Dose-specific effectiveness of 7- and 13-valent pneumococcal conjugate vaccines against vaccine-serotype *Streptococcus pneumoniae* colonization in children

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SUPPORTING INFORMATION

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Text S1: Modified case-control sampling and inference method

In this section we describe bias arising under standard case-control analysis methods for the estimation of pneumococcal conjugate vaccine (PCV) effectiveness against vaccine-serotype *Streptococcus pneumoniae* colonization. We then describe an alternative approach we have formulated in the present study to avoid such bias.

Standard case-control analysis

Take Z_i=1 to indicate that a child *i* is vaccinated, for *i* in 1, 2, 3, …, *N* children, and take Z_i=0 to indicate child *i* is unvaccinated. Define $V = \sum_i \mathbb{I}(Z_i = 1)\ /N$ as the proportion of children vaccinated. Take Y_i=1 to indicate a child carries vaccine-serotype *S. pneumoniae*, and let Y_i=0 indicate the child does not carry vaccine-serotype *S. pneumoniae* (due to the absence of colonization or carriage of another serotype). Define $P = \Pr\ (Y_i = 1|Z_i = 0)$ as the prevalence of vaccine-serotype colonization among the unvaccinated, and define θ as the relative prevalence of vaccine-serotype colonization among the vaccinated versus unvaccinated, due only to receipt of the vaccine.

Thus, $\Pr(Y_i = 1|Z_i = 1) = \theta P$, and the vaccine effectiveness (VE) is equal to $1 - \theta$. A two-by-two table constructed from these inputs is:

	Vaccine-serotype carriage (Y_i=1)	**No vaccine-serotype carriage (Y_i=0)**
PCV received (Z_i=1)	$\Pr(Y_i = 1 \cap Z_i = 1)\ N$ $= \Pr(Y_i = 1\|Z_i = 1)\ \Pr(Z_i = 1)N$ $= \boldsymbol{\theta PVN}$	$\Pr(Y_i = 0 \cap Z_i = 1)\ N$ $= \Pr(Y_i = 0\|Z_i = 1)\ \Pr(Z_i = 1)\ N$ $= \boldsymbol{(1 - \theta P)VN}$
PCV not received (Z_i=0)	$\Pr(Y_i = 1 \cap Z_i = 0)\ N$ $= \Pr(Y_i = 1\|Z_i = 0)\ \Pr(Z_i = 0)N$ $= \boldsymbol{P(1 - V)N}$	$\Pr(Y_i = 0 \cap Z = 0)\ N$ $= \Pr(Y = 0\|Z = 0)\ \Pr(Z = 0)\ N$ $= \boldsymbol{(1 - P)(1 - V)N}$

Under traditional case-control designs, the odds of vaccination among controls is assumed to provide a "null" measure against which the odds of vaccination among persons who experience the outcome can be compared. However, in this instance,

$$1 - P = \Pr\ (Y_i = 0|Z_i = 0) \neq \Pr(Y_i = 0|Z_i = 1) = 1 - \theta P$$

in contrast to the typical assumption. Thus, the odds ratio of vaccination given case status ($OR_{Z|Y}$), assembled from inputs as defined above, does not reduce to the estimand (θ) and $1 - OR_{Z|Y}$ cannot be interpreted as an estimate of vaccine effectiveness:

$$OR_{Z|Y} = \frac{[\Pr(Y_i = 1 \cap Z_i = 1)N][\Pr(Y_i = 0 \cap Z_i = 0)N]}{[\Pr(Y_i = 1 \cap Z_i = 0)\ N][\Pr(Y_i = 0 \cap Z_i = 1)N]} = \frac{[\theta PVN]\ [(1 - P)(1 - V)N]}{[P(1 - V)N]\ [(1 - \theta P)VN]} = \frac{\theta(1 - P)}{1 - \theta P}$$

We therefore require an alternative definition of controls under which the relative odds of prior vaccination among cases and controls would reduce to θ.

Modified approach

In our analysis, we define controls as individuals sampled at random, irrespective of carriage status or vaccination; and cases as those not sampled as controls, who are also found to carry vaccine-serotype pneumococci. Defining S_i=1 as an indicator that an individual was sampled as a control, with $C = \sum_i \mathbb{I}(S_i = 1)\ /N$, we may construct a two-by-two table for the modified analysis approach as follows:

	Not sampled as control, and vaccine-serotype carriage (S_i=0, Y_i=1)	Sampled as control (S_i=1)
PCV received (Z_i=1)	$\Pr(Y_i = 1 \cap Z_i = 1 \cap S_i = 0)\, N$ $= \Pr(Y_i = 1 \mid Z_i = 1 \cap S_i = 0)\Pr(Z_i = 1 \cap S_i = 0) N$ Since Y_i and Z_i are each independent of S_i, $= \Pr(Y_i = 1 \mid Z_i = 1)\Pr(Z_i = 1)\Pr(S_i = 0)\, N$ $= \boldsymbol{\theta PV(1-C)N}$	$\Pr(Z_i = 1 \cap S_i = 1)\, N$ Since Z_i is independent of S_i, $= \Pr(Z_i = 1)\Pr(S_i = 1)\, N$ $= \boldsymbol{VCN}$
PCV not received (Z_i=0)	$\Pr(Y_i = 1 \cap Z_i = 0 \cap S_i = 0)\, N$ $= \Pr(Y_i = 1 \mid Z_i = 0 \cap S_i = 0)\Pr(Z_i = 0 \cap S_i = 0) N$ Since Y_i and Z_i are each independent of S_i, $= \Pr(Y_i = 1 \mid Z_i = 0)\Pr(Z_i = 0)\Pr(S_i = 0)\, N$ $= \boldsymbol{P(1-V)(1-C)N}$	$\Pr(Z_i = 0 \cap S_i = 1)\, N$ Since Z_i is independent of S_i, $= \Pr(Z_i = 0)\Pr(S_i = 1)\, N$ $= \boldsymbol{(1-V)CN}$

