Decline in pneumococcal disease in unimmunized adults is associated with vaccine-associated protection against colonization in toddlers and preschool-aged children

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ABSTRACT

Vaccinating children with pneumococcal conjugate vaccines disrupts transmission, reducing disease rates in unvaccinated adults. When considering changes in vaccine dosing strategies (e.g., removing doses), it is critical to understand which groups of children contribute most to transmission to adults. We used data from children and adults in Israel to evaluate how the build-up of vaccine-associated immunity in children was associated with declines in IPD due to vaccine-targeted serotypes in unimmunized adults. Data on vaccine uptake and prevalence of colonization with PCV-targeted serotypes were obtained from a unique study conducted among children visiting an emergency department in southern Israel and from surveys of colonization from central Israel. Data on invasive pneumococcal disease in adults were obtained from a nationwide surveillance study. We compared the trajectory of decline of IPD due to PCV-targeted serotypes in adults with the trajectory of decline of colonization prevalence and trajectory of increase in vaccine-derived protection against pneumococcal carriage among different age groupings of children. The declines in IPD in adults were most closely associated with the declines in colonization and increased vaccination coverage in children in the range of 36-59 months of age. This suggests that preschool-aged children, rather than infants and young toddlers, are responsible for maintaining the indirect benefits of PCVs.

INTRODUCTION

Pneumococcal conjugate vaccines (PCVs) have had a well-documented impact on the incidence of invasive pneumococcal disease (IPD) and pneumonia in young children (1-3). PCVs reduce the burden of disease in two ways: they directly protect vaccinated individuals who are exposed to the bacteria against invasive infections, and they indirectly protect vaccinated and unvaccinated individuals (including adults) by reducing the prevalence of carriage of vaccine-targeted serotypes and thus reducing transmission. Colonization of the nasopharynx of young children represents the main reservoir for transmission of pneumococcus, and PCVs reduce the proportion of children who are colonized with serotypes targeted by the vaccine (4). The reduction in the burden of disease in unvaccinated adult age groups resulting from this indirect protection greatly outweighs the reduction in the burden of disease seen in vaccinated children alone (5).

While PCV programs have effectively reduced the burden of disease in many countries, the cost of the vaccine remains a major concern. This is particularly an issue for countries that need to pay full price for the vaccine or that need to pay for the vaccine without subsidies. As additional countries “graduate” from being eligible for financial support from Gavi, this will become an increasingly important concern.

To reduce costs while maintaining widespread use of the vaccine, there has been interest in reducing the number of doses of PCVs delivered to children (6-8). Such a strategy could be used in populations that have already achieved strong reductions in disease due to the vaccine. Currently, most countries use either a 3+0 schedule (3 doses in the first six months of life, no booster dose) or a 2+1 schedule (2 doses in first six months of life, 1 booster dose administered at 9-15 months of age). The newly proposed schedule would include just one primary dose and

one booster dose (1+1). Reduced-dose schedules have been shown to be immunogenic (7, 9, 10). However, because of the importance of indirect protection that results from the use of PCVs, it would be desirable for any new dosing strategy to be able to maintain indirect protection (6).

To consider this issue, it is critical to determine which groups of young children contribute most to the indirect benefit of the vaccine for unimmunized adults. Epidemiological and modeling studies of transmission focused on households and daycare centers suggest that toddlers and older children, rather than infants, drive transmission in the population (11-14). Likewise, the decline in IPD due to vaccine-targeted serotypes in adults is delayed and slower than the decline observed in vaccinated children (15). This might indicate that the transmission benefit (i.e. indirect effect) of vaccinating children during the first year of life is not realized until a few years later when those children reach an older age group.

In this study, we evaluated how the build-up of vaccine-associated immunity against colonization in different age categories was associated with declines in IPD due to vaccine-targeted serotypes in unimmunized age groups. We used a unique and ongoing survey of children in Israel that allowed us to quantify vaccine uptake and IPD rates over time to evaluate these associations.

METHODS

Data sources

Carriage and vaccine uptake data for children were obtained from an ongoing study of children visiting the emergency department at Soroka University Medical Center (16). Each weekday, the first four Jewish children and first four Bedouin children under the age of 5 years who visited the emergency department (ED) were enrolled in the study. A nasopharyngeal swab

was collected and cultured, and serotype was determined using Quellung reactions, as described previously (16). These findings were previously used to represent PCV uptake in Israel, since data from the region are within the range of the average vaccine uptake nationwide (17). The number of doses of PCV7 and PCV13 received was recorded. We calculated uptake of PCV7/13 in each month post-PCV introduction in age bands that varied in width and ages included. Data on IPD in adults were collected as part of a national surveillance system in Israel (18). For our primary analyses, only data from Jewish individuals were included due to different demographics of the minority populations in southern Israel (where the carriage data were drawn from) compared with the entire country (where the IPD data were drawn from). We performed secondary analyses of the carriage data from Bedouin children for comparison. As a further evaluation of changes in prevalence among healthy children (rather than among children visiting the ED), we evaluated changes in the prevalence of PCV7-targeted serotypes among healthy children living in central Israel who were sampled as part of a series of cross-sectional surveys of nasopharyngeal colonization (19, 20). The study was approved by the Soroka University Medical Center Ethics Committee and the Sheba Medical Center Ethics Committee.

