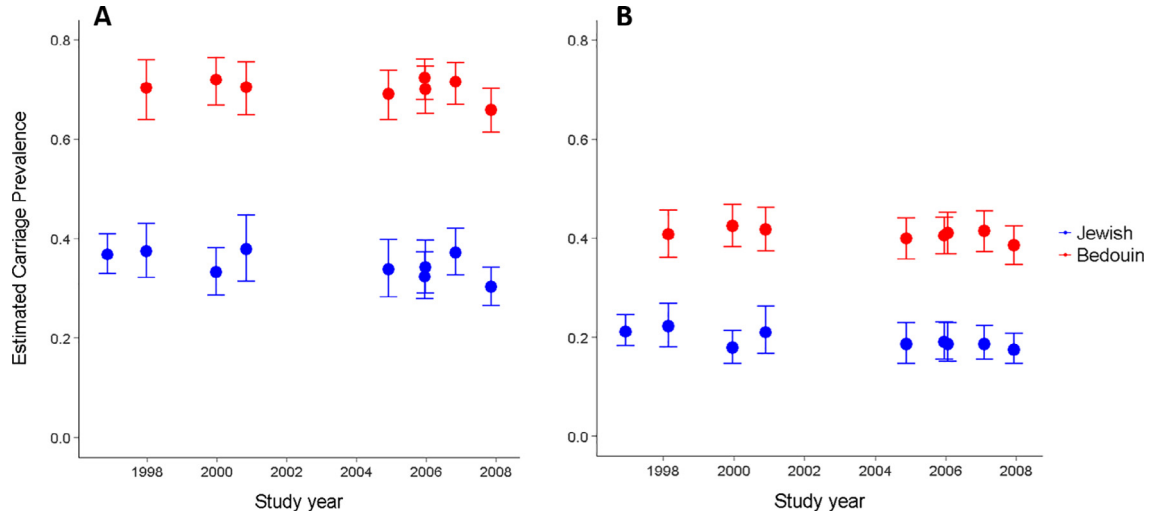

Fig. 1. Estimated total carriage prevalence (A) and VT prevalence (B) at 6 months of age for each of the studies in Table S1 (Supplementary Material) stratified by Jewish or Bedouin ethnicity. Years on the horizontal axis represent the midpoint of each of the study intervals and error bars represent 95% confidence intervals for prevalence estimates.

Estimated total SP carriage prevalence at 6 months of age was 34.8% (95% CI: 26, 44) for the Jewish children and 70.3% (95% CI, 62, 77) for the Bedouin children (percent difference between groups 35%; 95% CI: 29, 41; $p < 0.0005$). Vaccine-type carriage prevalence at 6 months of age was 19% (95% CI: 15, 24), and 41% (95% CI: 38, 45). For VT serotype carriage estimates the range of 95% confidence intervals across all studies corresponded to 15–27% and 34–45% respectively (percent difference between groups 21%; 95% CI, 16.7, 26.4, $p < 0.0005$). The overall proportion of each VT serotype is shown by group aggregated across the studies in Fig. 2. Orderings were similar for both groups (with 6B 6A 19F and 23F in higher proportions in each population) with VT strains representing 57% and 58% of total pneumococcal carriage respectively. Summaries of the models of overall and VT carriage for both groups are given respectively in SM Tables S3 and S4.

3.2. Longitudinal data analysis: comparing acquisition curves

Fig. 3 shows the Kaplan-Meier carriage acquisition curves for the 1997 and 2007 longitudinal carriage studies for Jewish (1997 and 2007) and Bedouin (2007) groups. For the 1997 study sample swabs were collected at approximately 2, 4, 6, 7, 12 and 13 months. The 2007 schedule was identical up to 12 months with no sample taken at 13 months. For the 2007 studies there were 190 and 88 infants respectively in the Jewish and Bedouin groups and for the 1997 study there were 99 infants (Jewish group) included.

Consistent with the cross-sectional carriage the estimated probability of pneumococcal acquisition before 6 months of age was significantly higher in the Bedouin group, 92.5% (95% CI: 83, 97), when compared to the Jewish groups, 50% (95% CI: 39, 60) in 2007 and 51% (95% CI: 41, 55) in 1997. A log-rank test of the