From this two-by-two table, we construct an odds ratio as follows:

$$VE = \frac{[\Pr(Y_i = 1 \cap Z_i = 1 \cap S_i = 0)\, N][\Pr(Z_i = 0 \cap S_i = 1) N]}{[\Pr(Y_i = 1 \cap Z_i = 0 \cap S_i = 0)\, N][\Pr(Z_i = 1 \cap S_i = 1) N]} = \frac{[\theta PV(1-C)N]\,[(1-V)CN]}{[P(1-V)(1-C)N]\,[VCN]} = \theta$$

Thus, the modified approach provides a strategy to recover unbiased estimates of the vaccine direct effect against pneumococcal carriage from the relative odds of vaccination among cases and controls, as defined.

Assumptions and limitations

Our analysis requires several assumptions: (1) that excluding children diagnosed with otitis media, conjunctivitis, upper respiratory infection, influenza, pneumonia/lower respiratory infection, sepsis/bacteremia, or meningitis removes any potential effect of PCV7/13 against pneumococcal disease progression from our estimates (thereby isolating the vaccine effect against carriage of vaccine-targeted pneumococci); (2) that the reduction in vaccine-serotype carriage prevalence provides a valid causal measure of the biological effect of PCV7/13 on pneumococcal vaccine-serotype carriage (comparable to the effect of vaccination on rates of acquisition and/or clearance of vaccine-serotype pneumococci, as derived in previous analyses[3]); and (3) that culture-positive pneumococcal carriage status with identification of a vaccine serotype provides a suitable measure for the vaccine-serotype pneumococcal carriage endpoint. Comparative studies have suggested that molecular detection methods may identify pneumococcal carriage in a greater proportion of children than traditional culture-based methods.[4,5] This may arise through detection of serotypes at low abundance in children otherwise found not to carry pneumococcus, or through identification of multiple serotypes among co-colonized children; it is unclear whether under-detection may differ between these two groups.[6]

As our study samples "control" children at random, irrespective of carriage determination, it is advantageous that our analysis approach is not subject to bias that would result from diagnostic issues affecting the control definition (as may arise in studies that define controls as children with no pneumococci or non-vaccine serotype pneumococci identified). However, our study, like others using traditional microbiological methods, may under-detect "true" cases (defined as children carrying vaccine-serotype pneumococci). This may lead to bias if likelihood of detection, given carriage, is associated with vaccination status, e.g. due to an effect of PCV7/13 on density of vaccine-serotype pneumococcal carriage in the nasopharynx.[7] It remains of interest to determine how low-density carriage, at levels potentially undetectable by traditional culture methods, contributes to transmission and disease risk.[4]

Statistical inference

To implement the analyses, we generated 5000 randomly-ordered lists of potential cases (carriers of vaccine-serotype pneumococci). For each independent iteration, we proceeded down the list matching 3 randomly-selected controls to each case, or more as allowed, without replacement. When vaccine-serotype carriers were selected as controls under this procedure, they were excluded from the case list; thus the probability of case status and vaccination status z was equal to $\Pr(Y_i = 1 \mid Z_i = z)\Pr(Z_i = z)\Pr(S_i = 0)$.

We obtained estimates of the matched odds ratio for each of the 5000 sampled match assignments via conditional logistic regression. The mean estimate across all 5000 iterations of the analysis provided our point estimate of protection; 95% confidence limits were generated from the 2.5%ile and 97.5%ile of estimates generated across all iterations.

Differential protection by serotype

We also sought to explore whether protection differed for serotypes targeted by PCV7, those targeted by PCV13, and for serotype 3, as previously suggested. Because analyses were underpowered for comparing age- and dose-specific effectiveness across strata, we used conditional logistic regression to assess protection via the continuous trend in the matched odds ratio for receipt of one to three doses, as compared to zero doses, among cases and controls. Matched sets were assembled according to the approach described above.

We quantified differences in protection according to two measures. First, we calculated the difference in the average per-dose reduction in odds of the various endpoints (here defined *i* and *j*) as

$$\text{Difference in reductions} = \left[(1 - OR_i) - (1 - OR_j)\right] = (1 - \theta_i) - (1 - \theta_j)$$

for θ_k regression coefficients indicating the average reduction, per PCV dose received, in odds of carrying serotype(s) *k*.

We also estimated the average marginal increase in protection against each outcome, relative to other outcomes, suggested by the trends in slopes. For the added degree of protection against serotype(s*) i* versus protection against serotype(s) *j*, this measure was

$$1 - \frac{OR_i}{OR_j} = 1 - \frac{\theta_i}{\theta_j}$$

for θ_i as defined above.