Calculation of the "Population Direct Effect" against colonization

The population direct effect provides an estimate for the overall effect of the vaccine that would be expected in the absence of indirect protection (21). The quantity is simply a function of the individual-level direct efficacy of the vaccine (as measured in a randomized controlled trial) and the proportion of the population that is vaccinated. For a given age band (a) and time point (t), the population direct effect is calculated by estimating the proportion of individuals in that strata

that have received 1, 2, or 3+ doses of vaccine and multiplying this by the individual-level vaccine efficacy of 1, 2, or 3 doses against colonization due to vaccine-targeted serotypes:

$$\begin{aligned} Pop\_Direct\_Effect_{a,t} = {} & prop\_dose1_{a,t} * (efficacy\_dose1) \\ & + prop\_dose2_{a,t} * (efficacy\_dose2) \\ & + prop\_dose3_{a,t} * (efficacy\_doses3) \end{aligned}$$

Vaccine efficacy was obtained from a randomized controlled trial of PCV7 among children in Israel that used a variety of dosing schedules (13, 22). The point estimate for efficacy against colonization was estimated at -0.1%, 27%, and 46% for 1, 2, or 3 doses, respectively. The observed estimates of the population direct effect for any given time point and stratum were based on small numbers, so we used cubic splines to smooth the trajectory of the population direct effect. This was accomplished using PROC GAM in SAS v9.4 (Cary, NC), where the outcome was the observed estimates of the population direct effect, and time was modeled with a cubic spline with 3 degrees of freedom. Separate smoothing models were fit for each age range and ethnicity.

Evaluating the association between carriage in different groups of children and IPD in adults

We hypothesize that as the population direct effect increases in a particular age group of children, the prevalence of colonization with vaccine-targeted serotypes will decline in that age group. When carriage declines in age groups critical for transmission to adults, we should also see a decline in IPD in adults. Carriage prevalence is thus an intermediary measure of the relationship between the population direct effect in children and declines in IPD in adults; however, it is imperfect because the prevalence of carriage in a particular age category is also influenced by changes in carriage prevalence in younger or older children. Nonetheless, carriage

prevalence provides the most directly observable measure of vaccine-associated changes in transmission in children We fit Poisson regression models where the outcome was the number of IPD cases due to PCV7-targeted serotypes in a particular month and adult age group. The sole covariate was log(carriage prevalence) in a given age band at each time point. Log(carriage prevalence) was smoothed using PROC GAM, as described above. For these analyses, we focused on PCV7 serotypes only (rather than the six additional serotypes that are were added into PCV13). This is because there was a brief period of time between the introduction of PCV7 and PCV13, which made it difficult to disentangle early serotype replacement from vaccine-associated effects. Since the PCV7 serotypes are present in both vaccines, focusing on these serotypes allowed for more interpretable trajectories.

Evaluating the association between direct protection and indirect effects

We fit Poisson regression models where the outcome was the number of cases of IPD due to PCV7-targeted serotypes in a particular month and specific adult age group. We controlled for seasonality using monthly dummy variables. The sole covariate in each model was the $Pop\_Direct\_Effect_{a,t}$, corresponding to a specific age band. We only used data from the Jewish population for this analysis, as noted above. AIC scores were converted into model weights (23), and these were used to compare goodness of fit among models where the estimate of the population direct effect covered different age ranges. By convention, models that were within 2 AIC points of the best model were considered to not be meaningfully different from the best model (24). To obtain a summary of the importance of each age group (i.e., 0-5m, 6-11m, 12-17m), we averaged the weights for all models in which the age band for the population direct effect variable covered that 6-month age group.

RESULTS

Description of the population

Nasopharyngeal swabs and vaccine status were obtained from 4,464 Jewish children <5 years of age visiting the ED between 2009 and 2016. Among these children, the prevalence of PCV7 serotypes declined from 21% in 2009 to 2.6% in 2016. These declines were apparent in all age groups of children <5 years of age, with the most rapid declines among 12-23 and 24-35 month olds and slower declines among <12 month and 36-59 month olds (**Figure 1, S1)**. The differences in these trajectories between age groups were similar among 5,933 Bedouin children (57% of samples) who visited the same ED and among healthy Jewish children living in central Israel (**Figures S1 and S2**). During this time period, vaccine coverage increased rapidly (**Figure 2)**.

Estimated increase in population direct protection against carriage by age group

We estimated the reduction in the prevalence of PCV7-targeted serotypes that would be expected in the absence of an effect of the vaccine on transmission (the "population direct effect"). Among children <12 months of age, the population direct effect remained low (<20%) and was stable throughout the study period (**Figure 2, S3**). This is because the vaccine effectiveness against carriage of the two primary doses received in the first year of life is low, and uptake of these two doses among infants was stable throughout the study period. The population direct effect in this age group was higher among Jewish children compared to Bedouin children due to higher uptake of the vaccine. In other age bands, the population direct effect against carriage increased rapidly following vaccine introduction, with the effect

plateauing at around 40% among 12-23 month old children by 2011 or 2012, consistent with the relatively high vaccine coverage and 46% effectiveness of three doses of PCV.

Declines in carriage in older children are associated with declines in disease in adults.

