Table 1: Effectiveness and impact of different dosing schedules of WHO prequalified Pneumococcal Conjugate Vaccine (PCV) products

Population:

Vaccinated children; unvaccinated older children and adults

Interventions Compared:

2 primary doses before 6 months of age and 1 booster dose at 9 months of age or later (2p+1) in infants <2 years of age with WHO prequalified PCV products

VS:

3 primary doses before 9 months of age without a booster dose (3p+0) in infants <2 years of age with WHO prequalified PCV products

Outcomes:

IgG response – mean GMC and percent responders in immunized infants for vaccine- serotypes (VT)

Mortality – vaccine effectiveness and/or change in mortality rates, pre/post vaccination, for all-cause mortality, pneumonia mortality, and IPD mortality for directly immunized and unimmunized populations through indirect effects; change in case fatality ratios, pre/post vaccination, for pneumonia and IPD.

Invasive Pneumococcal Disease (IPD) – vaccine effectiveness and/or change in incidence of VT or serotype specific IPD pre/post vaccination among directly immunized and unimmunized populations through indirect effects.

Pneumonia – vaccine effectiveness and/or change in incidence, pre/post vaccination, of either clinical pneumonia or chest x-ray (CXR) confirmed pneumonia among directly immunized and unimmunized populations through indirect effects

Carriage – vaccine effectiveness and/or change in incidence, pre/post vaccination, of vaccine type or serotype specific pneumococcal carriage among directly immunized and unimmunized populations through indirect effects

PICO Question: How does PCV administered to healthy children in a 2p+1 schedule compare with the vaccine administered in a 3p+0 schedule, with respect to immune response in vaccinated children and impact on clinical outcomes (IPD, pneumonia, and mortality), and nasopharyngeal carriage in the vaccinated children as well as unvaccinated age groups through indirect protection?				
			Rating	Adjustment to rating
Quality Assessment	No of studies/starting rating		55 out of 74 studies included are RCTs: rating 4	4
Quality Assessment Factors	Factors decreasing confidence	Limitation in study design	None serious	0
		Inconsistency	None serious	0
		Indirectness	Serious[1]	- 1
		Imprecision	None serious	0
		Publication bias	None serious	0
	Factors increasing confidence	Strength of association	None serious	0
		Dose-response	None serious	0
		Mitigated bias and confounding	None serious	0
	Final numerical rating of quality of evidence			**3**
Summary of Findings	**Statement on quality of evidence**			**Evidence supports a moderate level of confidence that the true effect lies close to that of the estimate of the effect on the health outcome.**
	Conclusion			**We are moderately confident that a 2+1 dosing schedule elicits a comparable immune response compared to a 3+0 dosing schedule in the general population.**

[1]Most studies are not head-to-head comparisons of different dosing schedules so the evidence is indirect and inter-study comparisons were the primary source of information. Studies included in the post primary analysis were:
- 10 studies with head to head 2p vs. 3p data: rating 4
- 50 studies with 2p or 3p data: rating 3

Studies included in the post dose 3 analysis were:
- 4 studies with head to head 2p+1 vs. 3p+0: rating 4
- 55 studies with 2p+1 or 3p+0 data: rating 3

References:

1. Zhu, FengCai, Hu, YueMei, Li, JingXin, . . . A. (2016). Immunogenicity and safety of 13-valent pneumococcal conjugate vaccine compared with 7-valent pneumococcal conjugate vaccine among healthy infants in China. Pediatric Infectious Disease Journal, 35(9), 999-1010.
2. Yeh, H, Gurtman, Hurley, C, Block, . . . A. (2010). Immunogenicity and safety of 13-Valent pneumococcal conjugate vaccine in infants and toddlers. Pediatrics, 126(3), e493-e505.
3. Wysocki, J, Tejedor, J, C., Grunert, D, . . . L. (2009). Immunogenicity of the 10-valent pneumococcal non-typeable Haemophilus influenzae protein D conjugate vaccine (PHiD-CV) when coadministered with different neisseria meningitidis serogroup C conjugate vaccines. Pediatr Infect Dis J, 28(4 Suppl), S77-88. doi:10.1097/INF.0b013e318199f609.

4. Wijmenga-Monsuur, A. J., Westen, E. v., Knol, M. J., Jongerius, R. M., Zancolli, M., Goldblatt, D., . . . Rots, N. Y. (2015). Direct Comparison of Immunogenicity Induced by 10- or 13-Valent Pneumococcal Conjugate Vaccine around the 11-Month Booster in Dutch Infants. PLoS One, 10(12), e0144739.
5. Weckx, Y, Thompson, Berezin, N, Faria, . . . A. (2012). A phase 3, randomized, double-blind trial comparing the safety and immunogenicity of the 7-valent and 13-valent pneumococcal conjugate vaccines, given with routine pediatric vaccinations, in healthy infants in Brazil. Vaccine, 30(52), 7566-7572.
6. W.Pomat, S. W. (2014). ACCELERATED SCHEDULE OF 10- AND 13-VALENT PNEUMOCOCCAL CONJUGATE VACCINE IS SAFE AND IMMUNOGENIC IN INFANTS IN PAPUA NEW GUINEA. ISPPD-9, 3, 114.
7. Vesikari, T., Forsten, A., Seppa, I., Kaijalainen, T., Puumalainen, T., Soininen, A., . . . Schuerman, L. (2016). Effectiveness of the 10-Valent Pneumococcal Nontypeable Haemophilus influenzae Protein D-Conjugated Vaccine (PHiD-CV) Against Carriage and Acute Otitis Media-A Double-Blind Randomized Clinical Trial in Finland. J Pediatric Infect Dis Soc.
8. Vesikari, T, Wysocki, J, Chevallier, B, . . . L. (2009). Immunogenicity of the 10-valent pneumococcal non-typeable Haemophilus influenzae protein D conjugate vaccine (PHiD-CV) compared to the licensed 7vCRM vaccine. Pediatr Infect Dis J, 28(4 Suppl), S66-76. doi:10.1097/INF.0b013e318199f8ef.
9. Vesikari, Karvonen, Lindblad, Korhonen, Lommel, Willems, . . . Schuerman. (2010). Safety and immunogenicity of a booster dose of the 10-valent pneumococcal nontypeable haemophilus influenzae protein D conjugate vaccine coadministered with measles-mumps-rubella-varicella vaccine in children aged 12 to 16 months. Pediatric Infectious Disease Journal, 29(6), e47-e56.
10. Vesikari, Karvonen, Korhonen, Karppa, Sadeharju, Fanic, . . . Schuerman. (2011). Immunogenicity of 10-valent pneumococcal nontypeable haemophilus influenzae protein D conjugate vaccine when administered as catch-up vaccination to children 7 months to 5 years of age. Pediatric Infectious Disease Journal, 30(8), e130-e141.
11. Verhagen, M, Rivera, Olivero, A, Hermsen, . . . H. (2016). Introduction of the 13-valent pneumococcal conjugate vaccine in an isolated pneumococcal vaccine-naïve indigenous population. European Respiratory Journal, 48(5), 1492-1496.
12. Vanderkooi, G, Scheifele, W, Girgenti, Halperin, . . . D. (2012). Safety and immunogenicity of a 13-valent pneumococcal conjugate vaccine in healthy infants and toddlers given with routine pediatric vaccinations in Canada. Pediatric Infectious Disease Journal, 31(1), 72-77.
13. Van, D., Bergh, R, Spijkerman, François, Swinnen, . . . M. (2011). Immunogenicity, safety, and reactogenicity of the 10-valent pneumococcal nontypeable haemophilus influenzae protein D conjugate vaccine and DTPa-IPV-Hib when coadministered as a 3-dose primary vaccination schedule in the Netherlands: A randomized controlled trial. Pediatric Infectious Disease Journal, 30(9), e170-e178.
14. van, d., Bergh, R, Spijkerman, Francois, Swinnen, . . . A. (2016). Immunogenicity, Safety and Reactogenicity of a Booster Dose of the 10-Valent Pneumococcal Nontypeable H. influenzae Protein D Conjugate Vaccine Coadministered With DTPa-IPV-Hib in Dutch Children: A Randomized Controlled Trial. Pediatr Infect Dis J, 35(7), e206-219.
15. Van, Westen, Wijmenga, Monsuur, J, Van, . . . M. (2015). Differential B-Cell Memory Around the 11-Month Booster in Children Vaccinated with a 10- or 13-Valent Pneumococcal Conjugate Vaccine. Clinical Infectious Diseases, 61(3), 342-349.
16. Trück, Mitchell, Jawad, Clutterbuck, A, Snape, . . . J. (2016). Divergent Memory B Cell Responses in a Mixed Infant Pneumococcal Conjugate Vaccine Schedule. Pediatric Infectious Disease Journal.
17. Truck, Jawad, Goldblatt, Roalfe, Snape, D, . . . J. (2016). The antibody response following a booster with either a 10- or 13-valent pneumococcal conjugate vaccine in toddlers primed with a 13-valent pneumococcal conjugate vaccine in early infancy. Pediatric Infectious Disease Journal, 35(7), 787-793.
18. Tregnaghi, W, Sáez, Llorens, López, Abate, . . . Schuerman. (2014). 451_PanamaArgentina_Efficacy of Pneumococcal Nontypable Haemophilus influenzae Protein D Conjugate Vaccine (PHiD-CV) in Young Latin American Children: A Double-Blind Randomized Controlled Trial. PLoS Medicine, 11(6), 1-18.
19. Togashi, Yamaji, Thompson, Giardina, C, Aizawa, . . . A. (2013). Immunogenicity and safety of a 13-valent pneumococcal conjugate vaccine in healthy infants in Japan. Pediatric Infectious Disease Journal, 32(9), 984-989.
20. Timo. (2010). Immunogenicity of the 10-valent pneumococcal non-typeable Haemophilus influenzae Protein D Conjugate Vaccine (PHiD-CV). Cocuk Enfeksiyon Dergisi, 4(SUPPL. 1), 9-15.
21. Temple, B., Vo, D. T. T., Balloch, A., Smith-Vaughan, H., Pham, H. T., Huynh, T. P., . . . Mulholland, K. (2016). HEAD-TO-HEAD COMPARISON OF PCV10 AND PCV13: POST-PRIMARY SERIES IMMUNOGENICITY AND IMPACT ON NASOPHARYNGEAL CARRIAGE AT 12 MONTHS OF AGE. ISPPD-10.
22. Spijkerman, Veenhoven, H, Wijmenga, Monsuur, J, . . . M. (2013). Immunogenicity of 13-valent pneumococcal conjugate vaccine administered according to 4 different primary immunization schedules in infants a randomized clinical trial. JAMA - Journal of the American Medical Association, 310(9), 930-937.
23. Snape, D, Klinger, L, Daniels, D, . . . J. (2010). Immunogenicity and reactogenicity of a 13-valent-pneumococcal conjugate vaccine administered at 2, 4, and 12 months of age: A double-blind randomized active-controlled trial. Pediatric Infectious Disease Journal, 29(12), e80-e90.
24. Singleton, Wenger, Klejka, A, Bulkow, R, . . . A. (2013). The 13-valent pneumococcal conjugate vaccine for invasive pneumococcal disease in alaska native children: Results of a clinical trial. Pediatric Infectious Disease Journal, 32(3), 257-263.
25. Silfverdal, S, A., Hogh, B, Bergsaker, M, R., . . . L. (2009). Immunogenicity of a 2-dose priming and booster vaccination with the 10-valent pneumococcal nontypeable Haemophilus influenzae protein D conjugate vaccine. Pediatr Infect Dis J, 28(10), e276-282. doi:10.1097/INF.0b013e3181b48ca3.
26. Ruiz, Palacios, M, Huang, M, Lin, . . . M. (2013). 798_Taiwan_Immunogenicity and safety of a booster dose of the 10-valent pneumococcal haemophilus influenzae protein D conjugate vaccine coadministered with the tetravalent meningococcal serogroups A, C, W-135 and y tetanus toxoid conjugate vaccine in toddlers: A randomized trial. Pediatric Infectious Disease Journal, 32(1), 62-71.
27. Ruiz, Palacios, M, Huang, M, Lin, . . . M. (2013). 798_Mexico_Immunogenicity and safety of a booster dose of the 10-valent pneumococcal haemophilus influenzae protein D conjugate vaccine coadministered with the tetravalent meningococcal serogroups A, C, W-135 and y tetanus toxoid conjugate vaccine in toddlers: A randomized trial. Pediatric Infectious Disease Journal, 32(1), 62-71.
28. Ruiz, Palacios, M, Guerrero, L, Hernández, . . . Schuerman. (2011). Immunogenicity, reactogenicity and safety of the 10-valent pneumococcal nontypeable Haemophilus influenzae protein D conjugate vaccine (PHiD-CV) in Mexican infants. Human Vaccines, 7(11), 1137-1145.
29. Pomat, W., Richmond, P., Francis, J., Wana, S., Solomon, V., Ford, R., . . . Lehmann, D. (2016). IMMUNOGENICITY OF 10-VALENT AND 13-VALENT PNEUMOCOCCAL CONJUGATE VACCINES GIVEN AT 1-2-3 MONTHS OF AGE IN PAPUA NEW GUINEAN INFANTS: A RANDOMISED CONTROLLED TRIAL. ISPPD-10.
30. Phan, T. V., Licciardi, P. V., Toh, Z. Q., Balloch, A., Vu, P. H. N., Vien, K. T., . . . Mulholland, E. K. (2016). IMMUNOGENICITY AND MEMORY B CELL RESPONSE FOLLOWING ALTERNATIVE PNEUMOCOCCAL VACCINATION STRATEGIES IN VIETNAM. ISPPD-10.
31. Payton, Girgenti, Frenck, W, Patterson, Love, . . . A. (2013). Immunogenicity, safety and tolerability of 3 lots of 13-valent pneumococcal conjugate vaccine given with routine pediatric vaccinations in the United States. Pediatric Infectious Disease Journal, 32(8), 871-880.
32. Odusanya, O, Kuyinu, A, Kehinde, A, . . . Schuerman. (2014). Safety and immunogenicity of 10-valent pneumococcal nontypeable Haemophilus influenzae protein D conjugate vaccine (PHiD-CV) in Nigerian children: Booster dose and 2-dose catch-up regimens in the second year of life. Human Vaccines and Immunotherapeutics, 10(3), 757-766.
33. Odusanya, O, Kuyinu, A, Kehinde, A, . . . Schuerman. (2013). Immunogenicity, safety and reactogenicity of the 10-valent pneumococcal non-typeable haemophilus influenzae protein D conjugate vaccine (PHiD-CV) in Nigerian Infants: a randomised trial. The Nigerian postgraduate medical journal, 20(4), 272-281.
34. Martinón, Torres, Wysocki, Center, J, Czajka, . . . Gurtman. (2016). Circulating Antibody 1 and 2 Years After Vaccination With the 13-Valent Pneumococcal Conjugate Vaccine in Preterm Compared with Term Infants. Pediatric Infectious Disease Journal.