Differential protection by ethnicity and time

We used the same approach to assess differences in protection conferred against various endpoints (carriage of PCV7 serotypes, PCV13 serotypes, +6PCV13 serotypes, serotypes 1, 5, 6A, 7F, and 19A, and serotype 3) in Bedouin and Jewish children. We estimated the difference in protection between the two populations via the difference in reductions (above), as

$$\text{Difference in reductions} = \left[\left(1 - OR_i^{\text{Bedouin}}\right) - \left(1 - OR_i^{\text{Jewish}}\right)\right].$$

Similarly, for analyses comparing protection in the period up to (and including) June 30, 2013, versus the period from July 1, 2013 onward, we defined

$$\text{Difference in reductions} = \left[\left(1 - OR_i^{\text{Late}}\right) - \left(1 - OR_i^{\text{Early}}\right)\right].$$

Text S2: Age of receipt for vaccine doses

While children in Israel are recommended to receive a booster dose at age 12m, real-world conditions of vaccine uptake are important to account for studies of vaccine effectiveness. We identified 10m as the nadir in the ages at which PCV7/13 doses were received between schedule-concordant peaks at the ages of 4m and 12m (**Figure S2**). Thus, 10m served as a natural transition between the ages at which children received "late" primary-series doses and "early" booster doses. Of all doses administered at ages ≥10 months in our study, 4.7% (210/4415) were given to children ages 10-11 months; for children receiving PCV13 exclusively, only 2.7% (68/2478) of doses were given at age 10-11 months (**Table S8**).

Because previous analyses have identified equal effectiveness of booster doses received during or after the second year of life,[1] we did not define an upper bound on the age of receipt of booster doses. Within our study, 90.0% (3977/4415) of all doses administered at ages ≥10 months were received by age 18 months, and 97.2% (4291/4415) were received by age 24 months (**Table S8**); most of this spread in ages was accounted for by the PCV7 catch-up campaign. Among children who received PCV13 only, 95.4% (2367/2480) of booster doses were received by age 18 months and 98.1% (2433/2480) were received by age 24 months.

Consistent with prior studies,[2] we defined primary-series doses as those received at ages ≤7 months, thus allowing an interval of up to one month for late doses. We restricted this period for primary-series doses due to the fact that certain low-income countries administer a booster dose at ages as early as 9m. While we do not define a lower-bound age for inclusion in the study, the use of matched odds ratios implicitly restricts the sample to children who were age-eligible for vaccination; the odds ratio is computed from discordant sets in which cases are unexposed while controls are exposed, versus sets in which cases are exposed while controls are unexposed.

Text S3: Supplemental references

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3. Rinta-Kokko H, Dagan R, Givon-Lavi N, Auranen K. Estimation of vaccine efficacy against acquisition of pneumococcal carriage. Vaccine. **2009**;27:3831-7.

4. Wyllie AL, Wijmenga-Monsuur AJ, van Houten MA, et al. Molecular surveillance of nasopharyngeal carriage of *Streptococcus pneumoniae* in children vaccinated with conjugated polysaccharide pneumococcal vaccines. Sci Rep. **2016**;6:23809.

5. Carvalho M, Pimeta FC, Jackson D, et al. Revisiting pneumococcal carriage by use of broth enrichment and PCR techniques for enhanced detection of carriage and serotypes. J Clin Microbiol. **2010**;48:1611-8.

6. Turner P, Hinds J, Turner C, et al. Improved detection of nasopharyngeal co-colonization by multiple pneumococcal serotypes by use of latex agglutination or molecular serotyping by microarray. J Clin Microbiol **2011**.49;1784-9.

7. Auranen K, Rinta-Kokko H, Goldblatt D, et al. Colonisation endpoints in *Streptococcus pneumoniae* vaccine trials. Vaccine **2013**. 32;153-8.

Table S1: Data availability among eligible, enrolled children.

Data item	Bedouin children	Jewish children
PCV7/13 receipt	3468/3477	2521/2524
Pneumococcal carriage		
Pneumococcus identified or not identified	3477/3477	2524/2524
Serotype identified, among pneumococcal carriers	1656/1656	990/990
Antibiotic receipt	3434/3477	2506/2524
Complete information (vaccine status, carriage, serotype, antibiotic receipt)	3425/3477	2503/2524

Analyses were limited to children with complete information available (as defined in this table) and in whom no diagnoses potentially related to *S. pneumoniae* were identified (**Table S2**).

Table S2: Clinical observations and risk factors among eligible and ineligible enrolled children.

Individual factor	Bedouin children, *n* (%)		Jewish children, *n* (%)	
	Eligible, complete data *N*=3425	Ineligible, complete data *N*=2276	Eligible, complete data *N*=2503	Ineligible, complete data *N*=1843
Sex (male)	1969 (57)	1363 (60)	1320 (53)	1036 (56)
Hospitalization	1888 (55)	1546 (68)	1047 (42)	1843 (50)
Diagnoses				
Otitis media	0 (0)	531 (23)	0 (0)	617 (33)
Conjunctivitis	0 (0)	51 (2)	0 (0)	58 (3)
Upper respiratory infection	0 (0)	633 (28)	0 (0)	1843 (30)
Influenza	0 (0)	40 (2)	0 (0)	22 (1)
Pneumonia/lower respiratory infection	0 (0)	1242 (55)	0 (0)	840 (46)
Bacteremia/sepsis	0 (0)	68 (3)	0 (0)	40 (2)
Meningitis	0 (0)	31 (1)	0 (0)	13 (1)
Preterm birth	286 (8)	269 (12)	259 (10)	196 (11)
Previous or current breastfeeding	3105 (91)	2075 (91)	1787 (71)	1315 (71)
Cigarette exposure	1173 (52)	1217 (53)	1120 (45)	816 (44)
Asthma	94 (3)	106 (5)	216 (9)	217 (12)
Number of siblings				
1-3	1696 (50)	1197 (53)	1655 (66)	1237 (67)
4 or more	1178 (34)	798 (35)	195 (8)	171 (9)
Mother's age (y)	28.2 (±5.9, SD)	28.4 (±5.9, SD)	31.2 (±5.4, SD)	31.2 (±5.2, SD)
Father's age (y)	32.6 (±8.0, SD)	32.6 (±8.0, SD)	34.2 (±6.3, SD)	34.2 (±6.2, SD)
Receipt of 1 or more PCV7/13 doses	2660 (78)	1812 (80)	2091 (84)	1607 (87)
Pneumococcal carriage	1636 (48)	1234 (54)	980 (39)	822 (45)
Receipt of antibiotic within preceding month	995 (29)	857 (38)	606 (24)	710 (39)

Analyses excluded children from whom data were incomplete (as enumerated in **Table S1**). Eligibility was defined by absence of diagnoses of otitis media, conjunctivitis, upper respiratory infection, influenza, pneumonia/lower respiratory infection, bacteremia/sepsis, and meningitis, due to the possible role of *S. pneumoniae* in these diagnoses.