We next evaluated the association between the carriage prevalence of PCV7-targeted serotypes at each time point in different age groupings of children and IPD in adults. Declines in carriage of PCV7-targeted serotypes in older children (≥24 months) and children <6 months of age were most strongly associated with the declines in IPD due to PCV7-targeted serotypes in adults (**Figure 3**). This pattern can be seen in Figure 3 where each horizontal band indicates an age range in which carriage prevalence was calculated. Horizontal bands that are higher on the y-axis better fit the decline of the PCV7 serotypes as causes of IPD in adults. Bands that were highlighted in color were not meaningfully different from each other (≤2 difference in AIC).

Increase in protection against carriage is associated with indirect protection against IPD

The association between carriage patterns in the <6 month old children and IPD in adults could mean two things; it could be that the <6 month olds are important for transmission to adults, or it could mean that the serotype patterns among the <6 month olds and the older adults are both influenced by changes in transmission from the same group of older children (i.e. confounding by the population direct effect among older children). To disentangle this issue, we evaluated the association between the decline in IPD in adults and the population direct effect against carriage in different age bands of children <5 years of age. The decline in IPD due to PCV7 serotypes among adults 18-39 y, 40-64 y and ≥65 y of age was most strongly associated with the increase in the population direct effect among 36-59 month old children (**Figure 4)**.

There was some uncertainty about which age band was most strongly correlated with IPD in adults, as all of the age bands colored in red in Figure 4 fit similarly. Despite this ambiguity, none of the best-fitting models included a population direct effect estimate among children <12 months of age. The importance of the 12-35 month olds was ambiguous, with some of the best-fitting age bands including these toddlers.

DISCUSSION

Indirect protection has been a critical component of the overall impact of PCV, as evidenced by the large declines in IPD among older adults who were not recipients of the vaccine. The decline in IPD due to vaccine-targeted serotypes in Israeli adults was most strongly correlated with the decline in carriage due to these serotypes in older children and infants <6 months old. The carriage patterns in infants and toddlers could themselves be influenced by the indirect effects of the vaccine. To disentangle the importance of these different age groups in driving indirect protection of adults, we evaluated the relationship with the population direct effect against carriage. This analysis unambiguously found that the decline in IPD due to vaccine-targeted serotypes in adults was associated with a build-up of vaccine-derived protection against colonization amongst toddlers and preschool-aged children rather than infants.

These findings have important implications for the possible success of reduced-dose schedules. Our findings suggest that vaccine uptake in infants plays a minor role in influencing the indirect effects of PCVs. This is partially because the two primary doses of the vaccine received in the first year of life have little effect on colonization. Rather, it is the third dose that provides protection against carriage, and thus, subsequently prevents transmission. This suggests that if the booster dose in a 1+1 schedule provides adequate protection against colonization, and

uptake rates of the vaccine in toddlers and older children are sufficiently high, then the reduced dose schedule should be effective at maintaining indirect protection. Recent immunological data suggests that the 1+1 and 2+1 schedules provide comparable levels of immunity after the booster dose, as measured by serum IgG (7). If these serum IgG levels correlate with mucosal immunity in the nasopharynx, the reduced-dose schedule would be expected to provide effective protection against colonization that is comparable to a 2+1 schedule in these older children.

Our results are consistent with previous epidemiological and modelling studies of pneumococcal colonization that suggest that toddlers and young school-aged children, rather than infants, drive transmission of pneumococcus in the population (11-14). This reinforces the notion that it is important to maintain strong immunity to colonization in these older children in order to maintain indirect protection of younger children and adults. This is particularly important if a single dose received in the first year of life has lower direct effectiveness against IPD or pneumonia among infants than two or three doses.

Our analyses focused primarily on the Jewish population in Israel, which has a population structure and sociodemographic profile similar to that of populations in high-income countries in Europe and North America. The contact structure, age-specific prevalence, and intensity of transmission will be different in a low-income setting. As a result, the age groups that contribute most to transmission and indirect protection could differ as well.

A strength of this study is the ability to extract data on vaccine uptake and colonization at a high resolution of time and age from a large sample of children. Thus, we were able to monitor the increases in uptake, changes in carriage prevalence, and declines in vaccine-targeted serotypes at an unusually detailed level across the population. Furthermore, the IPD data were obtained from a robust national surveillance system, allowing us to quantify the indirect effects

of the vaccine in adults. Limitations of the data include our reliance in the main analysis on carriage and vaccine uptake data from a study performed in an emergency department setting. However, our secondary analysis of carriage data from children living in central Israel suggests that the trajectory of decline of PCV-targeted serotypes is similar in the general pediatric population. Finally, we have used a relatively simple set of analyses based on regression models to evaluate this issue. Transmission patterns are complex and dynamic, and an age-structured transmission model could be used to further evaluate the importance of these different age cohorts in different populations and to evaluate the potential impact of changes to the vaccine schedule.

In summary, our findings suggest that protection of toddlers and preschool-aged children with PCVs might be most influential in maintaining indirect protection against IPD among older adults. Any changes in vaccine schedules should focus on maintaining immunity in these older children.

FIGURE LEGENDS

Figure 1: (A) Observed proportion of nasopharyngeal swabs that were positive for PCV7 serotypes by calendar year among Jewish children <5 years of age, stratified into 1-year age categories (<12m, 12-23m, 24-35m, 36-47m, 48-59m). (B) Smoothed proportion of children carrying PCV7 serotypes in each month 2009-2016.