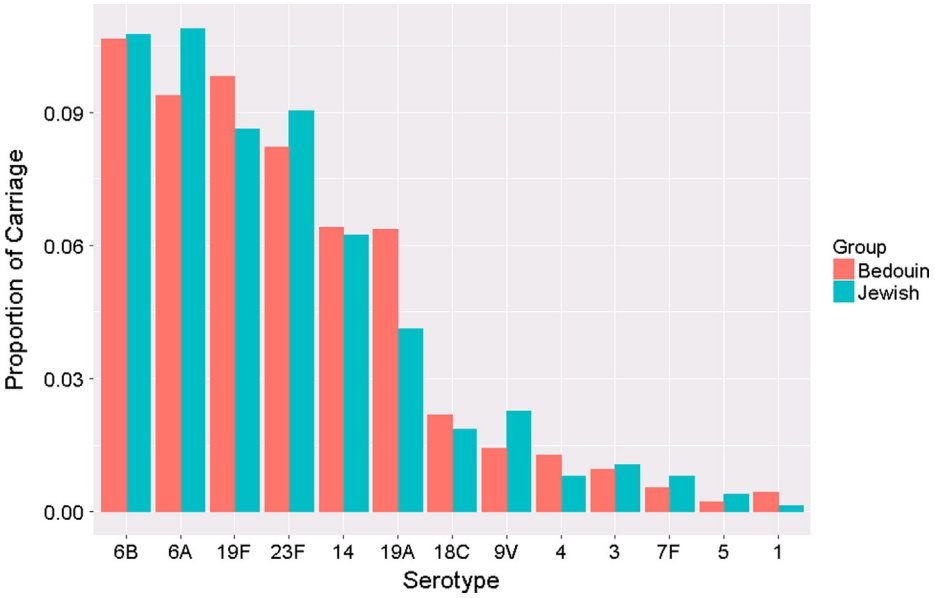

Fig. 2. Relative proportion of vaccine serotypes for children <2 years in Jewish and Bedouin groups aggregated across all included studies from 1997 to 2008.

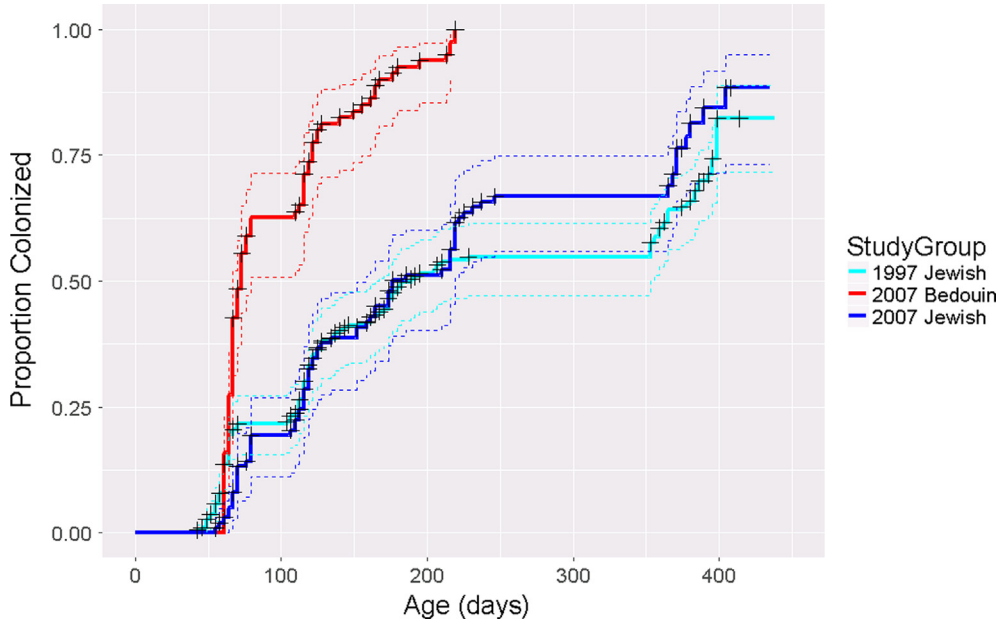

Fig. 3. Acquisition curves: Kaplan-Meier acquisition curves for the 1997 and 2007 longitudinal carriage studies in infants (see Table S1 in Supplementary Material) stratified by population group. For the 2007 study swabs were collected at approximately 2, 4 6, 7 and 12 months and in 1997 at 2, 4, 6 7, 12 and 13 months. Crosses indicate right-censored data and dashed curves represent pointwise 95% confidence intervals.

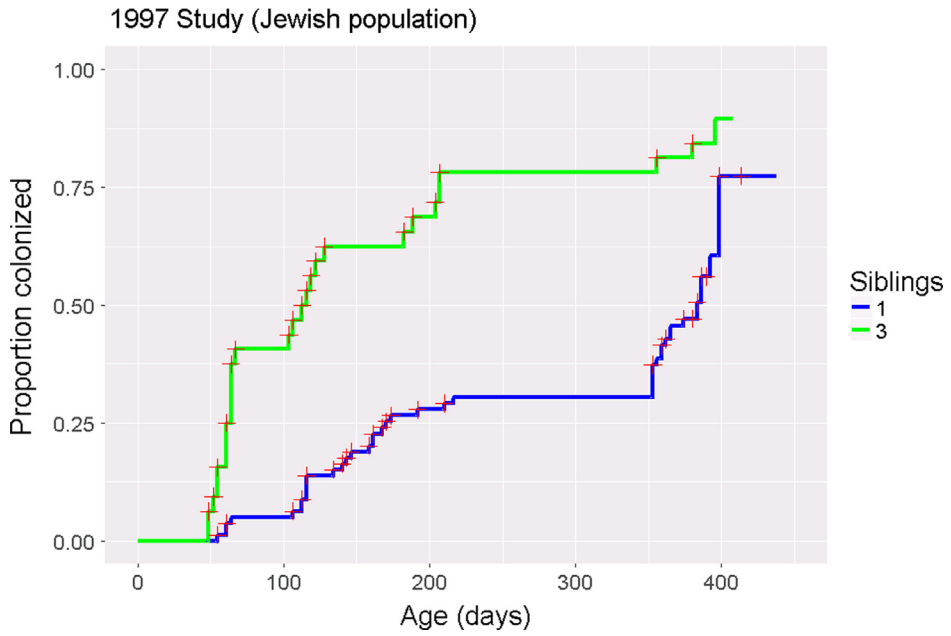

Fig. 4. Carriage Acquisition and Sibling Number. Kaplan-Meier acquisition curves for the 1997 carriage acquisition study stratified by 1 and 3 siblings corresponding to n = 80 and n = 32 infants respectively.