35. Martinón, Torres, Gimenez, Sanchez, Gurtman, Bernaola, . . . A. (2012). 13-valent pneumococcal conjugate vaccine given with meningococcal C-tetanus toxoid conjugate and other routine pediatric vaccinations: Immunogenicity and safety. Pediatric Infectious Disease Journal, 31(4), 392-399.
36. Martinón, Torres, Czajka, Center, J, Wysocki, . . . Gurtman. (2015). 13-Valent pneumococcal conjugate vaccine (PCV13) in preterm versus term infants. Pediatrics, 135(4), e876-e886.
37. Martinon, Torres, Czajka, Center, J, Wysocki, . . . Gurtman. (2015). 13-Valent pneumococcal conjugate vaccine (PCV13) in preterm versus term infants. Pediatrics, 135(4), e876-e886.
38. Martinez, R. P. A. C. (2014). IMMUNOGENICITY AND SAFETY OF 11- AND 12-VALENT PNEUMOCOCCAL NON-TYPEABLE HAEMOPHILUS INFLUENZAE PROTEIN D-CONJUGATE VACCINES (11VPHID-CV, 12VPHID-CV) IN INFANTS: PHASE-II STUDY. ISPPD-9, 3, 115.
39. M.R, Swinnen, K., François, N., Borys, D., Schuerman, L., Veenhoven, R. H., & Sanders, E. A. M. (2012). IMMUNOGENICITY OF A BOOSTER DOSE OF 10-VALENT PNEUMOCOCCAL NONTYPEABLE HAEMOPHILUS INFLUENZAE PROTEIN D-CONJUGATE VACCINE (PHID-CV) IN DUTCH CHILDREN. ISPPD 2012, 614.
40. M.Horn, G. B. (2014). SAFETY AND IMMUNOGENICITY OF AN INVESTIGATIONAL 12-VALENT PNEUMOCOCCAL NON-TYPEABLE HAEMOPHILUS INFLUENZAE PROTEIN D CONJUGATE VACCINE IN TODDLERS: PHASE I STUDY. ISPPD-9, 3, 110.
41. Lin, Y, Lu, Y, Chang, Y, . . . M. (2012). Immunogenicity and safety of 10-valent pneumococcal non-typeable Haemophilus influenzae protein D-conjugate vaccine (PHiD-CV) co-administered with routine childhood vaccines in Taiwan. Journal of the Formosan Medical Association, 111(9), 495-503.
42. Lim, S, Koh, T, Tan, K, . . . Borys. (2014). A randomised trial to evaluate the immunogenicity, reactogenicity, and safety of the 10-valent pneumococcal non-typeable Haemophilus influenzae protein D conjugate vaccine (PHiD-CV) co-administered with routine childhood vaccines in Singapore and Malaysia. BMC Infectious Diseases, 14(1).
43. Lalwani, Chatterjee, Chhatwal, Verghese, P, Mehta, . . . Schuerman. (2012). Immunogenicity, safety, and reactogenicity of the 10-valent pneumococcal non-typeable Hemophilus influenzae protein D conjugate vaccine (PHiD-CV) when co-administered with the DTPw-HBV/Hib vaccine in Indian infants: A single-blind, randomized, controlled study. Human Vaccines and Immunotherapeutics, 8(5), 612-622.
44. Lalwani, Chatterjee, Chhatwal, Simon, Ravula, Francois, . . . Borys. (2014). Randomized, open-label study of the impact of age on booster responses to the 10-valent pneumococcal nontypeable Haemophilus influenzae protein D conjugate vaccine in children in India. Clinical and Vaccine Immunology, 21(9), 1292-1300.
45. Lagos, M, Muñoz, E, Levine, M, . . . Schuerman. (2011). Safety and immunogenicity of the 10-valent pneumococcal nontypeable Haemophilus influenzae protein D conjugate vaccine (PHiD-CV) in Chilean children. Human Vaccines, 7(5), 511-522.
46. Ladhani, N, Andrews, J, Southern, Jones, . . . Miller. (2015). Antibody Responses After Primary Immunization in Infants Born to Women Receiving a Pertussis-containing Vaccine During Pregnancy: Single Arm Observational Study With a Historical Comparator. Clin Infect Dis.
47. Knuf, Pankow, Culot, Grunert, Rapp, Panzer, . . . Schuerman. (2012). Induction of immunologic memory following primary vaccination with the 10-valent pneumococcal nontypeable haemophilus influenzae protein D conjugate vaccine in infants. Pediatric Infectious Disease Journal, 31(1), e31-e36.
48. Kim, S, Shin, H, Lee, J, . . . A. (2013). Immunogenicity and safety of 13-valent pneumococcal conjugate vaccine given to Korean children receiving routine pediatric vaccines. Pediatric Infectious Disease Journal, 32(3), 266-273.
49. Kim, H, Kim, S, Cha, H, . . . H. (2011). Response to primary and booster vaccination with 10-valent pneumococcal nontypeable haemophilus influenzae protein D conjugate vaccine in Korean infants. Pediatric Infectious Disease Journal, 30(12), e235-e243.
50. Kieninger, M, Kueper, Steul, Juergens, Ahlers, . . . A. (2010). Safety, tolerability, and immunologic noninferiority of a 13-valent pneumococcal conjugate vaccine compared to a 7-valent pneumococcal conjugate vaccine given with routine pediatric vaccinations in Germany. Vaccine, 28(25), 4192-4203.
51. Juergens, Patterson, Trammel, Greenberg, Givon, Lavi, . . . Dagan. (2014). Post hoc analysis of a randomized double-blind trial of the correlation of functional and binding antibody responses elicited by 13-valent and 7-valent pneumococcal conjugate vaccines and association with nasopharyngeal colonization. Clinical and Vaccine Immunology, 21(9), 1277-1281.
52. Iwata, Kawamura, Kuroki, Tokoeda, Miyazu, Iwai, . . . Borys. (2015). Immunogenicity and safety of the 10-valent pneumococcal nontypeable Haemophilus influenzae protein D conjugate vaccine (PHiD-CV) co-administered with DTPa vaccine in Japanese children: A randomized, controlled study. Hum Vaccin Immunother, 11(4), 826-837.
53. Huang, M, Lin, Y, & Juergens. (2012). Immunogenicity and safety of a 13-valent pneumococcal conjugate vaccine given with routine pediatric vaccines in Taiwan. Vaccine, 30(12), 2054-2059.
54. Hamaluba, Kandasamy, Upreti, R, Subedi, R, . . . J. (2015). Comparison of two-dose priming plus 9-month booster with a standard three-dose priming schedule for a ten-valent pneumococcal conjugate vaccine in Nepalese infants: A randomised, controlled, open-label, non-inferiority trial. The Lancet Infectious Diseases, 15(4), 405-414.
55. Grimprel, Laudat, Patterson, Baker, A, Sidhu, . . . A. (2011). Immunogenicity and safety of a 13-valent pneumococcal conjugate vaccine (PCV13) when given as a toddler dose to children immunized with PCV7 as infants. Vaccine, 29(52), 9675-9683.
56. Grant, R, O'Brien, E, Burbidge, Haston, . . . Goldblatt. (2013). Comparative Immunogenicity of 7 and 13-Valent Pneumococcal Conjugate Vaccines and the Development of Functional Antibodies to Cross-Reactive Serotypes. PLoS One, 8(9).
57. Gadzinowski, Tansey, P, Wysocki, Kopińska, Majda, . . . A. (2015). Safety and immunogenicity of a 13-valent pneumococcal conjugate vaccine manufactured with and without polysorbate 80 given to healthy infants at 2, 3, 4 and 12 months of age. Journal of Pediatric Infectious Diseases, 34(2), 180-185.
58. Gadzinowski, Albrecht, Hasiec, Konior, Dziduch, Witor, . . . A. (2011). Phase 3 trial evaluating the immunogenicity, safety, and tolerability of manufacturing scale 13-valent pneumococcal conjugate vaccine. Vaccine, 29(16), 2947-2955.
59. Esposito, Tansey, Thompson, Razmpour, Liang, Jones, . . . Principi. (2010). Safety and immunogenicity of a 13-valent pneumococcal conjugate vaccine compared to those of a 7-valent pneumococcal conjugate vaccine given as a three-dose series with routine vaccines in healthy infants and toddlers. Clinical and Vaccine Immunology, 17(6), 1017-1026.
60. Diez, Domingo, Gurtman, Bernaola, Gimenez, Sanchez, . . . A. (2013). Evaluation of 13-valent pneumococcal conjugate vaccine and concomitant meningococcal group C conjugate vaccine in healthy infants and toddlers in Spain. Vaccine, 31(46), 5486-5494.
61. Dicko, Santara, Mahamar, Sidibe, Barry, Dicko, . . . Schuerman. (2013). Safety, reactogenicity and immunogenicity of a booster dose of the 10-valent pneumococcal non-typeable Haemophilus influenzae protein D conjugate vaccine (PHiD-CV) in Malian children. Human Vaccines and Immunotherapeutics, 9(2), 382-388.
62. Dicko, Odusanya, O, Diallo, I, Santara, . . . Schuerman. (2011). Primary vaccination with the 10-valent pneumococcal non-typeable Haemophilus influenzae protein D conjugate vaccine (PHiD-CV) in infants in Mali and Nigeria: a randomized controlled trial. BMC public health, 11, 882.
63. Dagan, Patterson, Juergens, Greenberg, Givon, Lavi, . . . A. (2013). Comparative immunogenicity and efficacy of 13-valent and 7-valent pneumococcal conjugate vaccines in reducing nasopharyngeal colonization: A randomized double-blind trial. Clinical Infectious Diseases, 57(7), 952-962.
64. Bryant, A, Block, L, Baker, A, . . . A. (2010). Safety and immunogenicity of a 13-valent pneumococcal conjugate vaccine. Pediatrics, 125(5), 866-875.
65. Brito, G, Thompson, Girgenti, Giardina, C, . . . A. (2013). Immunogenicity and safety of 13-valent pneumococcal conjugate vaccine in Mexico. Revista Panamericana de Salud Publica/Pan American Journal of Public Health, 33(6), 414-421.
66. Block, S. L., Shepard, J., Garfield, H., Xie, F., Han, L., Dull, P. M., & Smolenov, I. (2015). Immunogenicity and Safety of a 3- and 4-dose Vaccination Series of a Meningococcal ACWY Conjugate Vaccine in Infants: Results of a Phase 3b, Randomized, Open-label Trial. Pediatr Infect Dis J, 35(2), e48-59.

67. Bermal, Szenborn, Alberto, Hernandez, Pejcz, Majda, . . . Schuerman. (2011). 2367_Poland_Safety and immunogenicity of a booster dose of the 10-valent pneumococcal nontypeable haemophilus influenzae protein D conjugate vaccine coadministered with DTPW-HBV/HIB and poliovirus vaccines. Pediatric Infectious Disease Journal, 30(1), 69-72.
68. Bermal, Szenborn, Alberto, Hernandez, Pejcz, Majda, . . . Schuerman. (2011). Philippines_ Safety and immunogenicity of a booster dose of the 10-valent pneumococcal nontypeable haemophilus influenzae protein D conjugate vaccine coadministered with DTPW-HBV/HIB and poliovirus vaccines. Pediatric Infectious Disease Journal, 30(1), 69-72.
69. Balloch, A., Vo, D. T. T., Pham, H. T., Huynh, T. P., Them, L. N., Phan, T. V., . . . Mulholland, E. K. (2016). THE EFFECT OF TIMING ON THE RESPONSE OF TWO PCV10 DOSES AT 2 & 4 MONTHS OR 2 & 6 MONTHS OF AGE. ISPPD-10.
70. Balloch, A., Vo, D. T. T., Pham, H. T., Huynh, T. P., Lac, N. T., Phan, T. V., . . . Mulholland, E. (2016). IMMUNOGENICITY OF 1, 2 OR 3 DOSES OF PCV10 AT 4 WEEKS POST PRIMARY SERIES AND 6 MONTHS OF AGE. ISPPD-10.
71. Andrews, J, Waight, A, Burbidge, Pearce, . . . Goldblatt. (2014). Serotype-specific effectiveness and correlates of protection for the 13-valent pneumococcal conjugate vaccine: A postlicensure indirect cohort study. The Lancet Infectious Diseases, 14(9), 839-846.
72. Amdekar, K, Lalwani, K, Bavdekar, Balasubramanian, . . . A. (2012). Immunogenicity and safety of a 13-valent pneumococcal conjugate vaccine in healthy infants and toddlers given with routine vaccines in India. Pediatric Infectious Disease Journal.
73. Falup-Pecurariu, O.,Man… Borys, D. (2016). Effects of prophylactic ibuprofen and paracetamol administration on the immunogenicity and reactogenicity of the 10-valent pneumococcal non-typeable Haemophilus influenzae protein D conjugated vaccine (PHiD-CV) co-administered with DTPa-combined vaccines in children: An open-label, randomized, controlled, non-inferiority trial. Hum Vaccines.
74. JC Moïsi, S Yaro … Gessner. (2016). Immunogenicity and reactogenicity of 13-valent pneumococcal conjugate vaccine among infants, toddlers and children in Western Burkina Faso.

Table 2: Effectiveness and impact of PCV10 or PCV13 (WHO prequalified PCV products) in currently recommended dosing schedules

Population:

Vaccinated children; unvaccinated older children and adults.

Interventions Compared:

PCV10 administration in infants <2 years of age using either WHO recommended dosing schedules (2p+1 or 3p+0)
VS:
PCV13 administration in infants <2 years of age using either WHO recommended dosing schedules (2p+1 or 3p+0)

Outcomes:

IgG response – mean GMC and percent responders in immunized infants for vaccine- serotypes (VT)

Mortality – vaccine effectiveness and/or change in mortality rates, pre/post vaccination, for all-cause mortality, pneumonia mortality, and IPD mortality for directly immunized and unimmunized populations through indirect effects; change in case fatality ratios, pre/post vaccination, for pneumonia and IPD.

Invasive Pneumococcal Disease (IPD) – vaccine effectiveness and/or change in incidence of VT or serotype specific IPD pre/post vaccination among directly immunized and unimmunized populations through indirect effects.