Figure 2: Increase in the population direct effect against carriage by age group for Jewish children: <12m, 12-23m, 24-35m, 36-47m, 48-59m. The population direct effect represents the

expected vaccine effectiveness against carriage if there was no effect of the vaccine on transmission. Estimates were smoothed with splines prior to plotting

Figure 3: Relative goodness of fit between prevalence of PCV7 serotypes among healthy children in different age ranges (indicated by the horizontal bars) and invasive pneumococcal disease (IPD) in adults. Each horizontal bar indicates an age range in which (smoothed) carriage prevalence was calculated. The vertical position of the bar along the y-axis indicates the goodness of fit, as measured by model weights derived from the Akaike Information Criteria score. Therefore, carriage prevalence in age ranges that are placed higher on the y-axis fit the adult IPD data better. Bars colored in red were not meaningfully different than the best-fit model (AIC score within 2 points). The bottom panel represents the average goodness of fit at each age.

Figure 4: Relative goodness of fit between the population direct effect in different age ranges of children (indicated by the horizontal bars) and invasive pneumococcal disease (IPD) in adults. Each horizontal bar indicates a specific age range in which the population direct effect was calculated based on uptake of 1, 2, and 3 doses of the vaccine in that age group and expected efficacy of these doses against colonization. The vertical position of the bar along the y-axis indicates the goodness of fit, as measured by model weights derived from the Akaike Information Criteria score. Therefore, the population direct effect in age ranges that are placed higher on the y-axis fit the adult IPD data better. Bars colored in red were not meaningfully different than the best model (AIC score within 2 points). The bottom panel represents the average goodness of fit at each age.

Figure S1: Comparison of the decline of PCV7 serotypes among healthy carriers in the Jewish and Bedouin populations. Observed proportion of nasopharyngeal swabs that were positive for PCV7 serotypes by calendar year among Jewish children <5 years of age, stratified into 1-year age categories (<12m, 12-23m, 24-35m, 36-47m, 48-59m).

Figure S2: Observed proportion of nasopharyngeal swabs that were positive for PCV7 serotypes by calendar year among Jewish children <5 years of age living in central Israel, stratified into age categories (<12m, 12-23m, 24-59m).

Figure S3: Comparison of the increase in the population direct effect against carriage between Jewish and Bedouin children. The population direct effect represents the expected vaccine effectiveness against carriage if there was no effect of the vaccine on transmission. Estimates were smoothed with splines prior to plotting.

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FIGURE 1

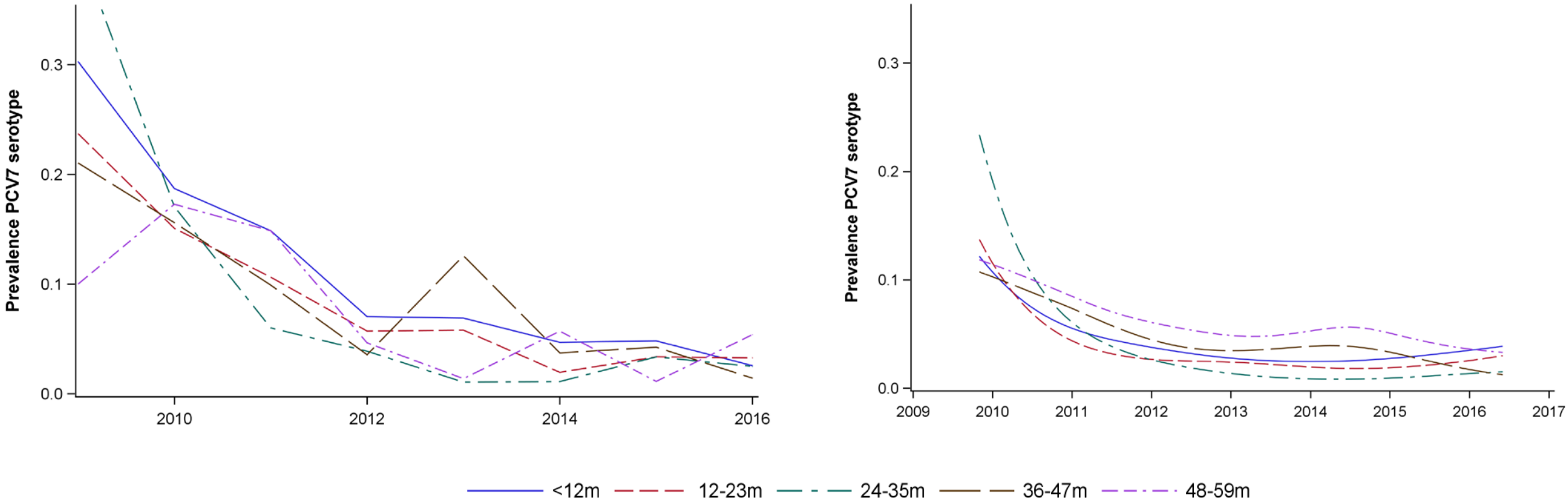

Prevalence PCV7 serotype
0.0
0.1
0.2
0.3
2010
2012
2014
2016
Prevalence PCV7 serotype
0.0
0.1
0.2
0.3
2009
2010
2011
2012
2013
2014
2015
2016
2017
<12m
12-23m
24-35m
36-47m
48-59m

