Title: Impact of reduced dose PCV10 schedules on pneumococcal carriage in Vietnam

Lay-Myint Yoshida[1,2]*, M.B.,B.S., Ph.D., Michiko Toizumi[1,2], M.D., Ph.D., Hien Anh Thi Nguyen[3], M.Sc., Billy J Quilty[7,8], Ph.D., Le Thuy Lien[4], M.Sc., Chihiro Iwasaki[1], M.D., Mizuki Takegata[1], Ph.D., Noriko Kitamura[1], M.D., Ph.D., Monica L Nation[5,6], M.PH., Jason Hinds[9], Ph.D., Kevin van Zandvoort[7,8], M.Sc., Belinda D Ortika[5,6], M.Sc., Eileen M Dunne[5], Ph.D., Catherine Satzke[5,6], Ph.D.,, Hung Do Thai, M.D., Ph.D., Kim Mulholland[5,6,7], M.B.,B.S., M.D., Stefan Flasche[7,8], Ph.D., Dang Duc Anh, Ph.D[3].

Affiliation

1. Nagasaki University, Institute of Tropical Medicine, Department of Pediatric Infectious Diseases, Nagasaki, Japan
2. Nagasaki University, Graduate School of Tropical Medicine and Global Health, Department of Global Health, Nagasaki, Japan
3. National Institute of Hygiene and Epidemiology, Department of Bacteriology, Hanoi, Viet Nam
4. Pasteur Institute in Nha Trang, Department of Bacteriology, Nha Trang, Viet Nam
5. Murdoch Children's Research Institute, Infection and Immunity, Melbourne, ACT, Australia,
6. University of Melbourne, Department of Paediatrics, Melbourne, VIC, Australia,
7. London School of Hygiene & Tropical Medicine, Department of Infectious Disease Epidemiology, London, United Kingdom
8. London School of Hygiene & Tropical Medicine, Centre for Mathematical Modelling of Infectious Diseases, London, United Kingdom
9. St Georges University, Institute for Infection and Immunity, London, United Kingdom

Corresponding author*

Lay-Myint Yoshida

Department of Pediatric Infectious Diseases

Institute of Tropical Medicine, Nagasaki University

1-12-4, Sakamoto, Nagasaki, 852-8523, JAPAN

Phone: +81 (0)95-819-7284

Email; lmyoshi@nagasaki-u.ac.jp

ABSTRACT

BACKGROUND

We investigated the non-inferiority of a single priming and booster dose (1p+1) compared to 3 dose schedules (2p+1 & 3p+0) in sustaining control of PCV10 type carriage.

METHODS

In PCV-naïve Nha Trang, Vietnam, a PCV10 (Synflorix) catch-up campaign was offered to children <3y old followed by a cluster randomized trial with routine use in four intervention arms (1p+1, 0p+1, 2p+1, 3p+0). Annual carriage surveys in infants and toddlers were conducted between 2016 and 2020. The primary endpoint was non-inferiority of 1p+1 in protecting against VT carriage in infants when compared to 2p+1 and 3p+0 arms, 3.5 years after introduction.

RESULTS

Overall VT carriage in infants in 2016 before PCV10 introduction in intervention arms was 160/1363 (11.7%) and in 2020 had reduced to 6/333 (1.8%), 5/340 (1.5%), and 4/313 (1.3%) in 1p+1, 2p+1, and 3p+0 arms respectively: a non-inferior difference of 1p+1 against 2p+1 and 3p+0 of 0.3% (-1.6, 2.2%) and 0.5% (-1.4, 2.4%). Similarly, 1p+1 was found non-inferior for protection against VT carriage in toddlers. Serotype 6A carriage prevalence in infants was 99/1363 (7.3%) in 2016 and reduced to 12/333 (3.6%), 10/340 (2.9%) and 3/313 (1.0%) in 1p+1, 2p+1, and 3p+0 arms in 2020. Protection offered by 0p+1 was also non-inferior in infants and toddlers compared to three dose schedules, although cross protection against 6A was less prominent.

CONCLUSIONS

The 1p+1 schedule of PCV10 sustained the combined direct and indirect protection against carriage in infants and toddlers. (ClinicalTrials.gov number, NCT02961231.)

INTRODUCTION

Streptococcus pneumoniae is a major cause of morbidity and mortality in children younger than 5 years globally with most cases occurring in low and middle income countries (LMICs).[1,2] Pneumococcal conjugate vaccines (PCVs) can prevent pneumococcal disease through direct and indirect protection by reduction of vaccine-types (VT) nasopharyngeal carriage.[3,4] WHO recommends PCVs as either three primary doses given during early infancy (3p+0) or two primary doses given in early infancy and a booster dose given from age 9 months onward (2p+1).[5] However, the high vaccine costs have proven a barrier for introduction in many middle income countries (MICs) and raise concerns for sustainability of the PCV program in LMICs who transition out of Gavi's support for vaccine costs.

Following the control of pneumococcal vaccine-type disease and colonization through vaccination, a PCV schedule with a single priming and booster dose (1p+1) may be sufficient to sustain that control at reduced costs. [6] Trials in England, South Africa, India and Vietnam with either immunogenicity or vaccine efficacy outcomes have demonstrated that a 1p+1 schedule indeed induces a similar protection to a 2p+1 schedule following administration of the booster dose, however, they also confirmed suspected inferior direction before the booster.[7,8,9,10] While the similar post-booster direct protection against VT carriage is thought to sustain indirect protection in the first year of life, there is currently no direct evidence for such.[11] Nasopharyngeal carriage is a pre-requisite for disease[12] and reduction of carriage is an indicator of reduction of disease as well as an indirect measure of herd immunity.[13] Thus, measuring the impact of a vaccination schedule on carriage is a proxy for measuring the impact of the schedule at a community level.

We conducted a cluster randomized non-inferiority trial to estimate the effect of PCV10 given in a reduced dosing schedule (1p+1 & 0p+1) compared to the WHO recommended 2p+1 and 3p+0 schedule in a PCV naïve population in Vietnam. We here report whether the 1p+1 or 0p+1 schedules were non-inferior compared to the three dose schedules in maintaining control of VT carriage.

METHODS

Study design: cRCT

An open-label, non-inferiority, cluster randomized trial, was conducted across the 27 communes of Nha Trang city, south-central Vietnam. Communes were deemed the natural unit of cluster-randomization as they represent organization units that allow for administration of different schedules in respective health centers and limit the risk for spill

over due to the commune-based educational system. Three communes in the north were selected to remain unvaccinated but monitored for changes in pneumococcal epidemiology in the trial area. The remaining 24 communes were randomized and assigned to four intervention arms/schedules (2p+1, 3p+0, 1p+1 and 0p+1). To ensure random but geographically balanced allocation of clusters that were similarly representative of rural and urban communities and that were included in the ongoing hospital-based pediatric ARI surveillance, we used automated rejection sampling as previously described (Figure 1A).[14]

Intervention: PCV10

PCV10 (Synflorix®, GSK Vaccines) was used since it was the only PCV registered at the time of the study initiation in Vietnam. To accelerate indirect protection, in February 2017 a catch-up vaccination campaign was conducted in the 24 intervention clusters (communes) offering PCV to all children <3y old and eligible for national immunization vaccination (2-6mth: 3 doses, 7-18mth: 2 doses and 19-36mth: 1 dose respectively).