Pneumonia – vaccine effectiveness and/or change in incidence, pre/post vaccination, of either clinical pneumonia or chest x-ray (CXR) confirmed pneumonia among directly immunized and unimmunized populations through indirect effects

Carriage – vaccine effectiveness and/or change in incidence, pre/post vaccination, of vaccine type or serotype specific pneumococcal carriage among directly immunized and unimmunized populations through indirect effects

PICO Question: Is the impact or effectiveness of PCV10 and PCV13 (using either WHO recommended dosing schedules) different, based on data reporting immune response following vaccination, and impact on NP Carriage and clinical outcomes (IPD, pneumonia and mortality) in vaccinated children as well as unvaccinated age groups through indirect protection?				
			Rating	Adjustment to rating
Quality Assessment Factors	No of studies/starting rating		55 out of 74 included studies are RCTs: rating 4	4
	Factors decreasing confidence	Limitation in study design	None serious	0
		Inconsistency	None serious	0
		Indirectness	Serious[1]	- 1
		Imprecision	None serious	0
		Publication bias	None serious	0
	Factors increasing confidence	Strength of association	None serious	0
		Dose-response	None serious	0
		Mitigated bias and confounding	None serious	0
	Final numerical rating of quality of evidence			**3**
Summary of Findings	**Statement on quality of evidence**			**Evidence supports a moderate level of confidence that the true effect lies close to that of the estimate of the effect on the health outcome.**
	Conclusion			**We are moderately confident that PCV10 elicits a comparable immune response to PCV13 for the shared serotypes in the general population.**

[1]Most studies are not head-to-head comparisons of PCV10 and PCV13 so the evidence is indirect and inter-study comparisons were the primary source of information. Studies included in the product choice analysis were:
- 5 studies with head to head PCV10 vs PCV13 data: rating 4
- 69 studies with non head-to-head data for PCV10 or PCV13: rating 3

References:

1. Zhu, FengCai, Hu, YueMei, Li, JingXin, . . . A. (2016). Immunogenicity and safety of 13-valent pneumococcal conjugate vaccine compared with 7-valent pneumococcal conjugate vaccine among healthy infants in China. Pediatric Infectious Disease Journal, 35(9), 999-1010.
2. Yeh, H, Gurtman, Hurley, C, Block, . . . A. (2010). Immunogenicity and safety of 13-Valent pneumococcal conjugate vaccine in infants and toddlers. Pediatrics, 126(3), e493-e505.
3. Wysocki, J, Tejedor, J, C., Grunert, D, . . . L. (2009). Immunogenicity of the 10-valent pneumococcal non-typeable Haemophilus influenzae protein D conjugate vaccine (PHiD-CV) when coadministered with different neisseria meningitidis serogroup C conjugate vaccines. Pediatr Infect Dis J, 28(4 Suppl), S77-88. doi:10.1097/INF.0b013e318199f609.
4. Wijmenga-Monsuur, A. J., Westen, E. v., Knol, M. J., Jongerius, R. M., Zancolli, M., Goldblatt, D., . . . Rots, N. Y. (2015). Direct Comparison of Immunogenicity Induced by 10- or 13-Valent Pneumococcal Conjugate Vaccine around the 11-Month Booster in Dutch Infants. PLoS One, 10(12), e0144739.

5. Weckx, Y, Thompson, Berezin, N, Faria, . . . A. (2012). A phase 3, randomized, double-blind trial comparing the safety and immunogenicity of the 7-valent and 13-valent pneumococcal conjugate vaccines, given with routine pediatric vaccinations, in healthy infants in Brazil. Vaccine, 30(52), 7566-7572.
6. W.Pomat, S. W. (2014). ACCELERATED SCHEDULE OF 10- AND 13-VALENT PNEUMOCOCCAL CONJUGATE VACCINE IS SAFE AND IMMUNOGENIC IN INFANTS IN PAPUA NEW GUINEA. ISPPD-9, 3, 114.
7. Vesikari, T., Forsten, A., Seppa, I., Kaijalainen, T., Puumalainen, T., Soininen, A., . . . Schuerman, L. (2016). Effectiveness of the 10-Valent Pneumococcal Nontypeable Haemophilus influenzae Protein D-Conjugated Vaccine (PHiD-CV) Against Carriage and Acute Otitis Media-A Double-Blind Randomized Clinical Trial in Finland. J Pediatric Infect Dis Soc.
8. Vesikari, T, Wysocki, J, Chevallier, B, . . . L. (2009). Immunogenicity of the 10-valent pneumococcal non-typeable Haemophilus influenzae protein D conjugate vaccine (PHiD-CV) compared to the licensed 7vCRM vaccine. Pediatr Infect Dis J, 28(4 Suppl), S66-76. doi:10.1097/INF.0b013e318199f8ef.
9. Vesikari, Karvonen, Lindblad, Korhonen, Lommel, Willems, . . . Schuerman. (2010). Safety and immunogenicity of a booster dose of the 10-valent pneumococcal nontypeable haemophilus influenzae protein D conjugate vaccine coadministered with measles-mumps-rubella-varicella vaccine in children aged 12 to 16 months. Pediatric Infectious Disease Journal, 29(6), e47-e56.
10. Vesikari, Karvonen, Korhonen, Karppa, Sadeharju, Fanic, . . . Schuerman. (2011). Immunogenicity of 10-valent pneumococcal nontypeable haemophilus influenzae protein D conjugate vaccine when administered as catch-up vaccination to children 7 months to 5 years of age. Pediatric Infectious Disease Journal, 30(8), e130-e141.
11. Verhagen, M, Rivera, Olivero, A, Hermsen, . . . H. (2016). Introduction of the 13-valent pneumococcal conjugate vaccine in an isolated pneumococcal vaccine-naïve indigenous population. European Respiratory Journal, 48(5), 1492-1496.
12. Vanderkooi, G, Scheifele, W, Girgenti, Halperin, . . . D. (2012). Safety and immunogenicity of a 13-valent pneumococcal conjugate vaccine in healthy infants and toddlers given with routine pediatric vaccinations in Canada. Pediatric Infectious Disease Journal, 31(1), 72-77.
13. Van, D., Bergh, R, Spijkerman, François, Swinnen, . . . M. (2011). Immunogenicity, safety, and reactogenicity of the 10-valent pneumococcal nontypeable haemophilus influenzae protein D conjugate vaccine and DTPa-IPV-Hib when coadministered as a 3-dose primary vaccination schedule in the Netherlands: A randomized controlled trial. Pediatric Infectious Disease Journal, 30(9), e170-e178.
14. van, d., Bergh, R, Spijkerman, Francois, Swinnen, . . . A. (2016). Immunogenicity, Safety and Reactogenicity of a Booster Dose of the 10-Valent Pneumococcal Nontypeable H. influenzae Protein D Conjugate Vaccine Coadministered With DTPa-IPV-Hib in Dutch Children: A Randomized Controlled Trial. Pediatr Infect Dis J, 35(7), e206-219.
15. Van, Westen, Wijmenga, Monsuur, J, Van, . . . M. (2015). Differential B-Cell Memory Around the 11-Month Booster in Children Vaccinated with a 10- or 13-Valent Pneumococcal Conjugate Vaccine. Clinical Infectious Diseases, 61(3), 342-349.
16. Trück, Mitchell, Jawad, Clutterbuck, A, Snape, . . . J. (2016). Divergent Memory B Cell Responses in a Mixed Infant Pneumococcal Conjugate Vaccine Schedule. Pediatric Infectious Disease Journal.
17. Truck, Jawad, Goldblatt, Roalfe, Snape, D, . . . J. (2016). The antibody response following a booster with either a 10- or 13-valent pneumococcal conjugate vaccine in toddlers primed with a 13-valent pneumococcal conjugate vaccine in early infancy. Pediatric Infectious Disease Journal, 35(7), 787-793.
18. Tregnaghi, W, Sáez, Llorens, López, Abate, . . . Schuerman. (2014). 451_PanamaArgentina_Efficacy of Pneumococcal Nontypable Haemophilus influenzae Protein D Conjugate Vaccine (PHiD-CV) in Young Latin American Children: A Double-Blind Randomized Controlled Trial. PLoS Medicine, 11(6), 1-18.
19. Togashi, Yamaji, Thompson, Giardina, C, Aizawa, . . . A. (2013). Immunogenicity and safety of a 13-valent pneumococcal conjugate vaccine in healthy infants in Japan. Pediatric Infectious Disease Journal, 32(9), 984-989.
20. Timo. (2010). Immunogenicity of the 10-valent pneumococcal non-typeable Haemophilus influenzae Protein D Conjugate Vaccine (PHiD-CV). Cocuk Enfeksiyon Dergisi, 4(SUPPL. 1), 9-15.
21. Temple, B., Vo, D. T. T., Balloch, A., Smith-Vaughan, H., Pham, H. T., Huynh, T. P., . . . Mulholland, K. (2016). HEAD-TO-HEAD COMPARISON OF PCV10 AND PCV13: POST-PRIMARY SERIES IMMUNOGENICITY AND IMPACT ON NASOPHARYNGEAL CARRIAGE AT 12 MONTHS OF AGE. ISPPD-10.
22. Spijkerman, Veenhoven, H, Wijmenga, Monsuur, J, . . . M. (2013). Immunogenicity of 13-valent pneumococcal conjugate vaccine administered according to 4 different primary immunization schedules in infants a randomized clinical trial. JAMA - Journal of the American Medical Association, 310(9), 930-937.
23. Snape, D, Klinger, L, Daniels, D, . . . J. (2010). Immunogenicity and reactogenicity of a 13-valent-pneumococcal conjugate vaccine administered at 2, 4, and 12 months of age: A double-blind randomized active-controlled trial. Pediatric Infectious Disease Journal, 29(12), e80-e90.
24. Singleton, Wenger, Klejka, A, Bulkow, R, . . . A. (2013). The 13-valent pneumococcal conjugate vaccine for invasive pneumococcal disease in alaska native children: Results of a clinical trial. Pediatric Infectious Disease Journal, 32(3), 257-263.
25. Silfverdal, S, A., Hogh, B, Bergsaker, M, R., . . . L. (2009). Immunogenicity of a 2-dose priming and booster vaccination with the 10-valent pneumococcal nontypeable Haemophilus influenzae protein D conjugate vaccine. Pediatr Infect Dis J, 28(10), e276-282. doi:10.1097/INF.0b013e3181b48ca3.
26. Ruiz, Palacios, M, Huang, M, Lin, . . . M. (2013). 798_Taiwan_Immunogenicity and safety of a booster dose of the 10-valent pneumococcal haemophilus influenzae protein D conjugate vaccine coadministered with the tetravalent meningococcal serogroups A, C, W-135 and y tetanus toxoid conjugate vaccine in toddlers: A randomized trial. Pediatric Infectious Disease Journal, 32(1), 62-71.
27. Ruiz, Palacios, M, Huang, M, Lin, . . . M. (2013). 798_Mexico_Immunogenicity and safety of a booster dose of the 10-valent pneumococcal haemophilus influenzae protein D conjugate vaccine coadministered with the tetravalent meningococcal serogroups A, C, W-135 and y tetanus toxoid conjugate vaccine in toddlers: A randomized trial. Pediatric Infectious Disease Journal, 32(1), 62-71.
28. Ruiz, Palacios, M, Guerrero, L, Hernández, . . . Schuerman. (2011). Immunogenicity, reactogenicity and safety of the 10-valent pneumococcal nontypeable Haemophilus influenzae protein D conjugate vaccine (PHiD-CV) in Mexican infants. Human Vaccines, 7(11), 1137-1145.
29. Pomat, W., Richmond, P., Francis, J., Wana, S., Solomon, V., Ford, R., . . . Lehmann, D. (2016). IMMUNOGENICITY OF 10-VALENT AND 13-VALENT PNEUMOCOCCAL CONJUGATE VACCINES GIVEN AT 1-2-3 MONTHS OF AGE IN PAPUA NEW GUINEAN INFANTS: A RANDOMISED CONTROLLED TRIAL. ISPPD-10.
30. Phan, T. V., Licciardi, P. V., Toh, Z. Q., Balloch, A., Vu, P. H. N., Vien, K. T., . . . Mulholland, E. K. (2016). IMMUNOGENICITY AND MEMORY B CELL RESPONSE FOLLOWING ALTERNATIVE PNEUMOCOCCAL VACCINATION STRATEGIES IN VIETNAM. ISPPD-10.
31. Payton, Girgenti, Frenck, W, Patterson, Love, . . . A. (2013). Immunogenicity, safety and tolerability of 3 lots of 13-valent pneumococcal conjugate vaccine given with routine pediatric vaccinations in the United States. Pediatric Infectious Disease Journal, 32(8), 871-880.
32. Odusanya, O, Kuyinu, A, Kehinde, A, . . . Schuerman. (2014). Safety and immunogenicity of 10-valent pneumococcal nontypeable Haemophilus influenzae protein D conjugate vaccine (PHiD-CV) in Nigerian children: Booster dose and 2-dose catch-up regimens in the second year of life. Human Vaccines and Immunotherapeutics, 10(3), 757-766.
33. Odusanya, O, Kuyinu, A, Kehinde, A, . . . Schuerman. (2013). Immunogenicity, safety and reactogenicity of the 10-valent pneumococcal non-typeable haemophilus influenzae protein D conjugate vaccine (PHiD-CV) in Nigerian Infants: a randomised trial. The Nigerian postgraduate medical journal, 20(4), 272-281.
34. Martinón, Torres, Wysocki, Center, J, Czajka, . . . Gurtman. (2016). Circulating Antibody 1 and 2 Years After Vaccination With the 13-Valent Pneumococcal Conjugate Vaccine in Preterm Compared with Term Infants. Pediatric Infectious Disease Journal.
35. Martinón, Torres, Gimenez, Sanchez, Gurtman, Bernaola, . . . A. (2012). 13-valent pneumococcal conjugate vaccine given with meningococcal C-tetanus toxoid conjugate and other routine pediatric vaccinations: Immunogenicity and safety. Pediatric Infectious Disease Journal, 31(4), 392-399.
36. Martinón, Torres, Czajka, Center, J, Wysocki, . . . Gurtman. (2015). 13-Valent pneumococcal conjugate vaccine (PCV13) in preterm versus term infants. Pediatrics, 135(4), e876-e886.