Table S3. Clinical observations and risk factors among eligible children, according to pneumococcal carriage.

Individual factors		**Bedouin children, *n* (%)**			**Jewish children, *n* (%)**		
		PCV13-type carriers	*NVT carriers*	*Non-carriers*	*PCV13-type carriers*	*NVT carriers*	*Non-carriers*
		N=446	*N*=1190	*N*=1789	*N*=184	*N*=796	*N*=1523
Sex (male)		247 (55)	676 (57)	1046 (58)	104 (57)	413 (52)	803 (53)
Hospitalization		236 (53)	644 (54)	1008 (56)	63 (34)	305 (38)	679 (45)
Clinical observations	Fever	280 (63)	677 (57)	1076 (60)	85 (46)	380 (48)	781 (51)
	Gastroenteritis	197 (44)	443 (37)	663 (37)	53 (29)	225 (28)	429 (28)
	Viral infection	21(5)	67 (6)	90 (5)	15 (8)	58 (7)	120 (8)
	Urinary tract infection	9 (2)	32 (3)	75 (4)	4 (2)	21 (3)	48 (3)
Preterm birth		31 (7)	97 (8)	158 (9)	26 (14)	80 (10)	153 (10)
Previous or current breastfeeding		402 (90)	1086 (91)	1617 (90)	139 (76)	600 (75)	1048 (69)
Cigarette exposure		229 (51)	639 (54)	905 (51)	86 (47)	322 (40)	712 (47)
Asthma		15 (3)	34 (3)	45 (3)	24 (13)	68 (9)	124 (8)
Number of siblings	1-3	208 (47)	589 (49)	899 (50)	130 (71)	557 (70)	968 (64)
	4 or more	183 (41)	464 (39)	531 (30)	19 (10)	74 (9)	102 (7)
Mother's age (y)		28.5 (±5.9, SD)	28.5 (±5.8, SD)	27.9 (±6.0, SD)	32.3 (±5.2, SD)	31.6 (±5.2, SD)	30.9 (±5.4, SD)
Father's age (y)		32.6 (±7.8, SD)	32.8 (±8.1, SD)	32.4 (±8.0, SD)	34.7 (±5.8, SD)	34.4 (±6.1, SD)	34.0 (±6.4, SD)
Receipt of antibiotics in preceding month		136 (30)	238 (20)	621 (35)	37 (20)	87 (11)	482 (32)

PCV: pneumococcal conjugate vaccine; NVT: nonvaccine-type (serotypes not included in PCV13); SD: standard deviation

Table S4: Vaccine schedules received by age, ethnicity, and carriage status.

Age (m)	Schedule	Doses	Bedouin children					Jewish children				
			Total	*PCV7 type carriage*	*+6PCV13 type carriage*	*NVT carriage*	*No carriage*	*Total*	*PCV7 type carriage*	*+6PCV13 type carriage*	*NVT carriage*	*No carriage*
≤12	Unvaccinated	0p PCV	511	29	31	148	303	186	6	6	28	146
	Primary series	1p PCV7	97	18	9	28	42	29	5	2	8	14
		2p PCV7	130	25	9	41	55	110	5	6	24	75
		3p PCV7	0	0	0	0	0	7	0	1	1	5
		1p PCV13	322	15	26	118	163	170	4	3	53	110
		2p PCV13	617	25	28	226	338	446	10	6	136	294
		3p PCV13	7	0	0	4	3	1	0	0	0	1
		1p PCV7/13	419	33	35	146	205	199	9	5	61	124
		2p PCV7/13	772	57	41	272	402	569	15	12	164	378
		3p PCV7/13	8	0	0	5	3	8	0	1	1	6
13-24	Unvaccinated	0p+0b PCV	34	7	1	12	14	35	5	1	14	15
	Primary series only	1p+0b PCV7	3	0	0	2	1	0	0	0	0	0
		2p+0b PCV7	30	6	3	11	10	26	0	5	5	16
		3p+0b PCV7	0	0	0	0	0	4	0	0	1	3
		1p+0b PCV13	10	0	1	0	9	3	0	0	1	2
		2p+0b PCV13	53	7	3	17	26	72	1	2	26	43
		3p+0b PCV13	4	0	0	3	1	1	0	0	1	0
		1p+0b PCV7/13	13	0	1	2	10	3	0	0	1	2
		2p+0b PCV7/13	86	15	6	29	36	99	1	7	31	60
		3p+0b PCV7/13	5	0	0	3	2	5	0	0	2	3
	Booster series only	0p+1b PCV7	24	5	3	7	9	13	1	2	3	7
		0p+2b PCV7	39	5	4	16	14	16	2	1	6	7
		0b+1p PCV13	4	0	0	1	3	4	0	0	2	2
		0b+2p PCV13	1	0	0	1	0	2	0	1	0	1
		0b+1p PCV7/13	28	5	3	8	12	17	1	2	5	9
		0b+2p PCV7/13	40	5	4	17	14	18	2	2	6	8
	Primary+booster series	1p+1b PCV7	13	2	0	6	5	6	1	2	2	1
		2p+1b PCV7	44	3	5	13	23	35	1	3	12	19
		3p+1b PCV7	6	0	1	2	3	12	0	0	3	9
		1p+1b PCV13	6	1	0	3	2	4	0	0	0	4
		2p+1b PCV13	361	11	12	127	211	358	10	2	152	194
		3p+1b PCV13	5	0	0	3	2	9	0	0	2	7
		1p+1b PCV7/13	21	3	0	10	8	12	1	2	2	7
		2p+1b PCV7/13	465	16	22	164	263	443	12	9	181	241
		3p+1b PCV7/13	11	0	1	5	5	21	0	0	5	16
25-59	Unvaccinated	0p+0b PCV	220	32	17	64	107	191	22	19	41	109
	Primary series only	1p+0b PCV7	2	0	1	0	1	3	0	1	0	2
		2p+0b PCV7	8	2	0	4	2	9	0	0	6	3
		3p+0b PCV7	0	0	0	0	0	3	0	0	2	1
		1p+0b PCV13	2	0	0	2	0	2	0	0	0	2
		2p+0b PCV13	7	0	0	3	4	16	1	1	7	7
		3p+0b PCV13	2	0	0	2	0	2	0	1	0	1
		1p+0b PCV7/13	4	0	1	2	1	5	0	1	0	4
		2p+0b PCV7/13	15	2	0	7	6	25	1	1	13	10
		3p+0b PCV7/13	2	0	0	2	0	5	0	1	2	2