From March 2017 PCV10 was integrated into the national immunization program of the 24 intervention clusters according to their designated PCV schedule. Children resident received PCV-10 at 2, 3 and 4 months in the 3p+0 arm, at 2, 4 and 12 months in the 2p+1 arm, at 2 and 12 months in the 1p+1 arm and at 12 month in the 0p+1 arm.

Outcome: VT carriage prevalence

Six carriage surveys; a pre-vaccination baseline carriage survey in all arms in 2016 October, a post PCV-10 catchup carriage survey in June 2017 (5 months after the catch-up), and annual carriage surveys in November 2017, October 2018, 2019, and 2020 were conducted. The census database and regularly updated EPI vaccination list of children were used to randomly select study participants. All children eligible to receive routine immunization were included in the randomization. For each carriage survey, we aimed to recruit 60 children 4 to 11 months old ("infants"), and 60 children 14 to 24 months old ("toddlers") from each communes.

After obtaining written informed consent, demographic information and nasopharyngeal samples were collected using standard procedures. DNA was extracted from the nasopharyngeal samples using a QiaCube HT instrument (QIAmp 96 DNA QIAcube HT Kit) and screened for *S.pneumoniae lytA* gene by realtime PCR at Pasteur Institute in Nha Trang. Positive samples were cultured, DNA extracted and the DNA was transported to Murdoch Children's Research Institute (MCRI) for serotype determination by microarray.[15]

Statistical analyses: changes in odds of VT carriage and non-inferiority

Sample size calculations deemed that with six clusters per intervention arm and 60 infants

recruited per cluster we would have >80% power under a type I error probability of 5% to detect a at least five percentage point higher VTs carriage between a reduced dose arms/schedule and a three-dose arm/schedule with an assumed residual VTs carriage prevalence of 5% once differences in the schedules had sufficient time to establish.[14]

PCV10-VTs carriage was defined as carriage of a serotype included in the PCV10 formulation (1, 4, 5, 6B, 7F, 9V, 14, 18C, 19F, or 23F). Due to the likely cross protection of PCV-10 against 6A, we repeated analyses including 6A as a VT. For assessing changes in carriage over time we calculated changes in the proportion of pneumococcal carriers who carry a VT, rather than carriage prevalence, due to the potential impact of COVID-19 control measures in 2020 on pneumococcal transmission and carriage. We used logistic regression to assess the change in odds of VT carriage in both the post-catchup survey and final carriage survey versus the baseline survey and tested for possible effect modification by age group and trial arm. Non-inferiority was assessed by estimating the absolute difference in vaccine-type prevalence between two arms in the final carriage survey in October 2020. If the 95% confidence intervals (CIs) of the difference in VTs prevalence included no difference but not the 5% non-inferiority margin, the non-inferiority criteria was met.[16] As a sensitivity analysis, we also assessed non-inferiority in the penultimate carriage survey in October 2019, just over 2.5 years after the start of routine vaccination according to the intervention schedules, but prior to the COVID-19 pandemic.

Ethical approval

Ethical approval for the study was obtained from the Ministry of Health, Vietnam (4875/QD-BYT), and Nagasaki University (15120149). Written informed consent was obtained from the parents or guardian of the study subjects and the study was conducted in accordance with the approved guidelines.

Results

Characteristics of subjects at baseline and subsequent carriage surveys

A total of 3124 children (2p+1: 692, 3p+0: 691, 1p+1: 674, 0p+1: 709, unvaccinated: 358) were enrolled in the baseline carriage survey. The detailed characteristics of the children are shown in supplementary table 1. Briefly about 55% of enrolled children were male, more than 99% had received at least one dose of BCG and DTP and less than 2% had received at least one dose of PCV. Children were generally healthy with <2% reporting underlying medical

conditions, albeit the prevalence of mild respiratory symptoms in the preceding two weeks was at almost 50% and more than 20% reported recent antibiotic use. The average household size was five and about 20% were living in households with at least one person regularly smoking inside. None of the socio-demographic characteristics differed across study arms (supplementary table 1).

A total of 15,528children were enrolled to the post catch-up (n=3181) and four annual carriage surveys (n=12,34), 15,526 (>99.9%) samples were serotyped, and serotype result was determined for 15,436 (>99.0%) (Figure 2A).

Changes in pneumococcal carriage

Overall pneumococcal carriage prevalence in the baseline survey in 2016 in all intervention arms was 23.0% (315/1371) in infants and 36.6% (510/1394) in toddlers (Figure 3A); of those carriers, 52.1% (160/307) in infants and 50.0% (246/492) in toddlers carried at least one serotype included in PCV10 (Figure 3B) for a PCV10-type prevalence of 11.7% (160/1363) and 17.9% (246/1376), respectively. Serotype 6A was predominant and was carried by 32.2% (99/307) and 35.8% (176/492) of infants and toddlers, respectively. The major vaccine types (VTs) at baseline were 19F, 6B, 23F, and 14 (Figure S2).

In June 2017, 5 months after the start of the catch-up campaign, 34.1% (291/854) of carriers carried at least one PCV10 type (infants: 37.7% (120/318), toddlers: 31.9% (171/536). The odds of a carrier carrying a PCV10 type were 50.0% lower (odds ratio (OR): 0.50, 95% CI: 0.41, 0.61, p<0.001) compared to the pre-PCV baseline in intervention clusters. There was no concomitant change in the odds of a carrier carrying serotype 6A after the catch-up campaign (34.4% (275/799) to 35.0% (299/854), OR: 1.03, 95% CI: 0.84, 1.26, p=0.8). No evidence was found of effect modification on the change in odds by age group or schedule (with 2p+1 as the reference category) for either PCV10 or serotype 6A.

Compared to the pre-PCV baseline, by October 2020 (>3.5y after vaccine introduction), 11.6% (68/585) of carriers carried at least one PCV10 type (infants: 14.4% (27/188), toddlers: 10.3% (41/397)). The odds of a carrier carrying a PCV10 type were 87.3% (OR: 0.13, 95% CI: 0.01, 0.17, p<0.001) lower across intervention clusters. A 45.5% reduction in the odds of carriage being serotype 6A was also observed (22.4% (131/585), OR: 0.55, 95% CI: 0.43, 0.70, p<0.001). No evidence was found of effect modification by age group or schedule (when 2p+1 was set as the reference category). The proportion of carriers carrying major PCV10 types was substantially reduced (Figure S2).

Non-inferiority of reduced dose schedules

In October 2020, 1p+1 was non-inferior to 2p+1 in maintaining control of PCV10 serotypes

in infants: VT carriage prevalence was 0.3 percentage points (%) (95% confidence interval (CI): -1.6, 2.2) higher in infants residing in the 1p+1 arm if compared to those in the 2p+1 arm and thus below the pre-specified 5% margin. Similarly, for toddlers the difference was 0.0% (95% CI: -2.8, 2.8%). The 1p+1 schedule was also non-inferior to the 3p+0 schedule in infants where VT carriage prevalence was 0.5% (95% CI: -1.4, 2.4%) higher and toddlers where it was 2.0% (95% CI: -0.5, 4.4%) higher (Figure 4A, Table S2).

The 0p+1 schedule was also non-inferior to 2p+1 in infants with a 2.3% (95% CI: -0.1, 4.8%) higher VT carriage prevalence in Oct 2020. In toddlers VT prevalence was 1.3% lower (-1.3% difference, 95% CI: -3.9, 1.3%). The 0p+1 schedule was similarly non-inferior to 3p+0 in infants and toddlers (Figure 4B, Table S2).