FIGURE 2

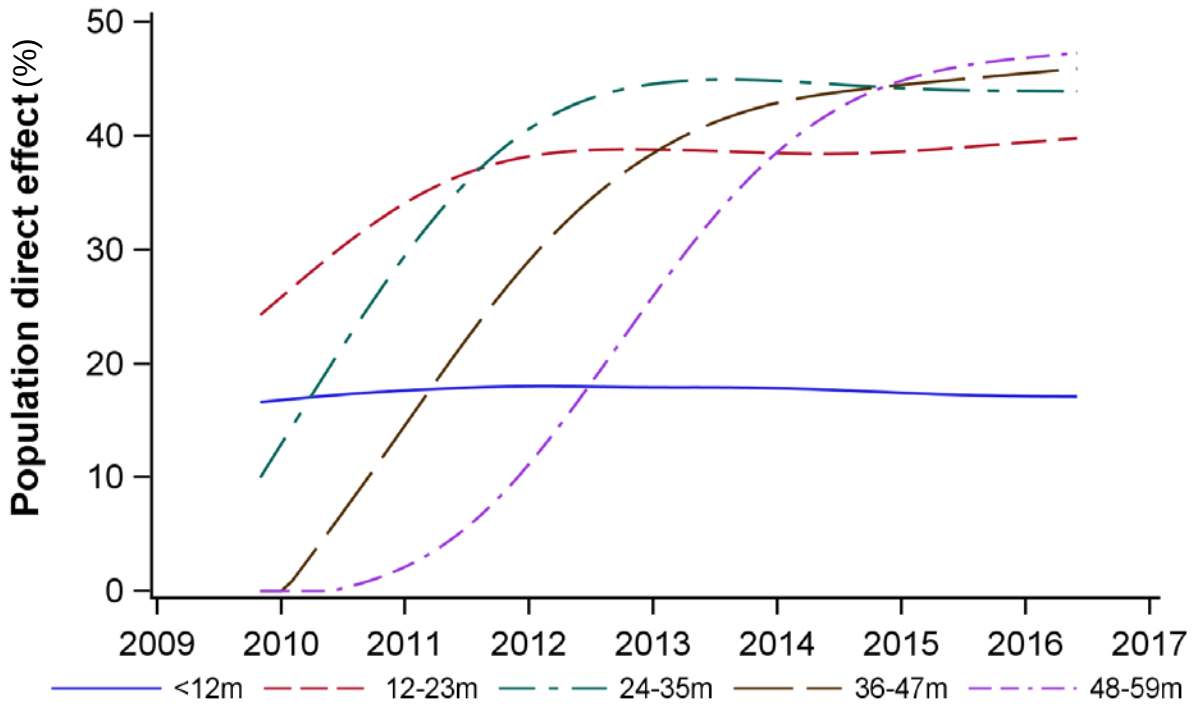

Population direct effect (%)
50
40
30
20
10
0
2009
2010
2011
2012
2013
2014
2015
2016
2017
<12m
12-23m
24-35m
36-47m
48-59m