37. Martinon, Torres, Czajka, Center, J, Wysocki, . . . Gurtman. (2015). 13-Valent pneumococcal conjugate vaccine (PCV13) in preterm versus term infants. Pediatrics, 135(4), e876-e886.
38. Martinez, R. P. A. C. (2014). IMMUNOGENICITY AND SAFETY OF 11- AND 12-VALENT PNEUMOCOCCAL NON-TYPEABLE HAEMOPHILUS INFLUENZAE PROTEIN D-CONJUGATE VACCINES (11VPHID-CV, 12VPHID-CV) IN INFANTS: PHASE-II STUDY. ISPPD-9, 3, 115.
39. M.R, Swinnen, K., François, N., Borys, D., Schuerman, L., Veenhoven, R. H., & Sanders, E. A. M. (2012). IMMUNOGENICITY OF A BOOSTER DOSE OF 10-VALENT PNEUMOCOCCAL NONTYPEABLE HAEMOPHILUS INFLUENZAE PROTEIN D-CONJUGATE VACCINE (PHID-CV) IN DUTCH CHILDREN. ISPPD 2012, 614.
40. M.Horn, G. B. (2014). SAFETY AND IMMUNOGENICITY OF AN INVESTIGATIONAL 12-VALENT PNEUMOCOCCAL NON-TYPEABLE HAEMOPHILUS INFLUENZAE PROTEIN D CONJUGATE VACCINE IN TODDLERS: PHASE I STUDY. ISPPD-9, 3, 110.
41. Lin, Y, Lu, Y, Chang, Y, . . . M. (2012). Immunogenicity and safety of 10-valent pneumococcal non-typeable Haemophilus influenzae protein D-conjugate vaccine (PHiD-CV) co-administered with routine childhood vaccines in Taiwan. Journal of the Formosan Medical Association, 111(9), 495-503.
42. Lim, S, Koh, T, Tan, K, . . . Borys. (2014). A randomised trial to evaluate the immunogenicity, reactogenicity, and safety of the 10-valent pneumococcal non-typeable Haemophilus influenzae protein D conjugate vaccine (PHiD-CV) co-administered with routine childhood vaccines in Singapore and Malaysia. BMC Infectious Diseases, 14(1).
43. Lalwani, Chatterjee, Chhatwal, Verghese, P, Mehta, . . . Schuerman. (2012). Immunogenicity, safety, and reactogenicity of the 10-valent pneumococcal non-typeable Hemophilus influenzae protein D conjugate vaccine (PHiD-CV) when co-administered with the DTPw-HBV/Hib vaccine in Indian infants: A single-blind, randomized, controlled study. Human Vaccines and Immunotherapeutics, 8(5), 612-622.
44. Lalwani, Chatterjee, Chhatwal, Simon, Ravula, Francois, . . . Borys. (2014). Randomized, open-label study of the impact of age on booster responses to the 10-valent pneumococcal nontypeable Haemophilus influenzae protein D conjugate vaccine in children in India. Clinical and Vaccine Immunology, 21(9), 1292-1300.
45. Lagos, M, Muñoz, E, Levine, M, . . . Schuerman. (2011). Safety and immunogenicity of the 10-valent pneumococcal nontypeable Haemophilus influenzae protein D conjugate vaccine (PHiD-CV) in Chilean children. Human Vaccines, 7(5), 511-522.
46. Ladhani, N, Andrews, J, Southern, Jones, . . . Miller. (2015). Antibody Responses After Primary Immunization in Infants Born to Women Receiving a Pertussis-containing Vaccine During Pregnancy: Single Arm Observational Study With a Historical Comparator. Clin Infect Dis.
47. Knuf, Pankow, Culot, Grunert, Rapp, Panzer, . . . Schuerman. (2012). Induction of immunologic memory following primary vaccination with the 10-valent pneumococcal nontypeable haemophilus influenzae protein D conjugate vaccine in infants. Pediatric Infectious Disease Journal, 31(1), e31-e36.
48. Kim, S, Shin, H, Lee, J, . . . A. (2013). Immunogenicity and safety of 13-valent pneumococcal conjugate vaccine given to Korean children receiving routine pediatric vaccines. Pediatric Infectious Disease Journal, 32(3), 266-273.
49. Kim, H, Kim, S, Cha, H, . . . H. (2011). Response to primary and booster vaccination with 10-valent pneumococcal nontypeable haemophilus influenzae protein D conjugate vaccine in Korean infants. Pediatric Infectious Disease Journal, 30(12), e235-e243.
50. Kieninger, M, Kueper, Steul, Juergens, Ahlers, . . . A. (2010). Safety, tolerability, and immunologic noninferiority of a 13-valent pneumococcal conjugate vaccine compared to a 7-valent pneumococcal conjugate vaccine given with routine pediatric vaccinations in Germany. Vaccine, 28(25), 4192-4203.
51. Juergens, Patterson, Trammel, Greenberg, Givon, Lavi, . . . Dagan. (2014). Post hoc analysis of a randomized double-blind trial of the correlation of functional and binding antibody responses elicited by 13-valent and 7-valent pneumococcal conjugate vaccines and association with nasopharyngeal colonization. Clinical and Vaccine Immunology, 21(9), 1277-1281.
52. Iwata, Kawamura, Kuroki, Tokoeda, Miyazu, Iwai, . . . Borys. (2015). Immunogenicity and safety of the 10-valent pneumococcal nontypeable Haemophilus influenzae protein D conjugate vaccine (PHiD-CV) co-administered with DTPa vaccine in Japanese children: A randomized, controlled study. Hum Vaccin Immunother, 11(4), 826-837.
53. Huang, M, Lin, Y, & Juergens. (2012). Immunogenicity and safety of a 13-valent pneumococcal conjugate vaccine given with routine pediatric vaccines in Taiwan. Vaccine, 30(12), 2054-2059.
54. Hamaluba, Kandasamy, Upreti, R, Subedi, R, . . . J. (2015). Comparison of two-dose priming plus 9-month booster with a standard three-dose priming schedule for a ten-valent pneumococcal conjugate vaccine in Nepalese infants: A randomised, controlled, open-label, non-inferiority trial. The Lancet Infectious Diseases, 15(4), 405-414.
55. Grimprel, Laudat, Patterson, Baker, A, Sidhu, . . . A. (2011). Immunogenicity and safety of a 13-valent pneumococcal conjugate vaccine (PCV13) when given as a toddler dose to children immunized with PCV7 as infants. Vaccine, 29(52), 9675-9683.
56. Grant, R, O'Brien, E, Burbidge, Haston, . . . Goldblatt. (2013). Comparative Immunogenicity of 7 and 13-Valent Pneumococcal Conjugate Vaccines and the Development of Functional Antibodies to Cross-Reactive Serotypes. PLoS One, 8(9).
57. Gadzinowski, Tansey, P, Wysocki, Kopińska, Majda, . . . A. (2015). Safety and immunogenicity of a 13-valent pneumococcal conjugate vaccine manufactured with and without polysorbate 80 given to healthy infants at 2, 3, 4 and 12 months of age. Journal of Pediatric Infectious Diseases, 34(2), 180-185.
58. Gadzinowski, Albrecht, Hasiec, Konior, Dziduch, Witor, . . . A. (2011). Phase 3 trial evaluating the immunogenicity, safety, and tolerability of manufacturing scale 13-valent pneumococcal conjugate vaccine. Vaccine, 29(16), 2947-2955.
59. Esposito, Tansey, Thompson, Razmpour, Liang, Jones, . . . Principi. (2010). Safety and immunogenicity of a 13-valent pneumococcal conjugate vaccine compared to those of a 7-valent pneumococcal conjugate vaccine given as a three-dose series with routine vaccines in healthy infants and toddlers. Clinical and Vaccine Immunology, 17(6), 1017-1026.
60. Diez, Domingo, Gurtman, Bernaola, Gimenez, Sanchez, . . . A. (2013). Evaluation of 13-valent pneumococcal conjugate vaccine and concomitant meningococcal group C conjugate vaccine in healthy infants and toddlers in Spain. Vaccine, 31(46), 5486-5494.
61. Dicko, Santara, Mahamar, Sidibe, Barry, Dicko, . . . Schuerman. (2013). Safety, reactogenicity and immunogenicity of a booster dose of the 10-valent pneumococcal non-typeable Haemophilus influenzae protein D conjugate vaccine (PHiD-CV) in Malian children. Human Vaccines and Immunotherapeutics, 9(2), 382-388.
62. Dicko, Odusanya, O, Diallo, I, Santara, . . . Schuerman. (2011). Primary vaccination with the 10-valent pneumococcal non-typeable Haemophilus influenzae protein D conjugate vaccine (PHiD-CV) in infants in Mali and Nigeria: a randomized controlled trial. BMC public health, 11, 882.
63. Dagan, Patterson, Juergens, Greenberg, Givon, Lavi, . . . A. (2013). Comparative immunogenicity and efficacy of 13-valent and 7-valent pneumococcal conjugate vaccines in reducing nasopharyngeal colonization: A randomized double-blind trial. Clinical Infectious Diseases, 57(7), 952-962.
64. Bryant, A, Block, L, Baker, A, . . . A. (2010). Safety and immunogenicity of a 13-valent pneumococcal conjugate vaccine. Pediatrics, 125(5), 866-875.
65. Brito, G, Thompson, Girgenti, Giardina, C, . . . A. (2013). Immunogenicity and safety of 13-valent pneumococcal conjugate vaccine in Mexico. Revista Panamericana de Salud Publica/Pan American Journal of Public Health, 33(6), 414-421.
66. Block, S. L., Shepard, J., Garfield, H., Xie, F., Han, L., Dull, P. M., & Smolenov, I. (2015). Immunogenicity and Safety of a 3- and 4-dose Vaccination Series of a Meningococcal ACWY Conjugate Vaccine in Infants: Results of a Phase 3b, Randomized, Open-label Trial. Pediatr Infect Dis J, 35(2), e48-59.
67. Bermal, Szenborn, Alberto, Hernandez, Pejcz, Majda, . . . Schuerman. (2011). 2367_Poland_Safety and immunogenicity of a booster dose of the 10-valent pneumococcal nontypeable haemophilus influenzae protein D conjugate vaccine coadministered with DTPW-HBV/HIB and poliovirus vaccines. Pediatric Infectious Disease Journal, 30(1), 69-72.
68. Bermal, Szenborn, Alberto, Hernandez, Pejcz, Majda, . . . Schuerman. (2011). Philippines_ Safety and immunogenicity of a booster dose of the 10-valent pneumococcal nontypeable haemophilus influenzae protein D conjugate vaccine coadministered with DTPW-HBV/HIB and poliovirus vaccines. Pediatric Infectious Disease Journal, 30(1), 69-72.

69. Balloch, A., Vo, D. T. T., Pham, H. T., Huynh, T. P., Them, L. N., Phan, T. V., . . . Mulholland, E. K. (2016). THE EFFECT OF TIMING ON THE RESPONSE OF TWO PCV10 DOSES AT 2 & 4 MONTHS OR 2 & 6 MONTHS OF AGE. ISPPD-10.
70. Balloch, A., Vo, D. T. T., Pham, H. T., Huynh, T. P., Lac, N. T., Phan, T. V., . . . Mulholland, E. (2016). IMMUNOGENICITY OF 1, 2 OR 3 DOSES OF PCV10 AT 4 WEEKS POST PRIMARY SERIES AND 6 MONTHS OF AGE. ISPPD-10.
71. Andrews, J, Waight, A, Burbidge, Pearce, . . . Goldblatt. (2014). Serotype-specific effectiveness and correlates of protection for the 13-valent pneumococcal conjugate vaccine: A postlicensure indirect cohort study. The Lancet Infectious Diseases, 14(9), 839-846.
72. Amdekar, K, Lalwani, K, Bavdekar, Balasubramanian, . . . A. (2012). Immunogenicity and safety of a 13-valent pneumococcal conjugate vaccine in healthy infants and toddlers given with routine vaccines in India. Pediatric Infectious Disease Journal.
73. Falup-Pecurariu, O.,Man… Borys, D. (2016). Effects of prophylactic ibuprofen and paracetamol administration on the immunogenicity and reactogenicity of the 10-valent pneumococcal non-typeable Haemophilus influenzae protein D conjugated vaccine (PHiD-CV) co-administered with DTPa-combined vaccines in children: An open-label, randomized, controlled, non-inferiority trial. Hum Vaccines.
74. JC Moïsi, S Yaro … Gessner. (2016). Immunogenicity and reactogenicity of 13-valent pneumococcal conjugate vaccine among infants, toddlers and children in Western Burkina Faso.

Table 1: Effectiveness and impact of different dosing schedules of WHO prequalified Pneumococcal Conjugate Vaccine (PCV) products

Population:

Vaccinated children; unvaccinated older children and adults

Interventions Compared:

2 primary doses before 6 months of age and 1 booster dose at 9 months of age or later (2p+1) in infants <2 years of age with WHO prequalified PCV products

VS.

3 primary doses before 9 months of age without a booster dose (3p+0) in infants <2 years of age with WHO prequalified PCV products

Outcomes:

IgG response – mean GMC and percent responders in immunized infants for vaccine- serotypes (VT)

Mortality – vaccine effectiveness and/or change in mortality rates, pre/post vaccination, for all-cause mortality, pneumonia mortality, and IPD mortality for directly immunized and unimmunized populations through indirect effects; change in case fatality ratios, pre/post vaccination, for pneumonia and IPD.

Invasive Pneumococcal Disease (IPD) – vaccine effectiveness and/or change in incidence of VT or serotype specific IPD pre/post vaccination among directly immunized and unimmunized populations through indirect effects.

Pneumonia – vaccine effectiveness and/or change in incidence, pre/post vaccination, of either clinical pneumonia or chest x-ray (CXR) confirmed pneumonia among directly immunized and unimmunized populations through indirect effects

Carriage – vaccine effectiveness and/or change in incidence, pre/post vaccination, of vaccine type or serotype specific pneumococcal carriage among directly immunized and unimmunized populations through indirect effects

PICO Question: How does PCV administered to healthy children in a 2p+1 schedule compare with the vaccine administered in a 3p+0 schedule, with respect to immune response in vaccinated children and impact on clinical outcomes (IPD, pneumonia, and mortality), and nasopharyngeal carriage in the vaccinated children as well as unvaccinated age groups through indirect protection?				
			Rating	Adjustment to rating
Quality Assessment Factors	No of studies/starting rating		41 observational studies	2
	Factors decreasing confidence	Limitation in study design	None serious	0
		Inconsistency	None serious	0
		Indirectness	Serious[1]	-1
		Imprecision	Serious[2]	-1
		Publication bias	Not assessed	0
	Factors increasing confidence	Strength of association	None serious[3]	0
		Dose-response	Not applicable	0
		Mitigated bias and confounding	Not applicable	0
	Final numerical rating of quality of evidence			**1**
Summary of Findings	**Statement on quality of evidence**			**Evidence supports a very low level of confidence that the true effect lies close to that of the estimate of the effect on the health outcome.**
	Conclusion			**We have a very low level of confidence in the ability of the available evidence to detect any differences in the overall effectiveness of a 2+1 dosing schedule compared to a 3+0 dosing schedule in the general population.**

[1]The review found no studies that made direct comparisons between 3-dose schedules (2p+1 or 3p+0). A single clinical trial (Palmu et al., 2016) used only one of the 2 schedules under consideration (2+1) and no RCTs with 3+0 schedule were available. Observational studies data were used to make between-study comparisons (downgraded evidence for indirectness as no head-to head studies available), each schedule was associated with strong direct and indirect effects on IPD

[2]The available evidence was highly heterogeneous therefore a meta-analysis was not conducted in order to provide a point estimate or confidence intervals

[3]The strength of association for direct comparisons between 3-dose schedules (2p+1 or 3p+0) could not be assessed but for each schedule, studies consistently found strong associations.

References:

1. Palmu, et al., *Effectiveness of the ten-valent pneumococcal Haemophilus influenzae protein D conjugate vaccine (PHiD-CV10) against invasive pneumococcal disease: A cluster randomised trial.* The Lancet, 2013. 381(9862): p. 214-222.
2. Palmu, A., et al., *LONG-TERM EFFECTIVENESS OF PNEUMOCOCCAL HAEMOPHILUS INFLUENZAE PROTEIN D CONJUGATE VACCINE (PHID-CV10) AGAINST CONFIRMED AND NON-CONFIRMED INVASIVE PNEUMOCOCCAL DISEASE (IPD) - FINIP TRIAL EXTENDED FOLLOW-UP.* ISPPD-10, 2016.