With the inclusion of 6A as a VT the 1p+1 schedule remained non-inferior to 2p+1 but not to 3p+0. The 0p+1 schedule only remained non-inferior to 2p+1 in toddlers (Figure S1, Table S2).

These results did not change qualitatively when assessing non-inferiority in the last pre-pandemic year of the trial (in October 2019 survey), i.e. just over 2.5 years after the start of vaccination for PCV10 with the exception of 1p+1 and 0p+1 being inferior to 2p+1 and 3p+0 in toddlers when including serotype 6A as a VT (Figure S1).

Vaccination coverage

For the catch-up vaccination, 13,733 children <3 years old residing in the intervention communes were age-eligible, and 12,850 children without precluding medical conditions or previous PCV vaccination were invited to receive PCV10 catch-up vaccination in February 2017. With 20,434 doses given, 12,683 (98.7%) children received at least one dose of PCV10 and 12,129 (94.4%) completed the designated catch-up schedule and little differences in coverage between intervention arms were observed (Figure 2B).

As part of routine vaccination, a total of 31,385 PCV10 doses were given to eligible children during the study period. In the sixth and final survey in Oct 2020, >76% of infants and >66% toddlers had received at least the number of doses specified for their age group and trial arm (Figure 1B, Table 1).

Safety

During the study period, 50 (including 7 after catch-up campaign) serious adverse events were reported within 28 days of vaccination: in 0.11% out of 51,819 doses given. After review by an independent panel, it was deemed that none were related to PCV10 vaccination.

DISCUSSION

We report the findings of a cluster-randomized PCV10 reduced dosing schedule trial. We found that PCV10 reduced dose schedules (1p+1 or 0p+1) maintained combined direct and indirect protection against VT carriage similarly to 3-dose schedules.

Results from individually randomized reduced dosing schedules trials in the UK, South Africa, India, and Vietnam have consistently shown non-inferiority of the post-booster response of 1p+1 schedules across all three currently WHO recommended PCV products.[7-9,22] Similarly, studies from India and Vietnam have shown high efficacy against vaccine serotype carriage in the second year of life following a reduced dose schedule with either PCV10 or PCV13. While in the UK a 1p+1 schedule has been used since 2020, the COVID-19 pandemic has obscured any potential effects of increased risk for VT in infants thus far. We here show that in a setting with moderate pneumococcal infection rates, transmission concentrated in pre-school children, and high coverage, the direct protection from PCV against infection and transmission in 12m olds is sufficient to sustain control of VT circulation.

When serotype 6A was included in the definition of PCV10 as a cross protective serotype, 1p+1 remained noninferior to 2p+1 in both infants and toddlers but the non-inferiority criteria was no longer met in comparison with the 3p+0 schedule. This was also observed for the 0p+1 schedule. It is unclear why a schedule with 3 priming doses would elicit stronger protection against the circulation of cross protective 6A than all tested booster dose schedules, and we cannot rule out chance. Use of 6A-containing vaccines may be prioritized in settings, such as Vietnam, where 6A prevalence is high. A long-term follow-up is planned and may provide additional evidence for the indirect protection against 6A in the different dosing schedules.

We included an explorative 0p+1 arm and found little evidence for its inferiority compared to three dose schedules. This adds further credibility to recent findings in that a single dose of PCV10 can elicit a reasonably strong immune response even in very young children[25] and an estimated direct vaccine efficacy against VT carriage of about 50% following a single dose of PCV10 given at 12m[22]. It also provides evidence that single dose campaigns in children as young as 12m could help prevent a considerable burden in settings where multi dose administration may prove difficult[26].

Limitations

Due to the COVID-19 pandemic in Vietnam, non-pharmaceutical interventions were introduced in the study site between April and July 2020. As a result, pneumococcal carriage prevalence reduced by about 30% and decreased our power to detect a 5% absolute difference

and detect potential inferiority. However, through annual surveys we showed consistent declines in VT prevalence before 2020 and we conducted a sensitivity analysis of the primary endpoint based on 2019 data which confirmed our findings (Figure S1). Owing to the single city setup of the trial there may have been some inter-cluster contamination which in principle could have obscured differences in vaccine effects between study arms. However, study clusters were deliberately chosen as administrative units that govern school attendance, the primary age groups for pneumococcal transmission in this setting[14], thus limiting contamination. Also, we included three unvaccinated communes in the same city, bordering the intervention arms and showed limited effects of PCV vaccination in the intervention arms on VT transmission in the unvaccinated parts of the city. Finally, it remains unclear if reliance on indirect protection is sufficient to sustain protection in settings with more intensive pneumococcal transmission, particularly in older age groups and with poorer booster dose coverage. The ongoing trial in the Gambia and mathematical modelling can help to explore the generalizability of our findings further.

Conclusion:

In a large cRCT in Vietnam, after more than 3.5 years of use at high coverage, a PCV10 1p+1 dosing schedule was non-inferior to 2p+1 or 3p+0 in infants and toddlers in controlling VT carriage in the community.

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Funding agency and role in the study

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Data sharing

In accordance with the Bill & Melinda Gates Foundation policy on open data access, data will be shared on request from the corresponding author on a collaborative basis. Personal information will be removed in the shared data.

Conflict of interest (Please add if you have any)

KM and CS are investigators on a clinical research collaboration with Pfizer on PCV vaccination in Mongolia and are investigators on a Merck Investigator Studies Program grant funded by MSD on pneumococcal serotype epidemiology in children. The other authors have no conflict of interest in conducting the study.

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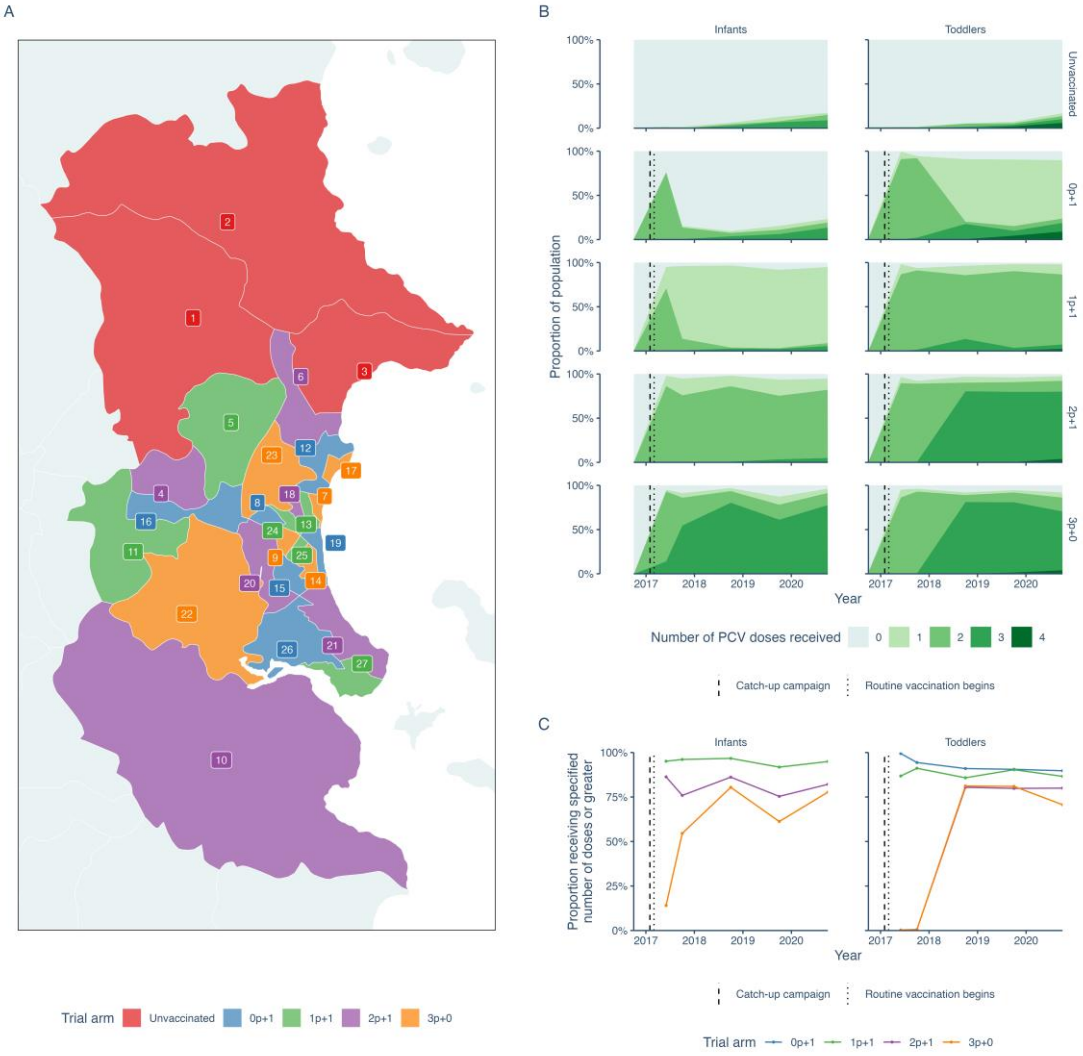