Booster series only	0p+1b PCV7	20	1	2	6	11	11	0	0	4	7
	0p+2b PCV7	73	4	7	35	27	55	1	6	13	35
	0b+1p PCV13	4	0	0	2	2	1	0	0	1	0
	0b+2p PCV13	6	1	0	2	3	2	0	0	0	2
	0b+1p PCV7/13	24	1	2	8	13	12	0	0	5	7
	0b+2p PCV7/13	85	5	7	39	34	58	1	6	14	37
Primary+booster series	1p+1b PCV7	6	0	0	4	2	5	0	0	2	3
	2p+1b PCV7	42	2	3	13	24	49	1	0	20	28
	3p+1b PCV7	6	0	0	2	4	27	0	1	7	19
	1p+1b PCV13	3	0	0	2	1	6	0	0	4	2
	2p+1b PCV13	281	12	3	100	166	319	4	7	125	183
	3p+1b PCV13	8	0	1	3	4	20	0	2	6	12
	1p+1b PCV7/13	13	1	0	7	5	11	0	0	6	5
	2p+1b PCV7/13	391	15	7	146	223	429	9	7	164	249
	3p+1b PCV7/13	14	0	1	5	8	47	0	3	13	31

Numbers of children for whom matches existed, and who were thus eligible for inclusion in analyses estimating vaccine effectiveness, are presented in **Table 2** of the main text.

Table S5: Relative vaccine effectiveness of 2p+1b dosing versus alternative series.

Age (m)	Exposure assessed	Reference exposure	PCV7/13	PCV13 only			PCV7 only
			PCV7 serotypes VE (95% CI), %	*All PCV13 serotypes* VE (95% CI), %	*+6PCV13 serotypes* VE (95% CI), %	*PCV7 serotypes* VE (95% CI), %	*PCV7 serotypes* VE (95% CI), %
≤12	2p						
		0p	35.1 (7.7 to 54.7)	52.9 (31.9 to 67.3)	41.6 (6.8 to 63.2)	63.6 (43.3 to 77.9)	0.4 (–71.9 to 41.4)
		1p	39.3 (13.9 to 57.4)	45.3 (21.9 to 61.8)	31.4 (2.8 to 53.8)	59.1 (33.2 to 75.3)	19.1 (–35.7 to 51.3)
13-24	2p+1b						
		0p+0b	62.4 (44.0 to 74.7)	39.7 (4.3 to 66.7)	– –	70.8 (50.0 to 83.3)	– –
		2p+0b	64.6 (46.6 to 77.0)	69.9 (56.1 to 79.7)	73.2 (61.2 to 83.7)	68.3 (48.6 to 81.1)	14.3 (–11.7 to 43.4)
		1p+1b	48.5 (5.2 to 77.3)	51.2 (10.3 to 80.0)	– –	66.2 (40.0 to 80.0)	32.5 (–37.4 to 68.8)
		0p+2b	4.7 (–109.6 to 56.2)	78.3 (57.3 to 83.3)	– –	– –	22.7 (–59.0 to 56.2)
25-59	2p+1b						
		0p+0b	64.2 (–90.7 to 84.2)	62.3 (33.3 to 83.3)	– –	– –	63.0 (59.2 to 75.1)
		2p+0b	44.0 (0.7 to 71.1)	–5.3 (–87.3 to 52.2)	49.7 (0.0 to 83.3)	68.3 (48.6 to 81.1)	28.0 (0.0 to 66.7)
		1p+1b	40.0 (0.0 to 66.7)	– –	– –	– –	– –
		0p+2b	– –	– –	– –	– –	– –

Information in this table recapitulates estimates presented in Tables 3 and 4 of the main text, but redefines the comparator group to assess the relative effectiveness of 2p+1b dosing, as compared to the alternative schedules.

Table S6: Differential protection by ethnicity.