3. Deceuninck, et al., *Effectiveness of three pneumococcal conjugate vaccines to prevent invasive pneumococcal disease in Quebec, Canada.* Vaccine, 2015. **33**(23): p. 2684-2689.
4. H.Rinta-Kokko, K.A., *EFFECTIVENESS OF 10-VALENT PNEUMOCOCCAL CONJUGATE VACCINE (PCV10) AGAINST INVASIVE PNEUMOCOCCAL DISEASE (IPD) DURING ONGOING NATIONAL VACCINATION PROGRAMME (NVP) IN FINLAND.* ISPPD-9, 2014. **3**: p. 140.
5. Knol, M.J., et al., *VACCINE EFFECTIVENESS OF 10-VALENT PNEUMOCOCCAL CONJUGATE VACCINE AGAINST INVASIVE PNEUMOCOCCAL DISEASE: INDIRECT COHORT DESIGN.* ISPPD-10, 2016.
6. Ali, A., et al., *EFFECTIVENESS OF PCV-10 VACCINE AGAINST VACCINE TYPE IPD IN PAKISTAN: IMPACT ASSESSMENT AFTER INTRODUCTION OF PCV-10 IN ROUTINE IMMUNIZATION PROGRAMME.* ISPPD-10, 2016.
7. Verani, J.R., C.M. Domingues, and J.C. Moraes, *Indirect cohort analysis of 10-valent pneumococcal conjugate vaccine effectiveness against vaccine-type and vaccine-related invasive pneumococcal disease.* Vaccine, 2015. **33**(46): p. 6145-8.
8. De, et al., *Impact of 2+1 pneumococcal conjugate vaccine program in the province of Quebec, Canada.* Vaccine, 2014. **32**(13): p. 1501-1506.
9. Knol, M.J., et al., *Invasive Pneumococcal Disease 3 Years after Introduction of 10-Valent Pneumococcal Conjugate Vaccine, the Netherlands.* Emerg Infect Dis, 2015. **21**(11): p. 2040-4.
10. Rinta-Kokko, H., et al., *COMPARISON OF DIFFERENT STUDY DESIGNS OF THE ESTIMATION OF PCV10 EFFECTIVENESS AGAINST INVASIVE PNEUMOCOCCAL DISEASE (IPD) DURING NATIONAL VACCINATION PROGRAMME (NVP) IN FINLAND.* ISPPD-10, 2016.
11. Jokinen, J., et al., *MONITORING THE EFFECTIVENESS OF FINNISH NATIONAL VACCINATION PROGRAMME (NVP) OF THE 10-VALENT PNEUMOCOCCAL CONJUGATE VACCINE (PCV10).* ISPPD 2012, 2012: p. 196.
12. H.Erlendsd, A.H., *AN EARLY REDUCTION OF INVASIVE PNEUMOCOCCAL INFECTIONS AFTER PCV-10 IMMUNISATION.* ISPPD-9, 2014. **3**: p. 176.
13. Scott, J.A.G., et al., *THE IMPACT OF INTRODUCING 10-VALENT PNEUMOCOCCCOCAL CONJUGATE VACCINE IN KENYA ON INVASIVE PNEUMOCOCCAL DISEASE AMONG CHILDREN UNDER 5 YEARS.* ISPPD 2012, 2012: p. 292.
14. dos Santos, S.R., et al., *Serotype distribution of Streptococcus pneumoniae isolated from patients with invasive pneumococcal disease in Brazil before and after ten-pneumococcal conjugate vaccine implementation.* Vaccine, 2013. **31**(51): p. 6150-4.
15. Rinta-Kokko, H., et al., *IMPACT OF 10-VALENT PNEUMOCOCCAL CONJUGATE VACCINE (PCV10) AMONG VACCINE-ELIGIBLE CHILDREN IN FINLAND, 2010-2015.* ISPPD-10, 2016.
16. Miller, et al., *Effectiveness of the new serotypes in the 13-valent pneumococcal conjugate vaccine.* Vaccine, 2011. **29**(49): p. 9127-9131.
17. Andrews, et al., *Serotype-specific effectiveness and correlates of protection for the 13-valent pneumococcal conjugate vaccine: A postlicensure indirect cohort study.* The Lancet Infectious Diseases, 2014. **14**(9): p. 839-846.
18. Tomczyk, S., et al., *EFFECTIVENESS OF 13-VALENT PNEUMOCOCCAL CONJUGATE (PCV13) IN THE DOMINICAN REPUBLIC: PRLEIMINARY RESULTS FROM A MATCHED-CASE CONTROL STUDY.* ISPPD-10, 2016.
19. Gottberg, A.v., et al., *EFFECTIVENESS OF THE 13-VALENT PNEUMOCOCCAL CONJUGATE VACCINE AGAINST INVASIVE PNEUMOCOCCAL DISEASE IN SOUTH AFRICAN CHILDREN: A CASE-CONTROL STUDY.* ISPPD-10, 2016.
20. Gidding, H., et al., *POPULATION-BASED ESTIMATES OF PNEUMOCOCCAL CONJUGATE VACCINE EFFECTIVENESS IN AUSTRALIA.* ISPPD-10, 2016.
21. Guevara, M., et al., *Direct, indirect and total effects of 13-valent pneumococcal conjugate vaccination on invasive pneumococcal disease in children in Navarra, Spain, 2001 to 2014: cohort and case-control study.* Euro Surveill, 2016. **21**(14).
22. Jayasinghe, S., et al., *A COMPARISON OF POPUATION IMPACT OF 13VPCV AND 7VPCV THREE YEARS POST INTRODUCTION USING A "3+0" SCHEDULE IN AUSTRALIA.* ISPPD-10, 2016.
23. Mackenzie, G.A., et al., *Effect of the introduction of pneumococcal conjugate vaccination on invasive pneumococcal disease in The Gambia: a population-based surveillance study.* Lancet Inf Dis, 2016. **16**: p. 703-11.
24. Ben, et al., *Early impact of sequential introduction of 7-valent and 13-valent pneumococcal conjugate vaccine on IPD in Israeli children <5 years: An active prospective nationwide surveillance.* Vaccine, 2014. **32**(27): p. 3452-3459.
25. Lepoutre, et al., *Impact of the pneumococcal conjugate vaccines on invasive pneumococcal disease in France, 2001-2012.* Vaccine, 2015. **33**(2): p. 359-366.
26. Waight, et al., *Effect of the 13-valent pneumococcal conjugate vaccine on invasive pneumococcal disease in England and Wales 4 years after its introduction: An observational cohort study.* The Lancet Infectious Diseases, 2015. **15**(5): p. 535-543.
27. Von Gottbergh, et al., *Effects of vaccination on invasive pneumococcal disease in South Africa.* New England Journal of Medicine, 2014. **371**(20): p. 1889-1899.
28. Harboe, et al., *Impact of 13-valent pneumococcal conjugate vaccination in invasive pneumococcal disease incidence and mortality.* Clinical infectious diseases : an official publication of the Infectious Diseases Society of America, 2014. **59**(8): p. 1066-1073.
29. Ben-Shimol, S., et al. (2015). "Differential impact of pneumococcal conjugate vaccines on bacteremic pneumonia versus other invasive pneumococcal disease." Pediatr Infect Dis J **34**(4): 409-416.
30. Diawara, I., et al. (2015). "Invasive pneumococcal disease among children younger than 5 years of age before and after introduction of pneumococcal conjugate vaccine in Casablanca, Morocco." Int J Infect Dis **40**: 95-101.
31. Domingues, C. M. A. S., et al. (2014). "Effectiveness of ten-valent pneumococcal conjugate vaccine against invasive pneumococcal disease in Brazil: a matched case-control study." The Lancet Respiratory Medicine **2**(6): 464-471.
32. Galanis, I., et al. (2016). "Effects of PCV7 and PCV13 on invasive pneumococcal disease and carriage in Stockholm, Sweden." Eur Respir J **47**(4): 1208-1218.
33. Andrews, N. J., et al. (2014). "Serotype-specific effectiveness and correlates of protection for the 13-valent pneumococcal conjugate vaccine: a postlicensure indirect cohort study." The Lancet Infectious Diseases **14**(9): 839-846.
34. Jayasinghe, S., et al. (2017). "Long-term Impact of a "3 + 0" Schedule for 7- and 13-Valent Pneumococcal Conjugate Vaccines on Invasive Pneumococcal Disease in Australia, 2002-2014." Clin Infect Dis **64**(2): 175-183.
35. Jokinen, J., et al. (2015). "Impact of ten-valent pneumococcal conjugate vaccination on invasive pneumococcal disease in Finnish children--a population-based study." PLoS One **10**(3): e0120290.
36. Miller, E., et al. (2011). "Effectiveness of the new serotypes in the 13-valent pneumococcal conjugate vaccine." Vaccine **29**(49): 9127-9131.
37. Porat, N., et al. (2016). "The impact of pneumococcal conjugate vaccines on carriage of and disease caused by Streptococcus pneumoniae serotypes 6C and 6D in southern Israel." Vaccine **34**(25): 2806-2812.
38. Su, W. J., et al. (2016). "Effectiveness of Pneumococcal Conjugate Vaccines of Different Valences Against Invasive Pneumococcal Disease Among Children in Taiwan: A Nationwide Study." Pediatr Infect Dis J **35**(4): e124-133.
39. Weinberger, R., et al. (2016). "Vaccine effectiveness of PCV13 in a 3+1 vaccination schedule." Vaccine **34**(18): 2062-2065.
40. Knol, M., et al., *INCIDENCE OF IPD IN THE NETHERLANDS UP TO FIVE YEARS AFTER INTRODUCTION OF PCV10.* ISPPD-10, 2016.
41. Von Gottberg, A., et al. ONGOING PNEUMOCOCCAL DISEASE DECLINES AND AN INDIRECT EFFECT OF VACCINATION, SOUTH AFRICA 2005-2015. ISPPD-10, 2016.

Table 2: Effectiveness and impact of PCV10 or PCV13 (WHO prequalified PCV products) in currently recommended dosing schedules

Population:

Vaccinated children; unvaccinated older children and adults.

Interventions Compared:

PCV10 administration in infants <2 years of age using either WHO recommended dosing schedules (2p+1 or 3p+0)

VS:

PCV13 administration in infants <2 years of age using either WHO recommended dosing schedules (2p+1 or 3p+0)

Outcomes:

IgG response – mean GMC and percent responders in immunized infants for vaccine- serotypes (VT)

Mortality – vaccine effectiveness and/or change in mortality rates, pre/post vaccination, for all-cause mortality, pneumonia mortality, and IPD mortality for directly immunized and unimmunized populations through indirect effects; change in case fatality ratios, pre/post vaccination, for pneumonia and IPD.

Invasive Pneumococcal Disease (IPD) – vaccine effectiveness and/or change in incidence of VT or serotype specific IPD pre/post vaccination among directly immunized and unimmunized populations through indirect effects.

Pneumonia – vaccine effectiveness and/or change in incidence, pre/post vaccination, of either clinical pneumonia or chest x-ray (CXR) confirmed pneumonia among directly immunized and unimmunized populations through indirect effects

Carriage – vaccine effectiveness and/or change in incidence, pre/post vaccination, of vaccine type or serotype specific pneumococcal carriage among directly immunized and unimmunized populations through indirect effects

PICO Question: Is the impact or effectiveness of PCV10 and PCV13 (using either WHO recommended dosing schedules) different, based on data reporting immune response following vaccination, and impact on NP Carriage and clinical outcomes (IPD, pneumonia and mortality) in vaccinated children as well as unvaccinated age groups through indirect protection?				
			Rating	Adjustment to rating
Quality Assessment Factors Quality Assessment	No of studies/starting rating		41 observational studies	2
	Factors decreasing confidence	Limitation in study design	None serious	0
		Inconsistency	None serious	0
		Indirectness	Serious[1]	-1
		Imprecision	Serious[2]	-1
		Publication bias	Not assessed	0
	Factors increasing confidence	Strength of association	None serious[3]	0
		Dose-response	Not applicable	0
		Mitigated bias and confounding	Not applicable	0
	Final numerical rating of quality of evidence			**1**
Summary of Findings	**Statement on quality of evidence**			**Evidence supports a very low level of confidence that the true effect lies close to that of the estimate of the effect on the health outcome.**
	Conclusion			**We have a very low level of confidence in the ability of the available evidence to detect any differences in the overall effectiveness of PCV13 compared to PCV10 in the general population.**

[1]The review found no studies that made direct comparisons between the products (PCV13 or PCV10). A single clinical trial (Palmu et al., 2016) used only one of the 2 products under consideration (PCV10) and no RCTs with PCV13 were available. Observational studies data were used to make between-study comparisons (downgraded evidence for indirectness as no head-to head studies available) Only between-study comparisons could be made in analysis.

[2]The available evidence was highly heterogeneous therefore a meta-analysis was not conducted in order to provide a point estimate or confidence intervals

[3]The strength of association for direct comparisons between the products (PCV13 or PCV10) could not be assessed but for each product, studies consistently found strong associations.

References:

1. Palmu, et al., *Effectiveness of the ten-valent pneumococcal Haemophilus influenzae protein D conjugate vaccine (PHiD-CV10) against invasive pneumococcal disease: A cluster randomised trial.* The Lancet, 2013. 381(9862): p. 214-222.
2. Palmu, A., et al., *LONG-TERM EFFECTIVENESS OF PNEUMOCOCCAL HAEMOPHILUS INFLUENZAE PROTEIN D CONJUGATE VACCINE (PHID-CV10) AGAINST CONFIRMED AND NON-CONFIRMED INVASIVE PNEUMOCOCCAL DISEASE (IPD) - FINIP TRIAL EXTENDED FOLLOW-UP.* ISPPD-10, 2016.
3. Deceuninck, et al., *Effectiveness of three pneumococcal conjugate vaccines to prevent invasive pneumococcal disease in Quebec, Canada.* Vaccine, 2015. **33**(23): p. 2684-2689.