Figure 1: A) Map of communes in Nha Trang with trial arm cluster allocation (unvaccinated, 0+1, 1p+1, 2p+1, 3p+0); B) PCV-10 uptake over time by trial arm and age group; C) Proportion receiving the specified and appropriate number of doses by trial arm and age group.

Number of 4-11 months and 14-24 months children enrolled and tested sample (n=18652)

	1st		2nd		3rd		4th		5th		6th	
	4-11m	14-24m	4-11m	14-24m	4-11m	14-24m	4-11m	14-24m	4-11m	14-24m	4-11m	14-24m
2P+1	351	341	358	359	332	346	354	358	345	357	341	350
3P+0	342	349	334	359	295	343	322	329	289	336	314	341
1P+1	328	346	347	356	333	339	363	359	341	362	334	351
0P+1	350	359	350	357	351	355	346	355	335	360	317	361
Control	181	177	181	180	174	180	180	179	180	179	178	183
Total	1,552	1,572	1,570	1,611	1,485	1,563	1,565	1,580	1,490	1,594	1,484	1,586

↓ → 3 children with pneumococcal carriage but unable to test by microarray

Number of 4-11 months and 14-24 months children' sample with pneumococcal carriage data for analyses (n=18649)

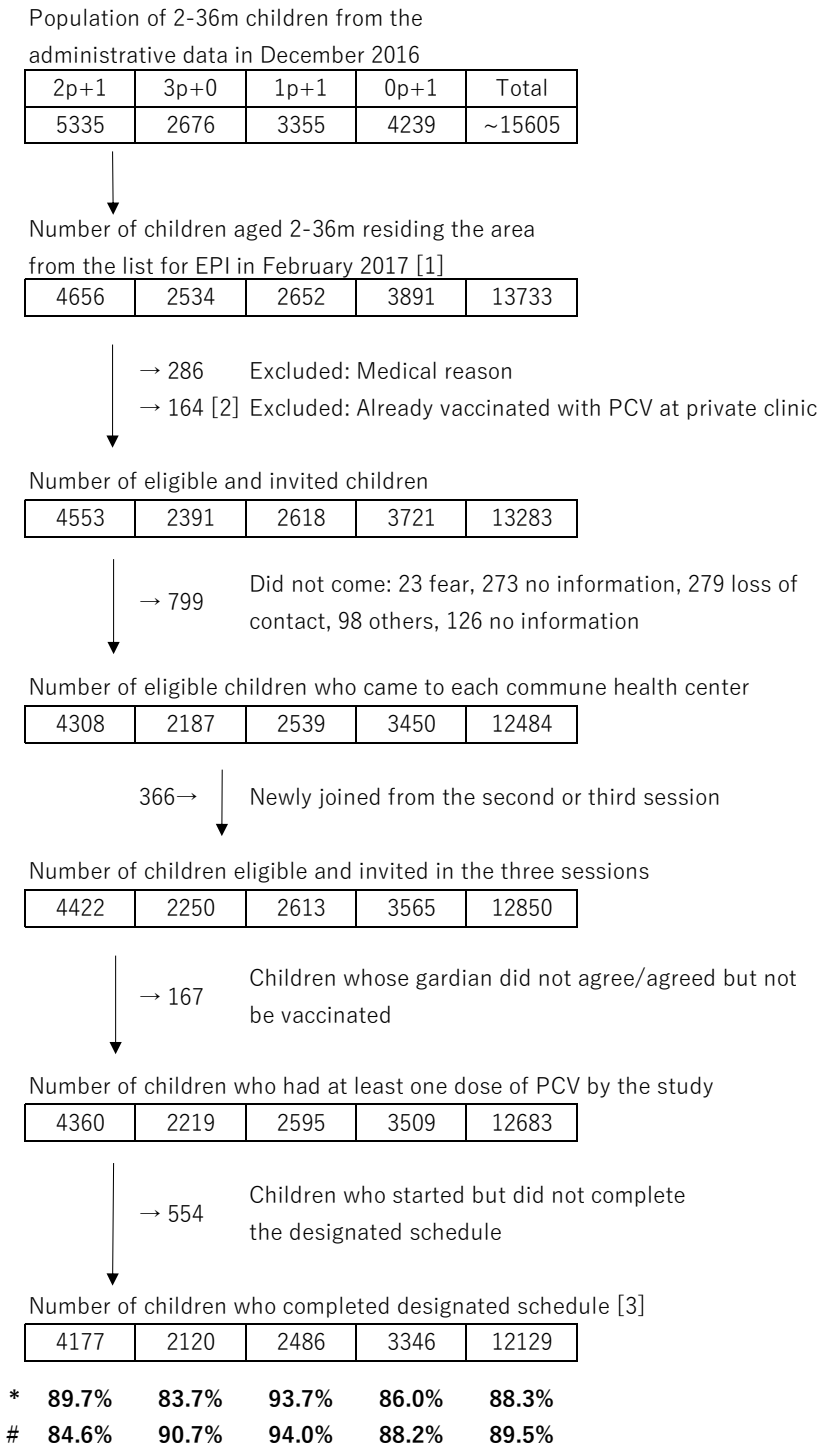
	1st		2nd		3rd		4th		5th		6th	
	4-11m	14-24m	4-11m	14-24m	4-11m	14-24m	4-11m	14-24m	4-11m	14-24m	4-11m	14-24m
2P+1	351	341	358	359	332	346	354	358	345	357	341	350
3P+0	342	348	334	359	295	343	322	329	289	336	314	341
1P+1	328	346	346	356	333	339	363	359	341	362	334	351
0P+1	350	359	350	357	351	355	346	355	334	360	317	361
Control	181	177	181	180	174	180	180	179	180	179	178	183
Total	1,552	1,571	1,569	1,611	1,485	1,563	1,565	1,580	1,489	1,594	1,484	1,586