Serotype	Vaccine	Average reduction per dose received (95% CI), %		Difference in average reduction per dose received (95% CI), %
		Jewish children	Bedouin children	Bedouin ref. Jewish children
PCV7 serotypes	PCV7/13	35 (23, 46)	29 (20, 37)	–6 (–20, 9)
All PCV13 serotypes	PCV13 only	30 (20, 40)	19 (3, 32)	–11 (–29, 6)
+6 PCV13 serotypes	PCV13 only	45 (26, 68)	–8 (–40, 13)	–54 (–91, –24)
Serotypes 1, 5, 6A, 7F, 19A	PCV13 only	32 (18, 47)	–3 (–28, 19)	–36 (–64, –8)
Serotype 3	PCV13 only	20 (–31, 59)	–111 (–261, –26)	–131 (–284, –25)

Vaccine effectiveness estimates are calculated as $1 - mOR$ (matched odds ratio) times 100%. Matched odds ratios are calculated from the relative odds of receipt of vaccine doses (defined as a continuous variable) among case children versus matched controls. The difference in reduction, per dose received, estimated as $(1 - \theta_B) - (1 - \theta_J)$ for a comparison of the magnitude of protection among Bedouin and Jewish children.

Table S7: Protection in the periods before and after July 1, 2013.

Serotype	Vaccine	Average reduction per dose received (95% CI), %		Difference in average reduction per dose received (95% CI), %
		Up to June 30, 2013	July 1, 2013 onwards	July 1, 2013 onwards ref. up to June 30, 2013
PCV7 serotypes	PCV7/13	31 (22, 39)	33 (21, 43)	2 (–12, 16)
All PCV13 serotypes	PCV13 only	25 (9, 37)	22 (7, 33)	–3 (–22, 17)

Vaccine effectiveness estimates are calculated as $1 - mOR$ (matched odds ratio) times 100%. Matched odds ratios are calculated from the relative odds of receipt of vaccine doses (defined as a continuous variable) among case children versus matched controls. The difference in reduction, per dose received, is estimated as $(1 - \theta_{Post}) - (1 - \theta_{Pre})$ for a comparison of the magnitude of protection before and after July 1, 2013.

Table S8: Age of receipt for all booster doses administered, for children ages ≥12m who received exclusively PCV7 or PCV13.

Age (m)	Bedouin children				Jewish children			
	All children		*VT7 carriers*		*All children*		*VT7 carriers*	
	PCV7 only, *N* (%)	PVC13 only, *N* (%)	PCV7 only, *N* (%)	PVC13 only, *N* (%)	PCV7 only, *N* (%)	PVC13 only, *N* (%)	PCV7 only, *N* (%)	PVC13 only, *N* (%)
≥10 (total)	712 (100)[1]	1285 (100)[1]	57 (100)[NC]	56 (100)[NC]	642 (100)[2]	1193 (100)[2]	28 (100)[NC]	23 (100)[NC]
10	42 (5.9)	31 (2.4)	5 (8.8)	2 (3.6)	25 (3.9)	6 (0.5)	0 (0)	0 (0)
11	26 (3.7)	23 (1.8)	4 (7.0)	1 (1.8)	16 (2.5)	8 (0.7)	2 (7.1)	1 (4.3)
12	205 (28.8)[3]	713 (55.5)[3]	19 (33.3)[4]	25 (44.6)[4]	227 (35.4)[5]	581 (48.7)[5]	8 (28.6)[6]	10 (43.5)[6]
13	69 (9.7)	190 (14.8)	4 (7.0)	9 (16.1)	88 (13.7)	267 (22.4)	6 (21.4)	4 (17.4)
14	77 (10.8)	101 (7.9)	7 (12.3)	5 (8.9)	56 (8.7)	125 (10.5)	3 (10.7)	1 (4.3)
15	48 (6.7)	55 (4.3)	2 (3.5)	1 (1.8)	41 (6.4)	75 (6.3)	3 (10.7)	2 (8.7)
16	30 (4.2)	45 (3.5)	3 (5.3)	2 (3.6)	30 (4.7)	51 (4.3)	1 (3.6)	2 (8.7)
17	19 (2.7)	29 (2.3)	0 (0)	2 (3.6)	7 (1.1)	21 (1.8)	0 (0)	1 (4.3)
18	51 (7.2)	26 (2.0)	2 (3.5)	1 (1.8)	54 (8.4)	18 (1.5)	2 (7.1)	1 (4.3)
19	27 (3.8)	11 (0.9)	2 (3.5)	2 (3.6)	30 (4.7)	10 (0.8)	1 (3.6)	0 (0)
20	27 (3.8)	12 (0.9)	2 (3.5)	0 (0)	33 (5.1)	5 (0.4)	1 (3.6)	1 (4.3)
21	28 (3.9)	6 (0.5)	2 (3.5)	0 (0)	10 (1.6)	5 (0.4)	0 (0)	0 (0)
22	21 (2.9)	7 (0.5)	1 (1.8)	0 (0)	7 (1.1)	1 (0.1)	0 (0)	0 (0)
23	18 (2.5)	8 (0.6)	3 (5.3)	1 (1.8)	6 (0.9)	1 (0.1)	0 (0)	0 (0)
24-29	22 (3.1)	17 (1.3)	0 (0)	3 (5.4)	8 (1.2)	11 (0.9)	1 (3.6)	0 (0)
30-35	2 (0.3)	6 (0.5)	1 (1.8)	1 (1.8)	4 (0.6)	7 (0.6)	0 (0)	0 (0)
36-47	0 (0)	4 (0.3)	0	1 (1.8)	0 (0)	1 (0.1)	0 (0)	0 (0)
48-59	0 (0)	1 (0.1)	0	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
10-12	273 (38.3)[7]	767 (59.7)[7]	28 (49.1)[11]	28 (50.0)[11]	268 (41.7)[15]	595 (49.9)[15]	10 (35.7)[19]	11 (47.8)[19]
10-14	419 (58.8)[8]	1058 (82.3)[8]	39 (68.4)[12]	42 (75.0)[12]	412 (64.2)[16]	987 (82.7)[16]	19 (67.9)[20]	16 (69.6)[20]
10-16	497 (69.8)[9]	1158 (90.1)[9]	44 (77.2)[13]	45 (80.4)[13]	483 (75.2)[17]	1113 (93.3)[17]	23 (82.1)[21]	20 (87.0)[21]
10-18	567 (79.6)[10]	1213 (94.4)[10]	46 (80.7)[14]	48 (85.7)[14]	544 (84.7)[18]	1152 (96.6)[18]	25 (89.3)[22]	22 (95.7)[22]
Mean age at receipt	15.5 (±4.1, SD)[23]	13.8 (±3.5, SD)[23]	15.0 (±4.5, SD)[24]	15.2 (±5.8, SD)[24]	14.9 (±3.6, SD)[25]	13.8 (±2.7, SD)[25]	14.7 (±3.3, SD)[26]	14.1 (±2.4, SD)[26]