FIGURE 3

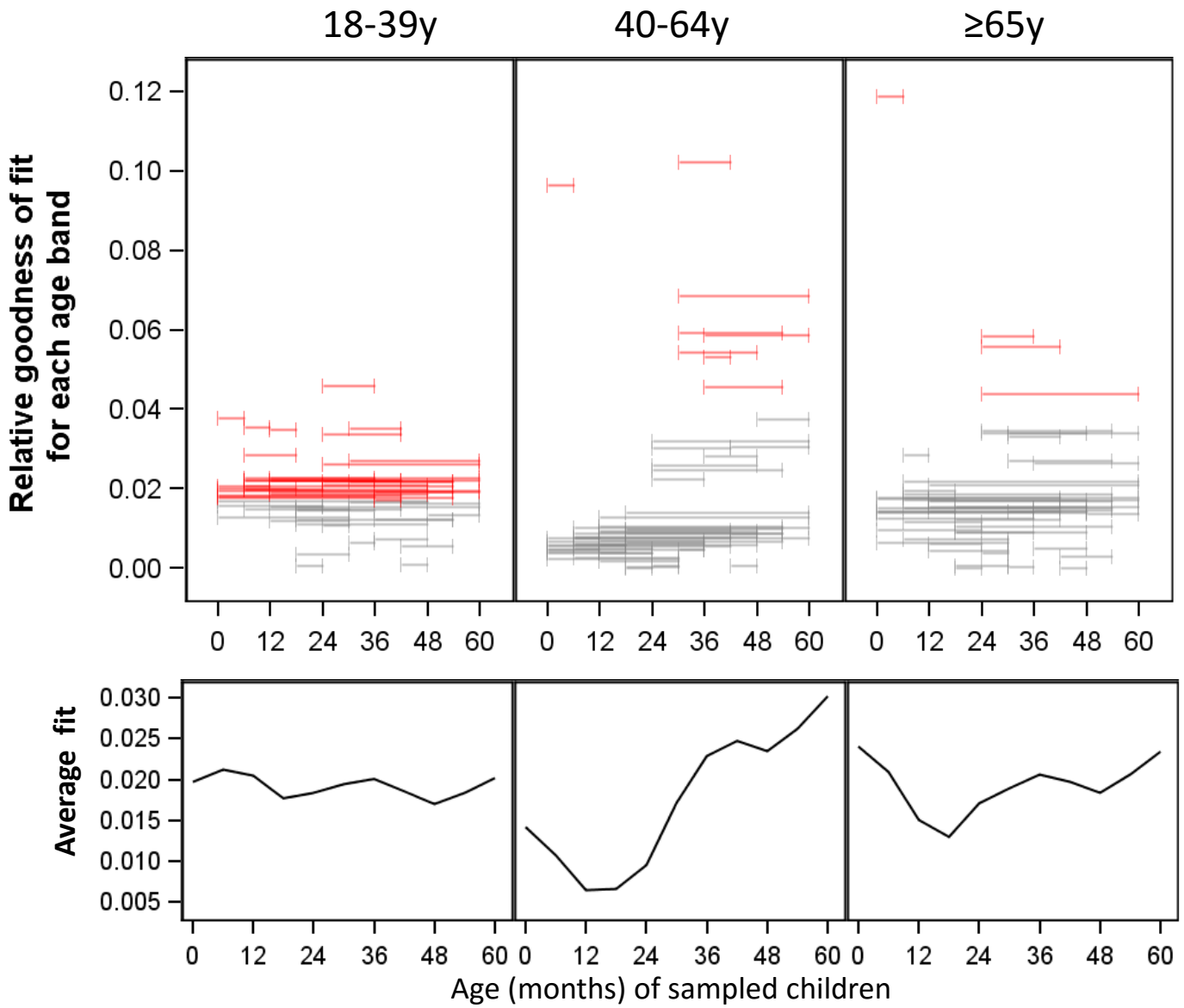

18-39y
40-64y
≥65y
Relative goodness of fit for each age band
0.12
0.10
0.08
0.06
0.04
0.02
0.00
0 12 24 36 48 60
Average fit
0.030
0.025
0.020
0.015
0.010
0.005
Age (months) of sampled children

FIGURE 4

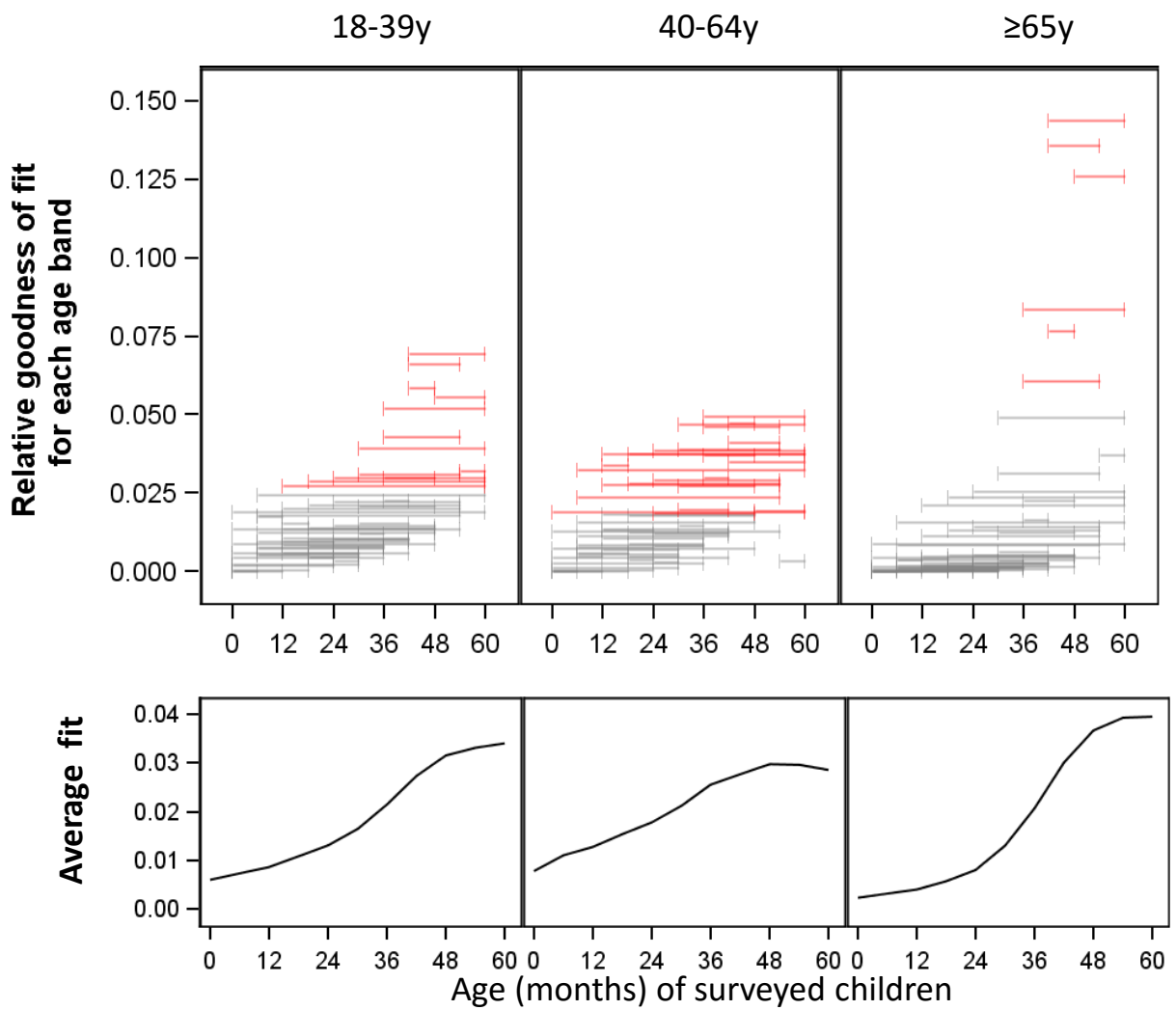

18-39y
40-64y
≥65y
Relative goodness of fit for each age band
0.150
0.125
0.100
0.075
0.050
0.025
0.000
0 12 24 36 48 60
Average fit
0.04
0.03
0.02
0.01
0.00
Age (months) of surveyed children