4. H.Rinta-Kokko, K.A., *EFFECTIVENESS OF 10-VALENT PNEUMOCOCCAL CONJUGATE VACCINE (PCV10) AGAINST INVASIVE PNEUMOCOCCAL DISEASE (IPD) DURING ONGOING NATIONAL VACCINATION PROGRAMME (NVP) IN FINLAND.* ISPPD-9, 2014. **3**: p. 140.
5. Knol, M.J., et al., *VACCINE EFFECTIVENESS OF 10-VALENT PNEUMOCOCCAL CONJUGATE VACCINE AGAINST INVASIVE PNEUMOCOCCAL DISEASE: INDIRECT COHORT DESIGN.* ISPPD-10, 2016.
6. Ali, A., et al., *EFFECTIVENESS OF PCV-10 VACCINE AGAINST VACCINE TYPE IPD IN PAKISTAN: IMPACT ASSESSMENT AFTER INTRODUCTION OF PCV-10 IN ROUTINE IMMUNIZATION PROGRAMME.* ISPPD-10, 2016.
7. Verani, J.R., C.M. Domingues, and J.C. Moraes, *Indirect cohort analysis of 10-valent pneumococcal conjugate vaccine effectiveness against vaccine-type and vaccine-related invasive pneumococcal disease.* Vaccine, 2015. **33**(46): p. 6145-8.
8. De, et al., *Impact of 2+1 pneumococcal conjugate vaccine program in the province of Quebec, Canada.* Vaccine, 2014. **32**(13): p. 1501-1506.
9. Knol, M.J., et al., *Invasive Pneumococcal Disease 3 Years after Introduction of 10-Valent Pneumococcal Conjugate Vaccine, the Netherlands.* Emerg Infect Dis, 2015. **21**(11): p. 2040-4.
10. Rinta-Kokko, H., et al., *COMPARISON OF DIFFERENT STUDY DESIGNS OF THE ESTIMATION OF PCV10 EFFECTIVENESS AGAINST INVASIVE PNEUMOCOCCAL DISEASE (IPD) DURING NATIONAL VACCINATION PROGRAMME (NVP) IN FINLAND.* ISPPD-10, 2016.
11. Jokinen, J., et al., *MONITORING THE EFFECTIVENESS OF FINNISH NATIONAL VACCINATION PROGRAMME (NVP) OF THE 10-VALENT PNEUMOCOCCAL CONJUGATE VACCINE (PCV10).* ISPPD 2012, 2012: p. 196.
12. H.Erlendsd, A.H., *AN EARLY REDUCTION OF INVASIVE PNEUMOCOCCAL INFECTIONS AFTER PCV-10 IMMUNISATION.* ISPPD-9, 2014. **3**: p. 176.
13. Scott, J.A.G., et al., *THE IMPACT OF INTRODUCING 10-VALENT PNEUMOCOCCOCAL CONJUGATE VACCINE IN KENYA ON INVASIVE PNEUMOCOCCAL DISEASE AMONG CHILDREN UNDER 5 YEARS.* ISPPD 2012, 2012: p. 292.
14. dos Santos, S.R., et al., *Serotype distribution of Streptococcus pneumoniae isolated from patients with invasive pneumococcal disease in Brazil before and after ten-pneumococcal conjugate vaccine implementation.* Vaccine, 2013. **31**(51): p. 6150-4.
15. Rinta-Kokko, H., et al., *IMPACT OF 10-VALENT PNEUMOCOCCAL CONJUGATE VACCINE (PCV10) AMONG VACCINE-ELIGIBLE CHILDREN IN FINLAND, 2010-2015.* ISPPD-10, 2016.
16. Miller, et al., *Effectiveness of the new serotypes in the 13-valent pneumococcal conjugate vaccine.* Vaccine, 2011. **29**(49): p. 9127-9131.
17. Andrews, et al., *Serotype-specific effectiveness and correlates of protection for the 13-valent pneumococcal conjugate vaccine: A postlicensure indirect cohort study.* The Lancet Infectious Diseases, 2014. **14**(9): p. 839-846.
18. Tomczyk, S., et al., *EFFECTIVENESS OF 13-VALENT PNEUMOCOCCAL CONJUGATE (PCV13) IN THE DOMINICAN REPUBLIC: PRLEIMINARY RESULTS FROM A MATCHED-CASE CONTROL STUDY.* ISPPD-10, 2016.
19. Gottberg, A.v., et al., *EFFECTIVENESS OF THE 13-VALENT PNEUMOCOCCAL CONJUGATE VACCINE AGAINST INVASIVE PNEUMOCOCCAL DISEASE IN SOUTH AFRICAN CHILDREN: A CASE-CONTROL STUDY.* ISPPD-10, 2016.
20. Gidding, H., et al., *POPULATION-BASED ESTIMATES OF PNEUMOCOCCAL CONJUGATE VACCINE EFFECTIVENESS IN AUSTRALIA.* ISPPD-10, 2016.
21. Guevara, M., et al., *Direct, indirect and total effects of 13-valent pneumococcal conjugate vaccination on invasive pneumococcal disease in children in Navarra, Spain, 2001 to 2014: cohort and case-control study.* Euro Surveill, 2016. **21**(14).
22. Jayasinghe, S., et al., *A COMPARISON OF POPUATION IMPACT OF 13VPCV AND 7VPCV THREE YEARS POST INTRODUCTION USING A "3+0" SCHEDULE IN AUSTRALIA.* ISPPD-10, 2016.
23. Mackenzie, G.A., et al., *Effect of the introduction of pneumococcal conjugate vaccination on invasive pneumococcal disease in The Gambia: a population-based surveillance study.* Lancet Inf Dis, 2016. **16**: p. 703-11.
24. Ben, et al., *Early impact of sequential introduction of 7-valent and 13-valent pneumococcal conjugate vaccine on IPD in Israeli children <5 years: An active prospective nationwide surveillance.* Vaccine, 2014. **32**(27): p. 3452-3459.
25. Lepoutre, et al., *Impact of the pneumococcal conjugate vaccines on invasive pneumococcal disease in France, 2001-2012.* Vaccine, 2015. **33**(2): p. 359-366.
26. Waight, et al., *Effect of the 13-valent pneumococcal conjugate vaccine on invasive pneumococcal disease in England and Wales 4 years after its introduction: An observational cohort study.* The Lancet Infectious Diseases, 2015. **15**(5): p. 535-543.
27. Von Gottbergh, et al., *Effects of vaccination on invasive pneumococcal disease in South Africa.* New England Journal of Medicine, 2014. **371**(20): p. 1889-1899.
28. Harboe, et al., *Impact of 13-valent pneumococcal conjugate vaccination in invasive pneumococcal disease incidence and mortality.* Clinical infectious diseases : an official publication of the Infectious Diseases Society of America, 2014. **59**(8): p. 1066-1073.
29. Ben-Shimol, S., et al. (2015). "Differential impact of pneumococcal conjugate vaccines on bacteremic pneumonia versus other invasive pneumococcal disease." Pediatr Infect Dis J **34**(4): 409-416.
30. Diawara, I., et al. (2015). "Invasive pneumococcal disease among children younger than 5 years of age before and after introduction of pneumococcal conjugate vaccine in Casablanca, Morocco." Int J Infect Dis **40**: 95-101.
31. Domingues, C. M. A. S., et al. (2014). "Effectiveness of ten-valent pneumococcal conjugate vaccine against invasive pneumococcal disease in Brazil: a matched case-control study." The Lancet Respiratory Medicine **2**(6): 464-471.
32. Galanis, I., et al. (2016). "Effects of PCV7 and PCV13 on invasive pneumococcal disease and carriage in Stockholm, Sweden." Eur Respir J **47**(4): 1208-1218.
33. Andrews, N. J., et al. (2014). "Serotype-specific effectiveness and correlates of protection for the 13-valent pneumococcal conjugate vaccine: a postlicensure indirect cohort study." The Lancet Infectious Diseases **14**(9): 839-846.
34. Jayasinghe, S., et al. (2017). "Long-term Impact of a "3 + 0" Schedule for 7- and 13-Valent Pneumococcal Conjugate Vaccines on Invasive Pneumococcal Disease in Australia, 2002-2014." Clin Infect Dis **64**(2): 175-183.
35. Jokinen, J., et al. (2015). "Impact of ten-valent pneumococcal conjugate vaccination on invasive pneumococcal disease in Finnish children--a population-based study." PLoS One **10**(3): e0120290.
36. Miller, E., et al. (2011). "Effectiveness of the new serotypes in the 13-valent pneumococcal conjugate vaccine." Vaccine **29**(49): 9127-9131.
37. Porat, N., et al. (2016). "The impact of pneumococcal conjugate vaccines on carriage of and disease caused by Streptococcus pneumoniae serotypes 6C and 6D in southern Israel." Vaccine **34**(25): 2806-2812.
38. Su, W. J., et al. (2016). "Effectiveness of Pneumococcal Conjugate Vaccines of Different Valences Against Invasive Pneumococcal Disease Among Children in Taiwan: A Nationwide Study." Pediatr Infect Dis J **35**(4): e124-133.
39. Weinberger, R., et al. (2016). "Vaccine effectiveness of PCV13 in a 3+1 vaccination schedule." Vaccine **34**(18): 2062-2065.
40. Knol, M., et al., *INCIDENCE OF IPD IN THE NETHERLANDS UP TO FIVE YEARS AFTER INTRODUCTION OF PCV10.* ISPPD-10, 2016.
41. Von Gottberg, A., et al. ONGOING PNEUMOCOCCAL DISEASE DECLINES AND AN INDIRECT EFFECT OF VACCINATION, SOUTH AFRICA 2005-2015. ISPPD-10, 2016.

Table 1: Effectiveness and impact of different dosing schedules of WHO prequalified Pneumococcal Conjugate Vaccine (PCV) products

Population:
Vaccinated children; unvaccinated older children and adults
Interventions Compared:
2 primary doses before 6 months of age and 1 booster dose at 9 months of age or later (2p+1) in infants <2 years of age with WHO prequalified PCV products
VS:
3 primary doses before 9 months of age without a booster dose (3p+0) in infants <2 years of age with WHO prequalified PCV products
Outcomes:
IgG response – mean GMC and percent responders in immunized infants for vaccine- serotypes (VT)
Mortality – vaccine effectiveness and/or change in mortality rates, pre/post vaccination, for all-cause mortality, pneumonia mortality, and IPD mortality for directly immunized and unimmunized populations through indirect effects; change in case fatality ratios, pre/post vaccination, for pneumonia and IPD.
Invasive Pneumococcal Disease (IPD) – vaccine effectiveness and/or change in incidence of VT or serotype specific IPD pre/post vaccination among directly immunized and unimmunized populations through indirect effects.
Pneumonia – vaccine effectiveness and/or change in incidence, pre/post vaccination, of either clinical pneumonia or chest x-ray (CXR) confirmed pneumonia among directly immunized and unimmunized populations through indirect effects
Carriage – vaccine effectiveness and/or change in incidence, pre/post vaccination, of vaccine type or serotype specific pneumococcal carriage among directly immunized and unimmunized populations through indirect effects

PICO Question: How does PCV administered to healthy children in a 2p+1 schedule compare with the vaccine administered in a 3p+0 schedule, with respect to immune response in vaccinated children and impact on clinical outcomes (IPD, pneumonia, and mortality), and nasopharyngeal carriage in the vaccinated children as well as unvaccinated age groups through indirect protection?

			Rating	Adjustment to rating
Quality Assessment Factors	No. of studies/starting rating		7 clinical trials (2 H2H)/21 observational	4
	Factors decreasing confidence	Limitation in study design	None serious	0
		Inconsistency	None serious	0
		Indirectness	None serious	0
		Imprecision	Serious[1]	-1
		Publication bias	None serious	0
	Factors increasing confidence	Strength of association	Not applicable	0
		Dose-response	Not applicable	0
		Mitigated bias and confounding	Not applicable	0
	Final numerical rating of quality of evidence			**3**
Summary of Findings	**Statement on quality of evidence**			Evidence supports a moderate level of confidence that the true effect lies close to that of the estimate of effect on health outcome.
	Conclusion			We are moderately confident that a 2+1 dosing schedule elicits a comparable overall effectiveness and impact on NP carriage compared to a 3+0 dosing schedule in the general population

[1]N=2 head-to-head randomized clinical trials were conducted, both of PCV10, both with non-PCV control groups and both in low carriage settings (9-20% NP carriage at age 12-15 months in controls). The Vietnam trial (Smith-Vaughan 2016 and Mulholland, personal communication, 2017) observed similar low carriage of PCV10-types between 2+1 schedule (4.5%, n=233), 3+0 (7.8%, n=129) and both schedules were lower than that in controls (VT=9.1%, n=187) but no differences were statistically significant due to low power. The trial in Finland (Vesikari 2016), which had large a sample size, also observed very similar PCV10-type carriage between the 2+1 schedule (12.5%, n=1289) and 3+0 (12.8%, n=1803). However, the 2+1 swabs were taken at 3 months older age and carriage in controls increased slightly during this period from 18.2% to 20.1% (n=1987). When differences between vaccinated and controls at comparable ages are considered, the 2+1 schedule may have had a slightly larger effect: i.e., 20.1% in placebo arm vs. 12.5% in 2+1 arm is a 37.8% relative reduction while 18.2% in placebo arm vs. 12.8% in 3+0 arm is a 29.7% relative reduction, but this difference was not statistically significant.

In the remaining RCTs and observational studies, the two products are not directly compared so comparisons must be made across studies and introduces considerable confounding and potential for bias. However, they support that both products reduce VT-type carriage to a similar degree.

References:

Head-to-head trials:

1. Smith-Vaughan, Heidi, Temple, Beth, Vothitrang, Dai, et al. Impact of different PCV10 schedules on nasopharyngeal carriage in Vietnamese children at 12 months of age. ISPPD 2016.
2. Temple, B., Vo, D. T. T., Balloch, A., Smith-Vaughan, H., Pham, H. T., Huynh, T. P., . . . Mulholland, K. (2016). HEAD-TO-HEAD COMPARISON OF PCV10 AND PCV13: POST-PRIMARY SERIES IMMUNOGENICITY AND IMPACT ON NASOPHARYNGEAL CARRIAGE AT 12 MONTHS OF AGE. ISPPD-10.

3. Vesikari, Timo, Forsten, Aino, Seppa, Ilkka, et al. Effectiveness of the 10-Valent Pneumococcal Nontypeable Haemophilus influenzae Protein D–Conjugated Vaccine (PHiD-CV) Against Carriage and Acute Otitis Media—A Double-Blind Randomized Clinical Trial in Finland. Journal of the Pediatric Infectious Diseases Society pp. 1–12, 2016. DOI:10.1093/jpids/piw010

Other RCTs and observational studies:

4. Hamaluba, Kandasamy, Upreti, R, Subedi, R, . . . J. (2015). Comparison of two-dose priming plus 9-month booster with a standard three-dose priming schedule for a ten-valent pneumococcal conjugate vaccine in Nepalese infants: A randomised, controlled, open-label, non-inferiority trial. The Lancet Infectious Diseases, 15(4), 405-414.
5. Russell, F., Reyburn, R., Tuivaga, E., Dunne, E., Devi, R., Kama, M., . . . Mulholland, K. (2016). DECLINE IN PNEUMOCOCCAL CARRIAGE IN ALL AGES, AND DECLINE IN PNEUMOCOCCAL DISEASE IN YOUNG CHILDREN FOLLOWING PCV10 INTRODUCTION IN FIJI. ISPPD-10.
6. Dunne, E., Satzke, C., Ratu, T., Rafai, E., Kama, M., Devi, R., . . . Russell, F. (2016). IMPACT OF 10-VALENT PNEUMOCOCCAL CONJUGATE VACCINE INTRODUCTION ON PNEUMOCOCCAL CARRIAGE IN FIJI: RESULTS FROM FOUR ANNUAL CROSS-SECTIONAL CARRIAGE SURVEYS. ISPPD-10.
7. Steens, Caugant, A, Aaberge, S, Vestrheim, & F. (2015). Decreased carriage and genetic shifts in the streptococcus pneumoniae population after changing the seven-valent to the thirteen-valent pneumococcal vaccine in Norway. Pediatric Infectious Disease Journal, 34(8), 875-883.
8. Moiane, B., Lessa, F., Pimenta, F., Massora, S., Verani, J., Acácio, S., . . . Betuel, S. (2016). DIFFERENCES IN PNEUMOCOCCAL COLONIZATION DENSITY AMONG HIV-INFECTED AND –UNINFECTED CHILDREN PRE- AND POST-INTRODUCTION OF 10-VALENT PNEUMOCOCCAL CONJUGATE VACCINE (PCV10) IN MOZAMBIQUE. ISPPD-10.
9. Sigaúque, B., Massora, S., Verani, J. R., Moiane, B., Acácio, S., Quintó, L., . . . Lessa, F. C. (2016). EARLY DECLINES IN VACCINE-TYPE PNEUMOCOCCAL CARRIAGE IN CHILDREN UNDER 5 YEARS OLD AFTER INTRODUCTION OF 10-VALENT PENUMOCOCCAL CONJUGATE VACCINE IN MOZAMBIQUE. ISPPD-10.
10. Borys, D., Sáez-Llorens, X., Prymula, R., Hoet, B., Lommel, P., Ruiz-Guiñazú, J., & Yarzábal, J. P. (2012). EFFECT OF 10- AND 11-VALENT PNEUMOCOCCAL NON-TYPEABLE HAEMOPHILUS INFLUENZAE PROTEIN D CONJUGATE VACCINES (PHID-CV AND 11PN-PD) ON NASOPHARYNGEAL BACTERIAL CARRIAGE. ISPPD 2012, 291.
11. A.Roca, A. B. (2014). EFFECT OF REPLACING PCV-7 WITH PCV-13 IN THE EXPANDED PROGRAM OF IMMUNIZATION ON NASOPHARYNGEAL CARRIAGE OF PNEUMOCOCCI IN THE GAMBIA. ISPPD-9, 3, 20.
12. Roca, A., Bojang, A., Bottomley, C., Gladstone, R. A., Adetifa, J. U., Egere, U., . . . Foster-Nyarko, E. (2015). Effect on nasopharyngeal pneumococcal carriage of replacing PCV7 with PCV13 in the Expanded Programme of Immunization in The Gambia. Vaccine, 33(51), 7144-7151. doi:10.1016/j.vaccine.2015.11.012
13. Vesikari, T., Forsten, A., Seppa, I., Kaijalainen, T., Puumalainen, T., Soininen, A., . . . Schuerman, L. (2016). Effectiveness of the 10-Valent Pneumococcal Nontypeable Haemophilus influenzae Protein D-Conjugated Vaccine (PHiD-CV) Against Carriage and Acute Otitis Media-A Double-Blind Randomized Clinical Trial in Finland. J Pediatric Infect Dis Soc.
14. Galanis, I., Lindstrand, A., Darenberg, J., Browall, S., Nannapaneni, P., Sjostrom, K., . . . Henriques-Normark, B. (2016). Effects of PCV7 and PCV13 on invasive pneumococcal disease and carriage in Stockholm, Sweden. Eur Respir J.
15. Van, D., Bergh, R, Spijkerman, Swinnen, M, . . . M. (2013). Effects of the 10-valent pneumococcal nontypeable haemophilus influenzae protein d-conjugate vaccine on nasopharyngeal bacterial colonization in young children: A randomized controlled trial. Clinical Infectious Diseases, 56(3), e30-e39.
16. Gladstone, A, Jefferies, M, Tocheva, S, . . . C. (2015). Five winters of pneumococcal serotype replacement in UK carriage following PCV introduction. Vaccine, 33(17), 2015-2021.
17. Devine, V., Cleary, D., Johanna, J., Anderson, R., Morris, D., Tuck, A., . . . Clarke, S. (2016). PNEUMOCOCCAL SEROTYPES IN CARRIAGE SEVEN YEARS AFTER PNEUMOCOCCAL CONJUGATE VACCINE INTRODUCTIONS – A UK PAEDIATRIC CARRIAGE STUDY 2006/07 – 2012/13. ISPPD-10.
18. Jones, J., Gladstone, R., Devine, V. T., Morris, D., Tuck, A., Jefferies, J. M., . . . Clarke, S. C. (2016). VACCINE-INDUCED CHANGES TO PNEUMOCOCCAL CARRIAGE IN CHILDREN IN THE UK: 2006 – 2015. ISPPD-10.
19. Kim, L., Bigogo, G., Conklin, L., Odoyo, A., Carvalho, M. D. G., Odiembo, H., . . . Breiman, R. (2016). IMPACT OF 10-VALENT PNEUMOCOCCAL CONJUGATE VACCINE (PCV10) ON PNEUMOCOCCAL COLONIZATION IN CHILDREN. ISPPD-10.
20. Kim, L. C. (2014). PNEUMOCOCCAL CARRIAGE IN KENYAN CHILDREN BEFORE AND AFTER 10-VALENT PNEUMOCOCCAL CONJUGATE VACCINE (PCV10) INTRODUCTION, 2009 AND 2012. ISPPD-9, 3, 35.
21. Danino, D., Givon-Lavi, N., Ben-Shimol, S., Greenberg, D., & Dagan, R. (2016). THE IMPACT OF PCV7/PCV13 ON THE DYNAMICS OF ANTIBIOTIC NON-SUSCEPTIBLE S. PNEUMONIAE CARRIAGE (NSSP-CAR) IN YOUNG CHILDREN IN TWO DISTINCT ETHNIC GROUPS. ISPPD-10.
22. Nzenze, T. S. (2014). THE IMPACT OF PNEUMOCOCCAL CONJUGATE VACCINE (PCV) ON THE EPIDEMIOLOGY OF INVASIVE PNEUMOCOCCAL DISEASE (IPD) AND PNEUMOCOCCAL CARRIAGE IN SOWETO. ISPPD-9, 3, 14.
23. Nzenze, S. A., Shiri, T., Chinyanganya, L., Niekerk, N. v., Kathleen, K., Twine, R., . . . Madhi, S. (2016). TEMPORAL CHANGES IN PNEUMOCOCCAL COLONIZATION IN A RURAL SETTING WITH HIGH HIV PREVALENCE FOLLOWING TRANSITIONING FROM 7-VALENT TO 13-VALENT PNEUMOCOCCAL CONJUGATE VACCINE, SOUTH AFRICA. ISPPD-10.
24. Nzenze, A, von, Gottberg, Shiri, van, . . . A. (2015). Temporal Changes in Pneumococcal Colonization in HIV-infected and HIV-uninfected Mother-Child Pairs Following Transitioning From 7-valent to 13-valent Pneumococcal Conjugate Vaccine, Soweto, South Africa. J Infect Dis, 212(7), 1082-1092.
25. Prymula, Hanovcova, Splino, Kriz, Motlova, Lebedova, . . . Schuerman. (2011). Impact of the 10-valent pneumococcal non-typeable Haemophilus influenzae Protein D conjugate vaccine (PHiD-CV) on bacterial nasopharyngeal carriage. Vaccine, 29(10), 1959-1967.
26. Dunais, Bruno, Touboul, Degand, Sakarovitch, Fontas, . . . Pradier. (2015). Impact of the 13-valent pneumococcal conjugate vaccine on nasopharyngeal carriage of Streptococcus pneumoniae among children attending group daycare in Southeastern France. Pediatric Infectious Disease Journal, 34(3), 286-288.
27. Jokinen, J., Toropainen, M., Siira, L., Syrjänen, R., Kilpi, T., & Palmu, A. (2016). LONG-TERM EFFECTIVENESS OF THE PNEUMOCOCCAL HAEMOPHILUS INFLUENZAE PROTEIN D CONJUGATE VACCINE (PHID-CV10) AGAINST NASOPHARYNGEAL CARRIAGE – FINIP CARRIAGE SATELLITE STUDY. ISPPD-10.
28. Vissers, M., Wijmenga-Monsuur, A., Knol, M., Badoux, P., Houten, M. v., Sanders, E., & Rots, N. (2016). NASOPHARYNGEAL CARRIAGE OF S. PNEUMONIAE AND OTHER BACTERIA 5 YEARS AFTER THE SWITCH FROM THE 7-VALENT TO THE 10-VALENT PNEUMOCOCCAL CONJUGATE VACCINE IN THE NETHERLANDS. ISPPD-10.
29. Bosch, A. A., Houten, M. A. v., Bruin, J. P., Wijmenga-Monsuur, A. J., Trzcinski, K., Bogaert, D., . . . Sanders, E. A. (2015). Nasopharyngeal carriage of Streptococcus pneumoniae and other bacteria in the 7th year after implementation of the pneumococcal conjugate vaccine in the Netherlands. Vaccine, 34(4), 531-539.

30. Bosch, R. H. V. (2014). A NEW BALANCE IN CARRIAGE OF NON-VACCINE PNEUMOCOCCAL SEROTYPES 6.5 YEARS AFTER PCV7 IMPLEMENTATION. ISPPD-9, 3, 21.
31. Swarthout, T., Mwalukomo, T., Everett, D., Bar-Zeev, N., Kamng'ona, A., Chipasula, T., . . . Heyderman, R. S. (2016). PERSISTENT VACCINE TYPE CARRIAGE OF STREPTOCOCCUS PNEUMONIAE FOUR YEARS AFTER INTRODUCING 13-VALENT PNEUMOCOCCAL CONJUGATE VACCINE IN A 3+0 SCHEDULE IN MALAWI. ISPPD-10.
32. Van, Hoek, J, Sheppard, L, Andrews, . . . Miller. (2014). Pneumococcal carriage in children and adults two years after introduction of the thirteen valent pneumococcal conjugate vaccine in England. Vaccine, 32(34), 4349-4355.
33. Moïsi, J., Kabore, L., Njanpop-Lafourcade, B. M., Yaro, S., Ouangraoua, S., & Gessner, B. (2016). PNEUMOCOCCAL CARRIAGE IN WESTERN BURKINA FASO AFTER THE INTRODUCTION OF PCV13. ISPPD-10.
34. Ben, Shimol, Givon, Lavi, Greenberg, & Dagan. (2015). Pneumococcal nasopharyngeal carriage in children <5 years of age visiting the pediatric emergency room in relation to PCV7 and PCV13 introduction in southern Israel. Hum Vaccin Immunother, 0.
35. Laura, L. H., Donald, O. A., Susan, C. M., Angela, K., Norbert, K., Sammy, N., . . . Scott, J. A. G. (2014). Population effect of 10- valent pneumococcal conjugate vaccine on nasopharyngeal carriage of Streptococcus pneumoniae and non- typeable Haemophilus influenzae in Kilifi, Kenya: findings from cross- sectional carriage studies. The Lancet Global Health, 2(7), e397-e405. doi:10.1016/S2214-109X(14)70224-4
36. Hammitt, L. L., Akech, D. O., Morpeth, S. C., Karani, A., Nyongesa, S., Ooko, M., . . . Scott, J. A. G. (2016). POPULATION IMPACT OF 10-VALENT PNEUMOCOCCAL CONJUGATE VACCINE (PCV) ON NASOPHARYNGEAL CARRIAGE OF STREPTOCOCCUS PNEUMONIAE IN KILIFI, KENYA. ISPPD-10.
37. Wyllie,,A, L.,Wijmenga, Monsuur,A, J.,van, Houten,M, A.,Bosch,,A, A.,Groot,,J, A.,van Engelsdorp, Gastelaars,J,,Bruin,,J, P.,Bogaert,,D,,Rots,,N, Y.,Sanders,,E, A.,Trzcinski,,K. (2016). Molecular surveillance of nasopharyngeal carriage of Streptococcus pneumoniae in children vaccinated with conjugated polysaccharide pneumococcal vaccines. Sci Rep.
38. Varon,,E,,Cohen,,R,,Béchet,,S,,Doit,,C,,Levy,,C, (2015). Invasive disease potential of pneumococci before and after the 13-valent pneumococcal conjugate vaccine implementation in children. Vaccine.
39. Leach, C. W. (2014). CARRIAGE OF PNEUMOCOCCUS AND NON-TYPEABLE HAEMOPHILUS INFLUENZAE IN CHILDREN VACCINATED WITH EITHER 7-VALENT OR 10-VALENT PNEUMOCOCCAL CONJUGATE VACCINES. ISPPD-9, 3, 37.
40. Suy K, Suon K, Ly S, P. Sar P, Tan P, Day N,Turner C, Turner P. PNEUMOCOCCAL COLONISATION IN CAMBODIAN CHILDREN ONE YEAR POST PCV-13 INTRODUCTION. ISPPD-10, 2016.
41. Steens, Caugant, A, Aaberge, S, Vestrheim, & F. (2015). Decreased carriage and genetic shifts in the streptococcus pneumoniae population after changing the seven-valent to the thirteen-valent pneumococcal vaccine in Norway. Pediatric Infectious Disease Journal, 34(8), 875-883.

Table 2: Effectiveness and impact of PCV10 or PCV13 (WHO prequalified PCV products) in currently recommended dosing schedules

Population:

Vaccinated children; unvaccinated older children and adults.

Interventions Compared:

PCV10 administration in infants <2 years of age using either WHO recommended dosing schedules (2p+1 or 3p+0)
VS:
PCV13 administration in infants <2 years of age using either WHO recommended dosing schedules (2p+1 or 3p+0)

Outcomes:

IgG response – mean GMC and percent responders in immunized infants for vaccine- serotypes (VT)

Mortality – vaccine effectiveness and/or change in mortality rates, pre/post vaccination, for all-cause mortality, pneumonia mortality, and IPD mortality for directly immunized and unimmunized populations through indirect effects; change in case fatality ratios, pre/post vaccination, for pneumonia and IPD.

Invasive Pneumococcal Disease (IPD) – vaccine effectiveness and/or change in incidence of VT or serotype specific IPD pre/post vaccination among directly immunized and unimmunized populations through indirect effects.

Pneumonia – vaccine effectiveness and/or change in incidence, pre/post vaccination, of either clinical pneumonia or chest x-ray (CXR) confirmed pneumonia among directly immunized and unimmunized populations through indirect effects

Carriage – vaccine effectiveness and/or change in incidence, pre/post vaccination, of vaccine type or serotype specific pneumococcal carriage among directly immunized and unimmunized populations through indirect effects

PICO Question: Is the impact or effectiveness of PCV10 and PCV13 (using either WHO recommended dosing schedules) different, based on data reporting immune response following vaccination, and impact on NP Carriage and clinical outcomes (IPD, pneumonia and mortality) in vaccinated children as well as unvaccinated age groups through indirect protection?

			Rating	Adjustment to rating
Quality Assessment Factors Quality Assessment	No of studies/starting rating		8 clinical trials (2 H2H)/ 21 observational[1]	4
	Factors decreasing confidence	Limitation in study design	Serious[2]	-1
		Inconsistency	None serious	0
		Indirectness	None serious	0
		Imprecision	Serious[3]	-1
		Publication bias	None serious	0
	Factors increasing confidence	Strength of association	Not applicable	0
		Dose-response	Not applicable	0
		Mitigated bias and confounding	Not applicable	0
	Final numerical rating of quality of evidence			**2**
Summary of Findings	**Statement on quality of evidence**			**Evidence supports a limited level of confidence that the true effect lies close to that of the estimate of the effect on the health outcome.**
	Conclusion			**We have a limited level of confidence in the ability of the available evidence to detect differences in the overall effectiveness and impact of PCV10 compared to PCV13 on PCV13-type NP carriage in the general population**

[1]Two trials directly compared PCV13-type NP carriage (defined as the proportion of children carrying PCV13-type serotypes) among children who received PCV13 vs. PCV10. One head-to-head trial (Orami 2016) was conducted in a high burden country (PNG) and had high carriage (>80% by age 4 months) and showed similar PCV13-type carriage between PCV13 (30%) and PCV10 (32%) at 9 months of age following a 3+0 schedule; however, there was no unvaccinated control group to demonstrate that they both reduced vaccine-type carriage. The other head-to-head trial conducted in Vietnam (Temple 2016) using a 2+1 schedule also saw similar PCV13-type carriage (11.6%) compared to PCV10 (13.5%) at 12 months of age; this study did have a control group (PCV13=17.4%), but because of low overall carriage (29% in controls), the reductions in PCV-vaccinated children compared to control rates were not statistically significant. The remaining RCTs and observational studies are indirect (i.e., the two products are not directly compared). However, they support that both products reduce PCV13-type carriage to a similar degree.

[2] The head to head trials were not evaluated in settings of typical low-income country use (ie 13 type carriage was very low). This limited the ability of the studies to evaluate impact of vaccines on individual serotypes especially those in PCV13 not in PCV10.

[3] The studies were not powered to detect differences between products for specific serotypes and were under powered given the low overall PCV13-type carriage observed.

References:

Head-to-head trials:

1. Temple, Beth, Trang, Dai Bo Thi, Balloch, Anne, et al. Head-to-head comparison of PCV10 and PCV13: immunogenicity and impact of nasopharyngeal carriage at 12 months of age. ISPPD 2016.