↓ → 119 children with pneumococcal carriage but serotype undetermined by microarray

Number of 4-11 months and 14-24 months children' sample with pneumococcal VT non-VT data for analysis (n=18530)

	1st		2nd		3rd		4th		5th		6th	
	4-11m	14-24m	4-11m	14-24m	4-11m	14-24m	4-11m	14-24m	4-11m	14-24m	4-11m	14-24m
2P+1	349	335	357	355	331	345	351	353	344	351	340	343
3P+0	341	342	334	355	294	341	321	329	287	333	313	340
1P+1	326	343	343	355	331	337	363	359	339	359	333	347
0P+1	347	356	350	354	351	353	345	352	334	359	316	360
Control	179	176	179	178	174	175	180	175	180	178	178	182
Total	1,542	1,552	1,563	1,597	1,481	1,551	1,560	1,568	1,484	1,580	1,480	1,572

Figure 2 A. Flowchart of enrolment and sample-tested children for the carriage surveys



*Completion rate (coverage of the catch-up campaign): ([3]/[1])

#Completion rate (coverage of PCV, assuming [2] completed a designated schedule): (([2]+[3])/(1))

Figure 2 B. Flowchart of enrolment and PCV administration for the catch-up campaign

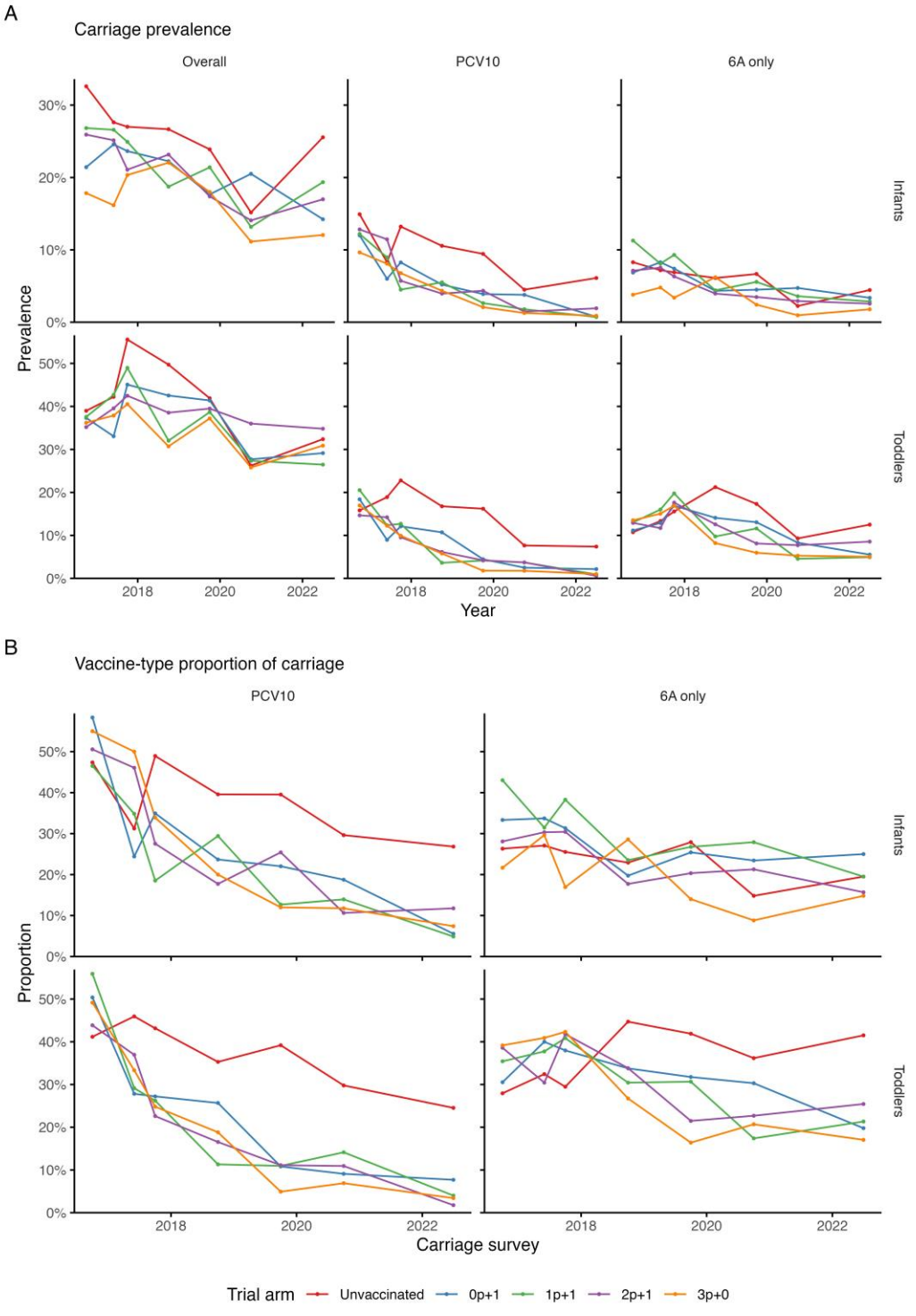


Figure 3: Prevalence of carriage (A) and proportion of carriage (B) by carriage survey, trial arm, age group, and vaccine type definition.