FIGURE S1

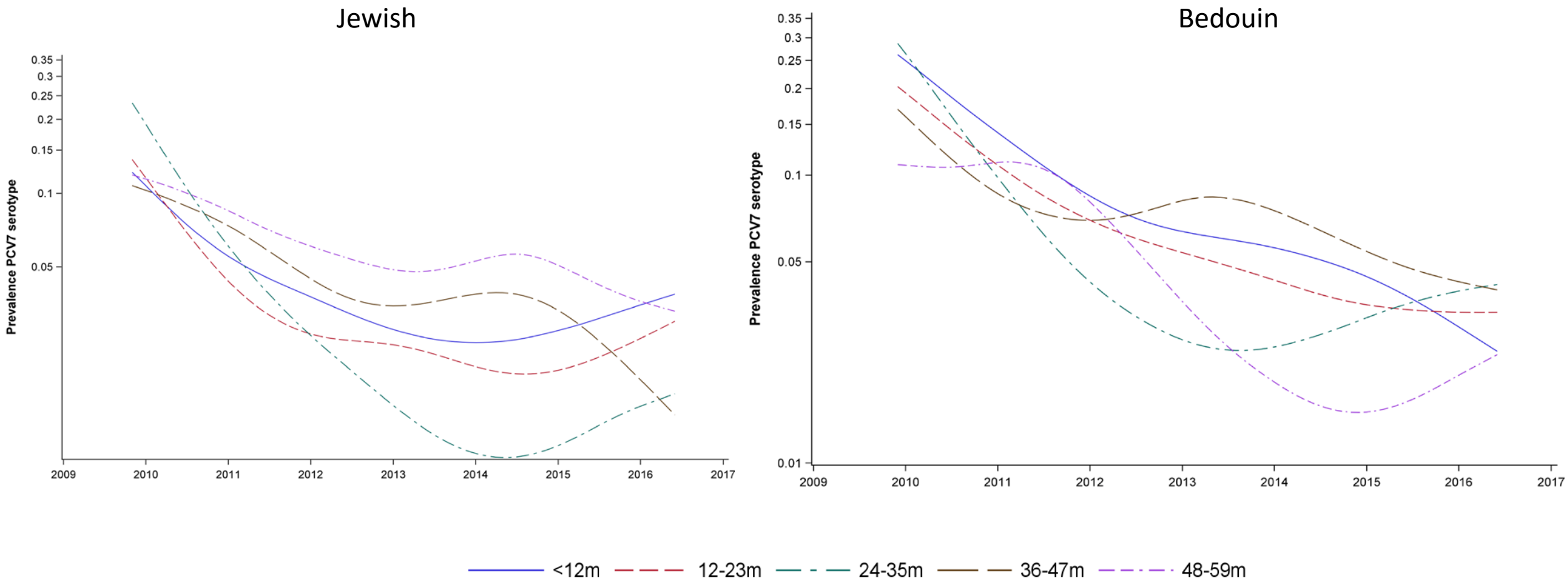

Jewish
Bedouin
Prevalence PCV7 serotype
0.35
0.3
0.25
0.2
0.15
0.1
0.05
0.01
2009
2010
2011
2012
2013
2014
2015
2016
2017
<12m
12-23m
24-35m
36-47m
48-59m