2. Orami, Tilda, Ford, Rebecca, Michael, Audrey, et al. Impact of 10-Valent and 13-Valent Pneumococcal Conjugate Vaccines on Pneumococcal Carriage among Papua New Guinean Infants.ISPPD 2016
3. Pomat, W., et al., IMMUNOGENICITY OF 10-VALENT AND 13-VALENT PNEUMOCOCCAL CONJUGATE VACCINES GIVEN AT 1-2-3 MONTHS OF AGE IN PAPUA NEW GUINEAN INFANTS: A RANDOMISED CONTROLLED TRIAL. ISPPD-10, 2016.

Other RCTs and observational studies:

4. Dagan, Patterson, Juergens, Greenberg, Givon, Lavi, . . . A. (2013). Comparative immunogenicity and efficacy of 13-valent and 7-valent pneumococcal conjugate vaccines in reducing nasopharyngeal colonization: A randomized double-blind trial. Clinical Infectious Diseases, 57(7), 952-962.
5. Hamaluba, Kandasamy, Upreti, R, Subedi, R, . . . J. (2015). Comparison of two-dose priming plus 9-month booster with a standard three-dose priming schedule for a ten-valent pneumococcal conjugate vaccine in Nepalese infants: A randomised, controlled, open-label, non-inferiority trial. The Lancet Infectious Diseases, 15(4), 405-414.
6. Russell, F., Reyburn, R., Tuivaga, E., Dunne, E., Devi, R., Kama, M., . . . Mulholland, K. (2016). DECLINE IN PNEUMOCOCCAL CARRIAGE IN ALL AGES, AND DECLINE IN PNEUMOCOCCAL DISEASE IN YOUNG CHILDREN FOLLOWING PCV10 INTRODUCTION IN FIJI. ISPPD-10.
7. Dunne, E., Satzke, C., Ratu, T., Rafai, E., Kama, M., Devi, R., . . . Russell, F. (2016). IMPACT OF 10-VALENT PNEUMOCOCCAL CONJUGATE VACCINE INTRODUCTION ON PNEUMOCOCCAL CARRIAGE IN FIJI: RESULTS FROM FOUR ANNUAL CROSS-SECTIONAL CARRIAGE SURVEYS. ISPPD-10.
8. Steens, Caugant, A, Aaberge, S, Vestrheim, & F. (2015). Decreased carriage and genetic shifts in the streptococcus pneumoniae population after changing the seven-valent to the thirteen-valent pneumococcal vaccine in Norway. Pediatric Infectious Disease Journal, 34(8), 875-883.
9. Moiane, B., Lessa, F., Pimenta, F., Massora, S., Verani, J., Acácio, S., . . . Betuel, S. (2016). DIFFERENCES IN PNEUMOCOCCAL COLONIZATION DENSITY AMONG HIV-INFECTED AND –UNINFECTED CHILDREN PRE- AND POST-INTRODUCTION OF 10-VALENT PNEUMOCOCCAL CONJUGATE VACCINE (PCV10) IN MOZAMBIQUE. ISPPD-10.
10. Sigaúque, B., Massora, S., Verani, J. R., Moiane, B., Acácio, S., Quintó, L., . . . Lessa, F. C. (2016). EARLY DECLINES IN VACCINE-TYPE PNEUMOCOCCAL CARRIAGE IN CHILDREN UNDER 5 YEARS OLD AFTER INTRODUCTION OF 10-VALENT PENUMOCOCCAL CONJUGATE VACCINE IN MOZAMBIQUE. ISPPD-10.
11. Borys, D., Sáez-Llorens, X., Prymula, R., Hoet, B., Lommel, P., Ruiz-Guiñazú, J., & Yarzábal, J. P. (2012). EFFECT OF 10- AND 11-VALENT PNEUMOCOCCAL NON-TYPEABLE HAEMOPHILUS INFLUENZAE PROTEIN D CONJUGATE VACCINES (PHID-CV AND 11PN-PD) ON NASOPHARYNGEAL BACTERIAL CARRIAGE. ISPPD 2012, 291.
12. A.Roca, A. B. (2014). EFFECT OF REPLACING PCV-7 WITH PCV-13 IN THE EXPANDED PROGRAM OF IMMUNIZATION ON NASOPHARYNGEAL CARRIAGE OF PNEUMOCOCCI IN THE GAMBIA. ISPPD-9, 3, 20.
13. Roca, A., Bojang, A., Bottomley, C., Gladstone, R. A., Adetifa, J. U., Egere, U., . . . Foster-Nyarko, E. (2015). Effect on nasopharyngeal pneumococcal carriage of replacing PCV7 with PCV13 in the Expanded Programme of Immunization in The Gambia. Vaccine, 33(51), 7144-7151. doi:10.1016/j.vaccine.2015.11.012
14. Vesikari, T., Forsten, A., Seppa, I., Kaijalainen, T., Puumalainen, T., Soininen, A., . . . Schuerman, L. (2016). Effectiveness of the 10-Valent Pneumococcal Nontypeable Haemophilus influenzae Protein D-Conjugated Vaccine (PHiD-CV) Against Carriage and Acute Otitis Media-A Double-Blind Randomized Clinical Trial in Finland. J Pediatric Infect Dis Soc.
15. Galanis, I., Lindstrand, A., Darenberg, J., Browall, S., Nannapaneni, P., Sjostrom, K., . . . Henriques-Normark, B. (2016). Effects of PCV7 and PCV13 on invasive pneumococcal disease and carriage in Stockholm, Sweden. Eur Respir J.
16. Van, D., Bergh, R, Spijkerman, Swinnen, M, . . . M. (2013). Effects of the 10-valent pneumococcal nontypeable haemophilus influenzae protein d-conjugate vaccine on nasopharyngeal bacterial colonization in young children: A randomized controlled trial. Clinical Infectious Diseases, 56(3), e30-e39.
17. Gladstone, A, Jefferies, M, Tocheva, S, . . . C. (2015). Five winters of pneumococcal serotype replacement in UK carriage following PCV introduction. Vaccine, 33(17), 2015-2021.
18. Devine, V., Cleary, D., Johanna, J., Anderson, R., Morris, D., Tuck, A., . . . Clarke, S. (2016). PNEUMOCOCCAL SEROTYPES IN CARRIAGE SEVEN YEARS AFTER PNEUMOCOCCAL CONJUGATE VACCINE INTRODUCTIONS – A UK PAEDIATRIC CARRIAGE STUDY 2006/07 – 2012/13. ISPPD-10.
19. Jones, J., Gladstone, R., Devine, V. T., Morris, D., Tuck, A., Jefferies, J. M., . . . Clarke, S. C. (2016). VACCINE-INDUCED CHANGES TO PNEUMOCOCCAL CARRIAGE IN CHILDREN IN THE UK: 2006 – 2015. ISPPD-10.
20. Kim, L., Bigogo, G., Conklin, L., Odoyo, A., Carvalho, M. D. G., Odiembo, H., . . . Breiman, R. (2016). IMPACT OF 10-VALENT PNEUMOCOCCAL CONJUGATE VACCINE (PCV10) ON PNEUMOCOCCAL COLONIZATION IN CHILDREN. ISPPD-10.
21. Kim, L. C. (2014). PNEUMOCOCCAL CARRIAGE IN KENYAN CHILDREN BEFORE AND AFTER 10-VALENT PNEUMOCOCCAL CONJUGATE VACCINE (PCV10) INTRODUCTION, 2009 AND 2012. ISPPD-9, 3, 35.
22. Danino, D., Givon-Lavi, N., Ben-Shimol, S., Greenberg, D., & Dagan, R. (2016). THE IMPACT OF PCV7/PCV13 ON THE DYNAMICS OF ANTIBIOTIC NON-SUSCEPTIBLE S. PNEUMONIAE CARRIAGE (NSSP-CAR) IN YOUNG CHILDREN IN TWO DISTINCT ETHNIC GROUPS. ISPPD-10.
23. Nzenze, T. S. (2014). THE IMPACT OF PNEUMOCOCCAL CONJUGATE VACCINE (PCV) ON THE EPIDEMIOLOGY OF INVASIVE PNEUMOCOCCAL DISEASE (IPD) AND PNEUMOCOCCAL CARRIAGE IN SOWETO. ISPPD-9, 3, 14.
24. Nzenze, S. A., Shiri, T., Chinyanganya, L., Niekerk, N. v., Kathleen, K., Twine, R., . . . Madhi, S. (2016). TEMPORAL CHANGES IN PNEUMOCOCCAL COLONIZATION IN A RURAL SETTING WITH HIGH HIV PREVALENCE FOLLOWING TRANSITIONING FROM 7-VALENT TO 13-VALENT PNEUMOCOCCAL CONJUGATE VACCINE, SOUTH AFRICA. ISPPD-10.
25. Nzenze, A, von, Gottberg, Shiri, van, . . . A. (2015). Temporal Changes in Pneumococcal Colonization in HIV-infected and HIV-uninfected Mother-Child Pairs Following Transitioning From 7-valent to 13-valent Pneumococcal Conjugate Vaccine, Soweto, South Africa. J Infect Dis, 212(7), 1082-1092.
26. Prymula, Hanovcova, Splino, Kriz, Motlova, Lebedova, . . . Schuerman. (2011). Impact of the 10-valent pneumococcal non-typeable Haemophilus influenzae Protein D conjugate vaccine (PHiD-CV) on bacterial nasopharyngeal carriage. Vaccine, 29(10), 1959-1967.
27. Dunais, Bruno, Touboul, Degand, Sakarovitch, Fontas, . . . Pradier. (2015). Impact of the 13-valent pneumococcal conjugate vaccine on nasopharyngeal carriage of Streptococcus pneumoniae among children attending group daycare in Southeastern France. Pediatric Infectious Disease Journal, 34(3), 286-288.
28. Jokinen, J., Toropainen, M., Siira, L., Syrjänen, R., Kilpi, T., & Palmu, A. (2016). LONG-TERM EFFECTIVENESS OF THE PNEUMOCOCCAL HAEMOPHILUS INFLUENZAE PROTEIN D CONJUGATE VACCINE (PHID-CV10) AGAINST NASOPHARYNGEAL CARRIAGE – FINIP CARRIAGE SATELLITE STUDY. ISPPD-10.
29. Vissers, M., Wijmenga-Monsuur, A., Knol, M., Badoux, P., Houten, M. v., Sanders, E., & Rots, N. (2016). NASOPHARYNGEAL CARRIAGE OF S. PNEUMONIAE AND OTHER BACTERIA 5 YEARS AFTER THE SWITCH FROM THE 7-VALENT TO THE 10-VALENT PNEUMOCOCCAL CONJUGATE VACCINE IN THE NETHERLANDS. ISPPD-10.
30. Bosch, A. A., Houten, M. A. v., Bruin, J. P., Wijmenga-Monsuur, A. J., Trzcinski, K., Bogaert, D., . . . Sanders, E. A. (2015). Nasopharyngeal carriage of Streptococcus pneumoniae and other bacteria in the 7th year after implementation of the pneumococcal conjugate vaccine in the Netherlands. Vaccine, 34(4), 531-539.

31. Bosch, R. H. V. (2014). A NEW BALANCE IN CARRIAGE OF NON-VACCINE PNEUMOCOCCAL SEROTYPES 6.5 YEARS AFTER PCV7 IMPLEMENTATION. ISPPD-9, 3, 21.
32. Swarthout, T., Mwalukomo, T., Everett, D., Bar-Zeev, N., Kamng'ona, A., Chipasula, T., . . . Heyderman, R. S. (2016). PERSISTENT VACCINE TYPE CARRIAGE OF STREPTOCOCCUS PNEUMONIAE FOUR YEARS AFTER INTRODUCING 13-VALENT PNEUMOCOCCAL CONJUGATE VACCINE IN A 3+0 SCHEDULE IN MALAWI. ISPPD-10.
33. Van, Hoek, J, Sheppard, L, Andrews, . . . Miller. (2014). Pneumococcal carriage in children and adults two years after introduction of the thirteen valent pneumococcal conjugate vaccine in England. Vaccine, 32(34), 4349-4355.
34. Moïsi, J., Kabore, L., Njanpop-Lafourcade, B. M., Yaro, S., Ouangraoua, S., & Gessner, B. (2016). PNEUMOCOCCAL CARRIAGE IN WESTERN BURKINA FASO AFTER THE INTRODUCTION OF PCV13. ISPPD-10.
35. Ben, Shimol, Givon, Lavi, Greenberg, & Dagan. (2015). Pneumococcal nasopharyngeal carriage in children <5 years of age visiting the pediatric emergency room in relation to PCV7 and PCV13 introduction in southern Israel. Hum Vaccin Immunother, 0.
36. Laura, L. H., Donald, O. A., Susan, C. M., Angela, K., Norbert, K., Sammy, N., . . . Scott, J. A. G. (2014). Population effect of 10-valent pneumococcal conjugate vaccine on nasopharyngeal carriage of Streptococcus pneumoniae and non- typeable Haemophilus influenzae in Kilifi, Kenya: findings from cross- sectional carriage studies. The Lancet Global Health, 2(7), e397-e405. doi:10.1016/S2214-109X(14)70224-4
37. Hammitt, L. L., Akech, D. O., Morpeth, S. C., Karani, A., Nyongesa, S., Ooko, M., . . . Scott, J. A. G. (2016). POPULATION IMPACT OF 10-VALENT PNEUMOCOCCAL CONJUGATE VACCINE (PCV) ON NASOPHARYNGEAL CARRIAGE OF STREPTOCOCCUS PNEUMONIAE IN KILIFI, KENYA. ISPPD-10.
38. Wyllie,,A, L.,Wijmenga, Monsuur,A, J.,van, Houten,M, A.,Bosch,,A, A.,Groot,,J, A.,van Engelsdorp, Gastelaars,J,,Bruin,,J, P.,Bogaert,,D,,Rots,,N, Y.,Sanders,,E, A.,Trzcinski,,K. (2016). Molecular surveillance of nasopharyngeal carriage of Streptococcus pneumoniae in children vaccinated with conjugated polysaccharide pneumococcal vaccines. Sci Rep.
39. Varon,,E,,Cohen,,R,,Béchet,,S,,Doit,,C,,Levy,,C, (2015). Invasive disease potential of pneumococci before and after the 13-valent pneumococcal conjugate vaccine implementation in children. Vaccine.
40. Leach, C. W. (2014). CARRIAGE OF PNEUMOCOCCUS AND NON-TYPEABLE HAEMOPHILUS INFLUENZAE IN CHILDREN VACCINATED WITH EITHER 7-VALENT OR 10-VALENT PNEUMOCOCCAL CONJUGATE VACCINES. ISPPD-9, 3, 37.
41. Suy K, Suon K, Ly S, P. Sar P, Tan P, Day N,Turner C, Turner P. PNEUMOCOCCAL COLONISATION IN CAMBODIAN CHILDREN ONE YEAR POST PCV-13 INTRODUCTION. ISPPD-10, 2016.
42. Steens, Caugant, A, Aaberge, S, Vestrheim, & F. (2015). Decreased carriage and genetic shifts in the streptococcus pneumoniae population after changing the seven-valent to the thirteen-valent pneumococcal vaccine in Norway. Pediatric Infectious Disease Journal, 34(8), 875-883.