Analyses present the number of doses administered at ages ≥10 months, by age, as well as the proportion of all doses administered at each age, calculated among all doses administered at ages ≥10 months. Footnotes denote comparisons highlighted for statistical tests. Data in the table are plotted in **Figure S2**.

NC: Test statistic not calculated due to insufficient counts.

1. Chi-squared test for difference in distributions: $p<0.001$.
2. Chi-squared test for difference in distributions: $p<0.001$.
3. Test for difference in proportions: $p<0.001$.
4. Test for difference in proportions: $p=0.1$.
5. Test for difference in proportions: $p<0.001$.
6. Test for difference in proportions: $p=0.1$.
7. Test for difference in proportions: $p<0.001$.
8. Test for difference in proportions: $p<0.001$.
9. Test for difference in proportions: $p<0.001$.
10. Test for difference in proportions: $p<0.001$.
11. Test for difference in proportions: $p=0.5$.
12. Test for difference in proportions: $p=0.2$.
13. Test for difference in proportions: $p=0.3$.
14. Test for difference in proportions: $p=0.2$.
15. Test for difference in proportions: $p<0.001$.
16. Test for difference in proportions: $p<0.001$.
17. Test for difference in proportions: $p<0.001$.
18. Test for difference in proportions: $p<0.001$.
19. Test for difference in proportions: $p=0.2$.
20. Test for difference in proportions: $p=0.4$.
21. Test for difference in proportions: $p=0.3$
22. Test for difference in proportions: $p=0.2$.
23. Test for difference in means: $p<0.001$.
24. Test for difference in means: $p<0.001$.
25. Test for difference in means: $p<0.001$.
26. Test for difference in means: $p<0.001$.