FIGURE S2

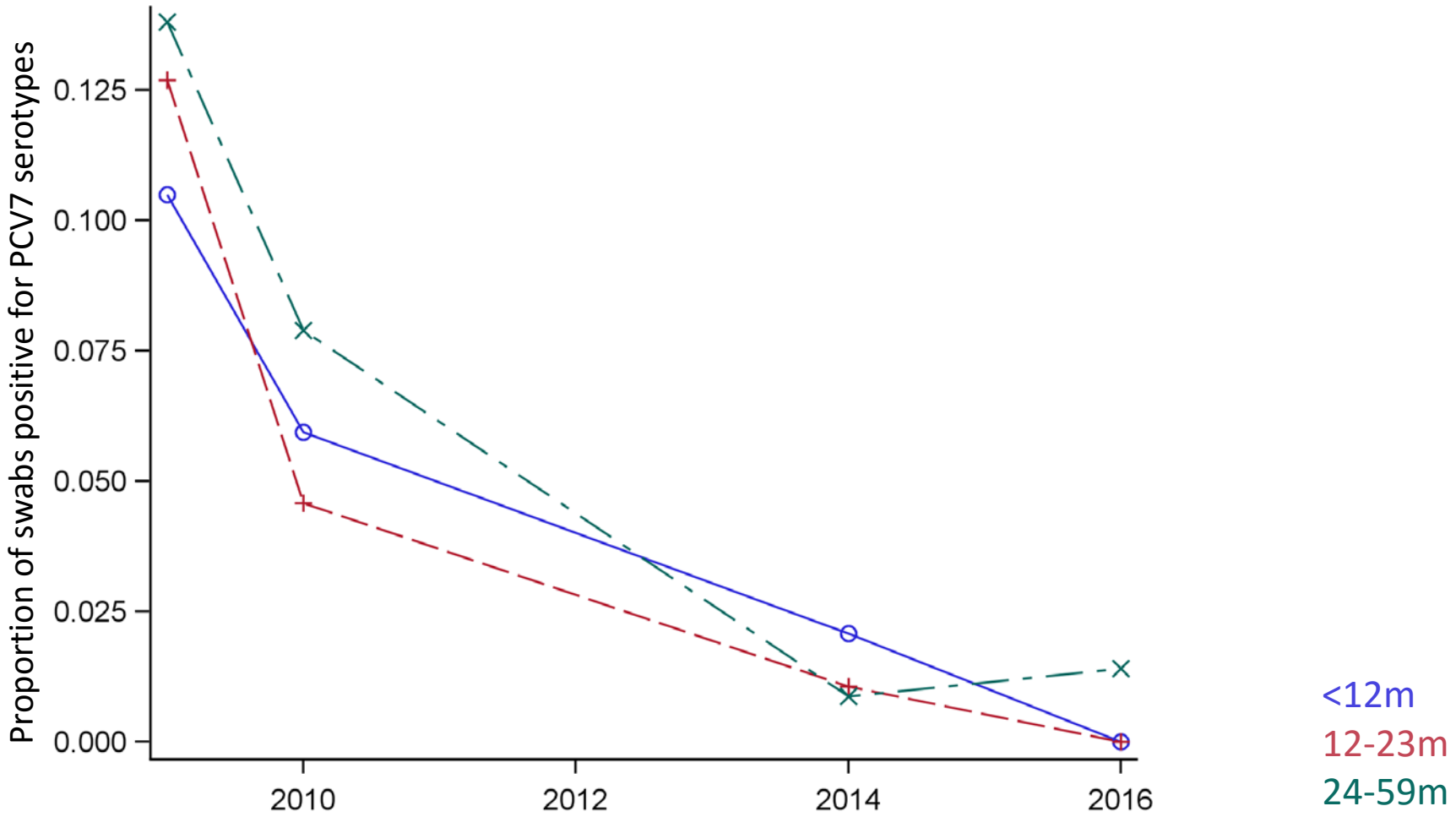
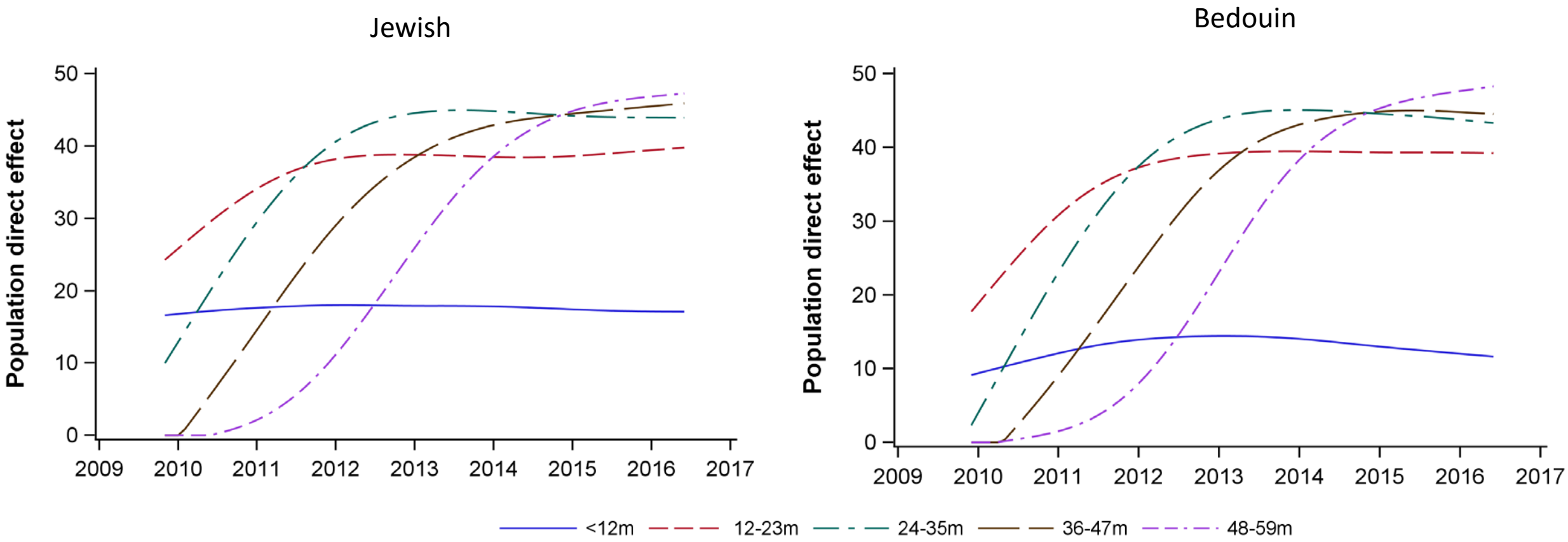

Proportion of swabs positive for PCV7 serotypes
0.125
0.100
0.075
0.050
0.025
0.000
2010
2012
2014
2016
<12m
12-23m
24-59m

FIGURE S3


Jewish
Bedouin
Population direct effect
50
40
30
20
10
0
2009
2010
2011
2012
2013
2014
2015
2016
2017
<12m
12-23m
24-35m
36-47m
48-59m