1997 and 2007 Jewish infant acquisition curves showed no significant difference between the time periods (chi-square statistic = 1.2, p = 0.28). Analogously, a log-rank test of 2007 Jewish and Bedouin acquisition curves show strong differences in acquisition probabilities between the populations as is visually discernable in Fig. 3 (chi-square statistic = 67, p < 0.001).

3.3. Cox proportional hazards model: inferring drivers of acquisition

Cox-proportional hazards models showed significant impact of both number of siblings and seasonality in acquisition for Jewish children: Each additional sibling was associated with a 1.3- fold increase (95% CI, 1.18, 1.43) in the rate of SP acquisition (Fig. 4). Similarly, Cox models for the Bedouin 2007 acquisition study showed the same qualitative effect of a 1.11-fold increase (95% CI: 1.01, 1.22) in acquisition rate per each additional sibling. Proportional hazards models for both Jewish and Bedouin infants are summarized in Table S5 in SM.

The effect of seasonality on acquisition was incorporated in the Cox model as a Fourier (sine and cosine) series, where the coefficient of each term in the Fourier series is associated with a single time-dependent covariate in the model. The seasonal covariates were found to be significant to first order in the Jewish groups, with increased acquisition beginning in November and decreased acquisition beginning in May. The log hazard ratio of the first order seasonal covariates is shown in SM Figure S1. The model for the Bedouin population in the 2007 study did not include seasonality due to the short swab collection window of a few months. No significant violations of the proportional hazards assumption were identified (see SM Table S6).

4. Conclusions

Through statistical analysis of over 10 years of SP surveillance and carriage studies in Southern Israel using hierarchical statistical modes of age-dependent carriage we show that pre-vaccination SP carriage levels are steady in Southern Israel, both in Bedouin and Jewish infants. We corroborated these results through survival analysis of a limited number of similarly designed acquisition studies, from 1997 and 2007, which showed very similar patterns of acquisition from birth through the first 13 months of life.

These results have strong implications for assessing the impact of PCV after introduction in a new population. In many settings there are a limited number of carriage acquisition or carriage prevalence studies prior to the introduction of PCV, and these will generally precede PCV rollout by some time. In the absence of other information, the true baseline level of pneumococcal carriage cannot be determined and it is unclear whether carriage prevalence and acquisition would have changed in the future in the absence of PCV (the counterfactual scenario). In the case of declining or ascending trends in carriage, this would result in over-estimates and under-estimates of impact, respectively. The results of this study show that estimating PCV impact on carriage based on steady-state dynamics prior to introduction is a valid approach in both medium and high force of infection settings. Though it could be argued that trends in the counterfactual dynamics could also be established via monitoring of NVT serotypes, this is largely complicated by strain replacement occurring over longer time scales, and thus would require an accurate measure of the degree of strain replacement that has occurred.

There is a question as to how generalizable the dynamics observed in these studies are to other populations. The fact that the stability in pre-PCV carriage was strongly reflected in both the Jewish and the Bedouin children suggests the generalizability of the results. Though these populations are located in the same geographic region and utilize the same health-care system they have different social structures and mixing patterns which are reflected in the large differences observed in pre-PCV carriage. Therefore, viewing the prevalence in a given setting as the product of the same SP biology and human social interaction, the observed stability in two environments with very different forces of infection lends support to the results being applicable across populations.

Many mechanistic mathematical models of SP transmission used in forecasting disease incidence and impact of vaccination assume stable equilibrium-type dynamics in a pre-vaccine era, and thus their predictions are subject to these issues regarding reliability of counterfactual dynamics [4]. The results of this study therefore lend validation to these models.

In addition to the primary analysis, this analysis of acquisition confirmed the relationship between increased sibling number and risk of pneumococcal carriage which has been established by other studies [18,19]. This analysis also showed (weakly) significant effects of seasonality in acquisition. Though the seasonality results roughly correspond with higher transmission starting during late November and lower carriage beginning in May, the length of intervals between swabs of 2–4 months may bias any absolute estimates of the timing of seasonal transmission patterns.

Accurate understanding of SP transmission dynamics is crucial to evaluating the impact of costly PCV vaccination campaigns and relies on assessing the steady state carriage prevalence of VT serotypes before implementing a new vaccine schedule. Results here validate methods to assess prevalence in resource-limited settings.

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Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Appendix A. Supplementary material

Supplementary data to this article can be found online at https://doi.org/10.1016/j.vaccine.2019.07.077.

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