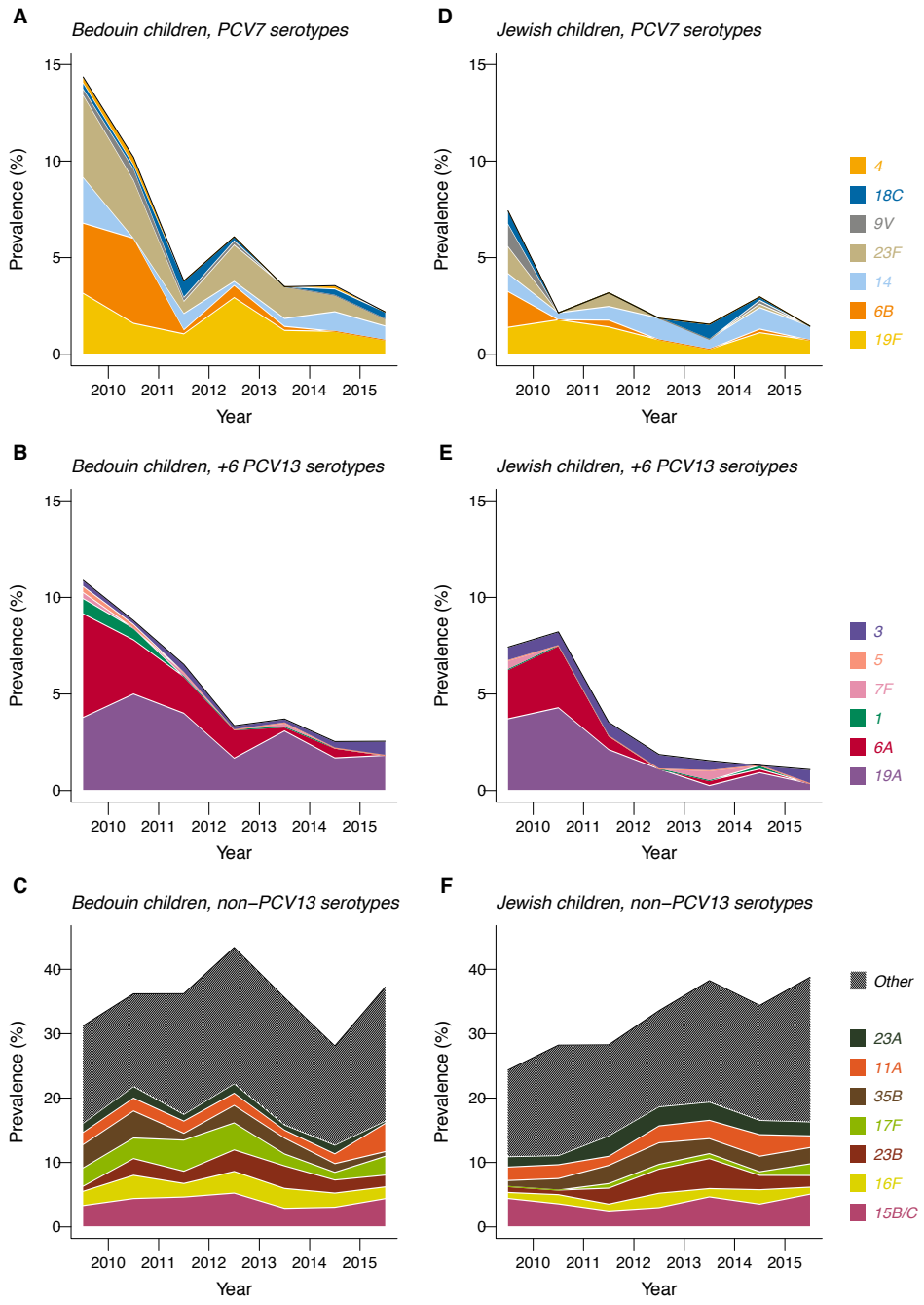

Figure S1: Serotype-specific carriage in the study population. We illustrate prevalence of individual serotypes by ethnicity, year, and vaccine type. The predominant PCV13-targeted serotypes persisting after vaccine introduction included 19F, 14, 19A, and 3. By the end of the study period, the most prevalent non-PCV13 replacement serotype was 15B/C.

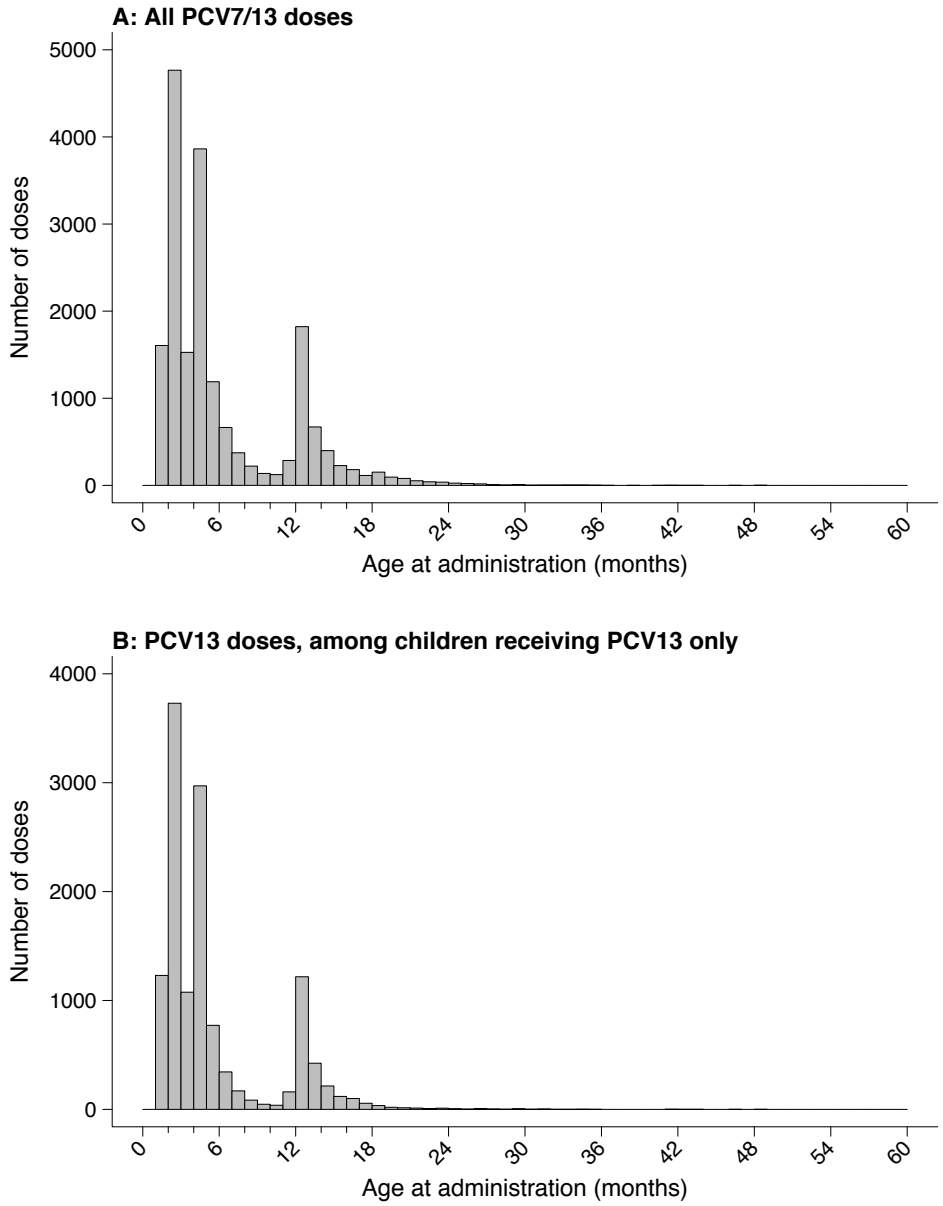

Figure S2: Age at receipt of PCV doses. We illustrate the number of doses administered by single month of life, for (**A**) all PCV7/13 doses, including PCV7 doses administered as part of a catch-up campaign, and (**B**) PCV13 doses among children receiving PCV13 only. Three modes in the plots correspond to the scheduled ages of 2, 4, and 12 months for receipt of PCV doses. The 10-month cutoff for the timing of booster doses in the analysis is based on the observed nadir in receipt at this age, suggesting to a transition point between the ages at which doses are received as “late” primary-series doses and “early” booster doses.