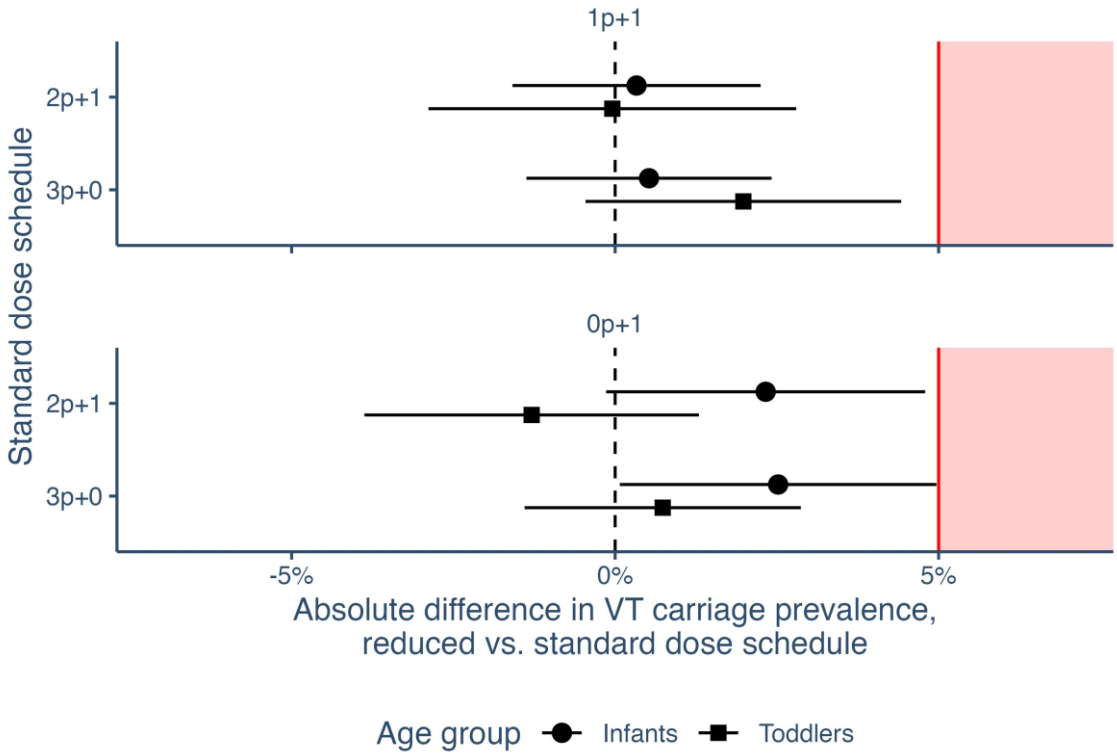


Figure 4: Non-inferiority of reduced dose schedules (1p+1 and 0p+1) versus standard dose schedules (2p+1 and 3p+0) by age group (infants: 4-11 months, toddlers: 14-24 months) by mean (point) and 95% confidence intervals (CI) (line) of the difference in absolute vaccine-type prevalence in the final carriage survey in October 2020 for PCV10 and PCV10 + serotype 6A. Red line and shaded area indicate the 5% non-inferiority margin; estimates with 95% CIs overlapping the 5% margin indicate inferiority.

Supplementary appendix

Table S1. Characteristics of children participated in the first carriage survey by arm (pre-PCV)

Characteristics	2p+1 Number (%)	3p+0 Number (%)	1p+1 Number (%)	0p+1 Number (%)	Unvaccianted Number (%)
	n=692	n=691	n=674	n=709	n=358
Demographic					
Age group					
4-11	351 (50.7)	342 (49.5)	328 (48.7)	350 (49.4)	181 (50.6)
14-24	341 (49.3)	349 (50.5)	346 (51.3)	359 (50.6)	177 (49.4)
Sex					
Boys	373 (53.9)	340 (49.2)	365 (54.2)	373 (52.6)	197 (55.0)
Girls	319 (46.1)	351 (50.8)	309 (45.9)	336 (47.4)	161 (45.0)
Perinatal & breastfeeding					
Low birth weight (<2500 gram)					
Yes	18 (2.6)	14 (2.0)	19 (2.8)	12 (1.7)	6 (1.7)
No	674 (97.4)	677 (98.0)	655 (97.2)	697 (98.3)	352 (98.3)
Preterm born (gestational age at birth <37 weeks)					
Yes	39 (5.6)	28 (4.1)	40 (5.9)	49 (6.9)	16 (4.5)
No	653 (94.4)	663 (96.0)	634 (94.1)	660 (93.1)	342 (95.5)
Mode of delivery					
Vaginal	407 (58.8)	376 (54.4)	396 (58.8)	367 (51.8)	191 (53.4)
Cesarean section	285 (41.2)	315 (45.6)	278 (41.3)	342 (48.2)	167 (46.7)
Current breastfeeding or breastfed until 6 months of age					
Yes	592 (85.6)	536 (77.6)	544 (80.7)	586 (82.7)	319 (89.1)
No	100 (14.5)	155 (22.4)	130 (19.3)	123 (17.4)	39 (10.9)
Current breastfeeding					
Yes	404 (58.4)	345 (49.9)	345 (51.2)	375 (52.9)	215 (60.1)
No	288 (41.6)	346 (50.1)	329 (48.8)	334 (47.1)	143 (39.9)
Medical problems					
Congenital disorder(s)					
Yes	7 (1.0)	9 (1.3)	2 (0.3)	8 (1.1)	4 (1.1)
No	685 (99.0)	682 (98.7)	672 (99.7)	701 (98.9)	354 (98.9)
Underlying illness(es)					
Yes	8 (1.2)	12 (1.7)	10 (1.5)	21 (3.0)	7 (2.0)
No	684 (98.8)	679 (98.3)	664 (98.5)	688 (97.0)	351 (98.0)
Ever hospitalized					
Yes	125 (18.1)	159 (23.0)	152 (22.6)	182 (25.7)	80 (22.4)
No	567 (81.9)	532 (77.0)	522 (77.5)	527 (74.3)	278 (77.7)
Cough in the preceeding two weeks					
Yes	311 (44.9)	300 (43.4)	328 (48.7)	345 (48.7)	155 (43.3)
No	381 (55.1)	391 (56.6)	346 (51.3)	364 (51.3)	203 (56.7)
Runny nose in the preceeding two weeks					
Yes	336 (48.6)	340 (49.2)	364 (54.0)	382 (53.9)	175 (48.9)
No	356 (51.5)	351 (50.8)	310 (46.0)	327 (46.1)	183 (51.1)
Difficult breathing in the preceeding two weeks					
Yes	16 (2.3)	18 (2.6)	29 (4.3)	23 (3.2)	20 (5.6)
No	676 (97.7)	673 (97.4)	645 (95.7)	686 (96.8)	338 (94.4)
Have taken antibiotics in the preceeding two weeks					
Yes	132 (19.1)	172 (24.9)	148 (22.0)	182 (25.7)	112 (31.3)
No	560 (80.9)	519 (75.1)	526 (78.0)	527 (74.3)	246 (68.7)

Vaccination history					
BCG					
Yes	690 (99.7)	691 (100.0)	669 (99.3)	708 (99.9)	355 (99.2)
No	2 (0.3)	0 (0.0)	5 (0.7)	1 (0.1)	3 (0.8)
DPT					
4 doses	65 (9.4)	112 (16.2)	105 (15.6)	111 (15.7)	43 (12)
3 doses	568 (82.1)	519 (75.1)	516 (76.6)	542 (76.5)	292 (81.6)
2 doses	45 (6.5)	48 (7.0)	42 (6.2)	42 (5.9)	19 (5.3)
1 dose	12 (1.7)	10 (1.5)	11 (1.6)	10 (1.4)	2 (0.6)
No	2 (0.3)	2 (0.3)	0 (0)	4 (0.6)	2 (0.6)
Measles					
2 doses	75 (10.8)	125 (18.1)	131 (19.4)	124 (17.5)	58 (16.2)
1 dose	347 (50.1)	310 (44.9)	315 (46.7)	319 (45)	161 (45)
No	270 (39)	256 (37.1)	228 (33.8)	266 (37.5)	139 (38.8)
PCV					
4 doses	1 (0.1)	0 (0.0)	0 (0.0)	3 (0.4)	0 (0.0)
3 doses	0 (0.0)	2 (0.3)	0 (0.0)	2 (0.3)	0 (0.0)
2 doses	3 (0.4)	6 (0.9)	4 (0.6)	3 (0.4)	2 (0.6)
1 dose	3 (0.4)	2 (0.3)	1 (0.2)	6 (0.9)	2 (0.6)
No	685 (99.0)	681 (98.6)	669 (99.3)	695 (98.0)	354 (98.9)
Socio-economic status					
Number of household members					
Median (interquartile range)	5 (4-6)	5 (4-7)	5 (4-7)	5 (4-6)	5 (4-6)
People density in household (people/100m^2)					
Median (interquartile range)	7.1 (5.0-10.0)	6.7 (4.7-10.0)	7.1 (5.0-10.0)	7.0 (4.7-10.0)	5.8 (4.7-10.0)
Usually in company with child(ren) <5 years old					
Yes	493 (71.2)	522 (75.5)	509 (75.5)	590 (83.2)	280 (78.2)
No	199 (28.8)	167 (24.2)	165 (24.5)	119 (16.8)	78 (21.8)
Unknown					
Ever attended day-care/kindergarten					
Yes	166 (24.0)	188 (27.2)	200 (29.7)	194 (27.4)	100 (27.9)
No	526 (76.0)	503 (72.8)	474 (70.3)	515 (72.6)	258 (72.1)
Currently attend day-care/kindergarden					
Yes	158 (22.8)	180 (26.1)	194 (28.8)	187 (26.4)	98 (27.4)
No	534 (77.2)	511 (74.0)	480 (71.2)	522 (73.6)	260 (72.6)
Smoker(s) in household					
Indoor smoker(s)	129 (18.6)	147 (21.3)	151 (22.4)	106 (15)	104 (29.1)
Outdoor only smoker(s)	278 (40.2)	297 (43.0)	285 (42.3)	273 (38.5)	111 (31.0)
No smoker	285 (41.2)	247 (35.8)	238 (35.3)	330 (46.5)	143 (39.9)
Have farm animal(s)					
Yes	91 (13.2)	55 (8.0)	94 (14.0)	77 (10.9)	74 (20.7)
No	601 (86.9)	636 (92)	580 (86.1)	632 (89.1)	284 (79.3)
Household income last month (one million Vietnamese dong)					
Median (interquartile range)	10 (7-15)	10 (8-15)	10 (8-15)	10 (8-20)	10 (7-15)
Highest education level in household					
No school/primary	178 (25.7)	180 (26.1)	167 (24.8)	95 (13.4)	115 (32.1)
Secondary	162 (23.4)	148 (21.4)	182 (27.0)	168 (23.7)	76 (21.2)
High school	185 (26.7)	202 (29.2)	194 (28.8)	203 (28.6)	102 (28.5)
College/university	167 (24.1)	161 (23.3)	131 (19.4)	243 (34.3)	65 (18.2)
Mother's education level in household					
No school/primary	70 (10.1)	34 (4.9)	78 (11.6)	34 (4.8)	38 (10.6)
Secondary	157 (22.7)	162 (23.4)	155 (23.0)	144 (20.3)	68 (19.0)
High school	208 (30.1)	224 (32.4)	208 (30.9)	215 (30.3)	131 (36.6)
College/university	257 (37.1)	271 (39.2)	233 (34.6)	316 (44.6)	121 (33.8)
Pneumococcal carriage (n=3123)					
Pneumococcal carriage					
Yes	211 (30.5)	187 (27.1)	218 (32.3)	209 (29.5)	128 (35.8)
No	481 (69.5)	503 (72.9)	456 (67.7)	500 (70.5)	230 (64.3)
PCV10-type pneumococcal carriage					
Yes	95 (13.7)	92 (13.3)	111 (16.5)	108 (15.2)	55 (15.4)
No	597 (86.3)	598 (86.7)	563 (83.5)	601 (84.8)	303 (84.6)

Table S2: Proportion of children completing the specified schedule for age group and trial arm in the final cross-sectional survey (October 2020). For infants, this represents finishing the specified primary series and for toddlers, this represents finishing both the specified primary series + booster.

^ no primary doses received in infancy.

Age group	Schedule	Proportion receiving at least one dose of PCV10	Proportion receiving the specified number of doses of PCV10 for age group and schedule	Proportion receiving over the specified number of doses of PCV10 for age group and schedule
Infants	Unvaccinated	17.4	82.6	17.4
	0p+1	23.4	76.6	23.4
	1p+1	95.2	86.2	9.01
	3p+0	96.2	77.0	0.639
	2p+1	95.0	77.4	5.00
Toddlers	Unvaccinated	17.0	83.0	17.0
	0p+1	90.0	66.1	23.9
	1p+1	98.0	79.3	7.20
	3p+0	92.1	66.5	4.12
	2p+1	97.4	75.8	4.08

Table S3: Non-inferiority of reduced dose schedules (A: 1p+1, B: 0p+1) versus standard dose schedules (2p+1 and 3p+0) by age group (infants: 4-11 months, toddlers: 14-24 months) by mean and 95% confidence intervals (CI) of the difference in absolute prevalence in the penultimate carriage survey in 2019 for PCV-10 and PCV-10 + serotype 6A.

Age group	Vaccine types	Standard dose schedule	Reduced dose schedule	Standard dose VT prevalence (%, n/N)	Reduced dose VT prevalence (%, n/N)	Absolute difference in VT carriage prevalence (percentage points, 95% CI)
Infants	PCV10	2p+1	0p+1	1.5 (5/340)	3.8 (12/316)	2.3 (-0.1, 4.8)
		3p+0		1.3 (4/313)	3.8 (12/316)	2.5 (0.1, 5)
		2p+1	1p+1	1.5 (5/340)	1.8 (6/333)	0.3 (-1.6, 2.2)
		3p+0		1.3 (4/313)	1.8 (6/333)	0.5 (-1.4, 2.4)
	PCV10 + 6A	2p+1	0p+1	4.4 (15/340)	8.5 (27/316)	4.1 (0.4, 7.9)*
		3p+0		2.2 (7/313)	8.5 (27/316)	6.3 (2.8, 9.8)*
		2p+1	1p+1	4.4 (15/340)	5.4 (18/333)	1 (-2.3, 4.3)
		3p+0		2.2 (7/313)	5.4 (18/333)	3.2 (0.2, 6.1)*
Toddlers	PCV10	2p+1	0p+1	3.8 (13/343)	2.5 (9/360)	-1.3 (-3.9, 1.3)
		3p+0		1.8 (6/340)	2.5 (9/360)	0.7 (-1.4, 2.9)
		2p+1	1p+1	3.8 (13/343)	3.7 (13/347)	0 (-2.9, 2.8)
		3p+0		1.8 (6/340)	3.7 (13/347)	2 (-0.5, 4.4)
	PCV10 + 6A	2p+1	0p+1	11.7 (40/343)	10.8 (39/360)	-0.8 (-5.5, 3.8)
		3p+0		7.1 (24/340)	10.8 (39/360)	3.8 (-0.4, 8)*
		2p+1	1p+1	11.7 (40/343)	8.4 (29/347)	-3.3 (-7.8, 1.2)
		3p+0		7.1 (24/340)	8.4 (29/347)	1.3 (-2.7, 5.3)*

Supplementary Figures

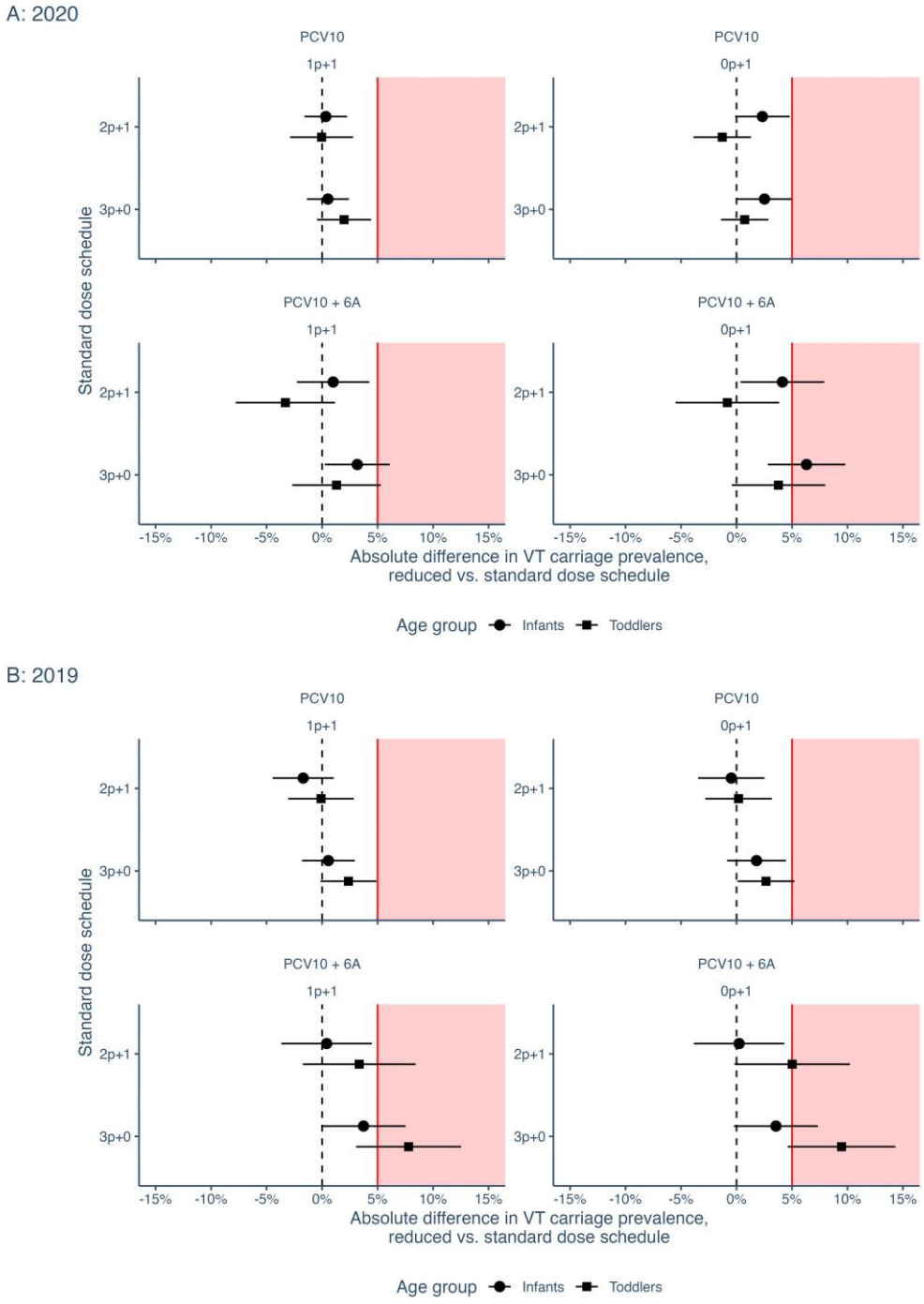


Figure S1: Non-inferiority of reduced dose schedules (1p+1, and 0p+1) versus standard dose schedules (2p+1 and 3p+0) by age group (infants: 4-11 months, toddlers: 14-24 months) by mean (point) and 95% confidence intervals (CI) (line) of the difference in absolute vaccine-type prevalence in 2020 (A) as well as in the penultimate carriage survey in October 2019 (B) for PCV-10 and PCV-10 + serotype 6A. Red line and shaded area indicate the 5% non-inferiority margin; estimates with 95% CIs overlapping the 5% margin indicate inferiority.

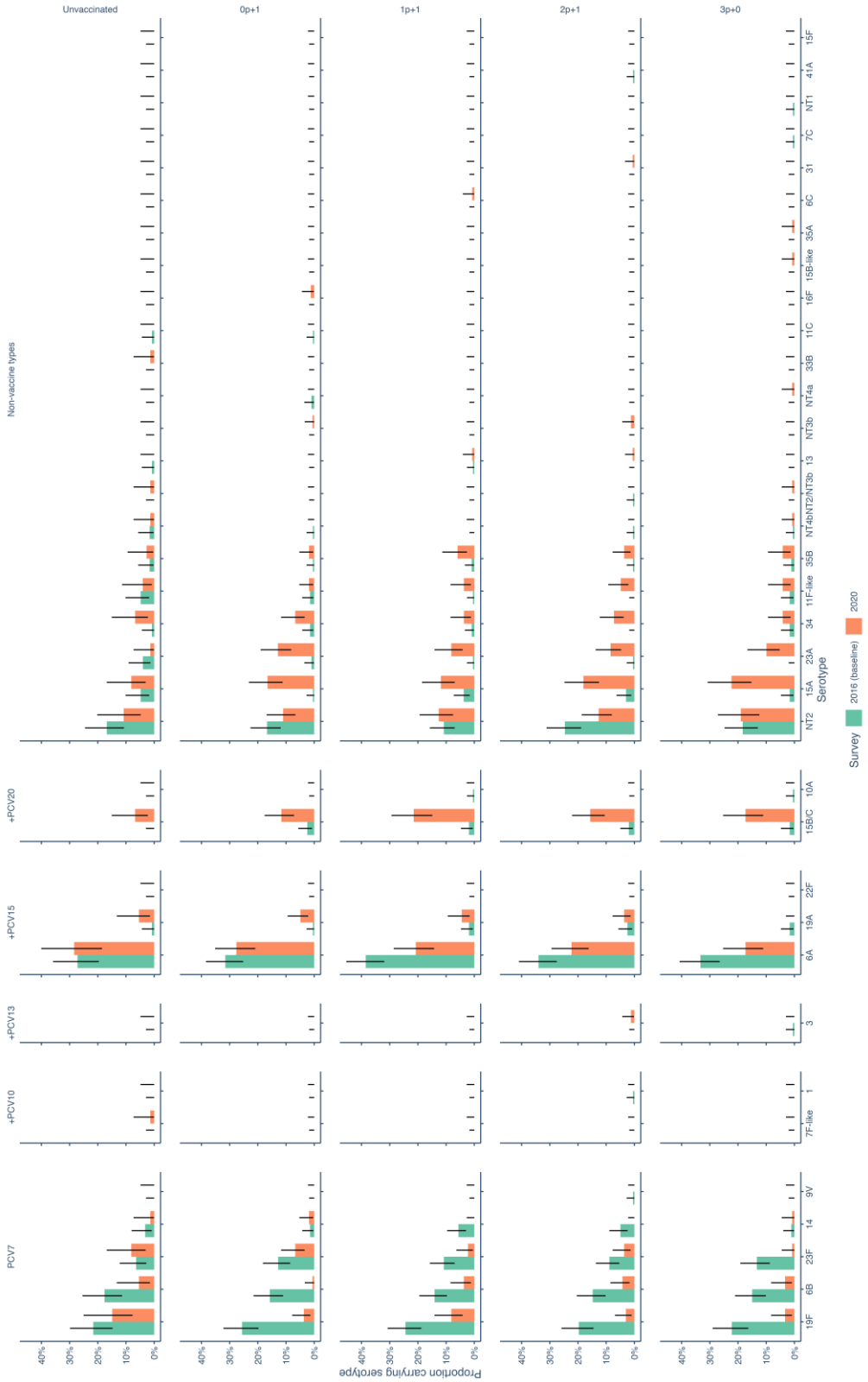


Figure S2: Change in the proportion of carriers carrying a given serotype, by trial arm and inclusion in different PCV formulations, between 2016 and 2020.