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COMMENTARY

Herd effects of child vaccination with pneumococcal conjugate vaccine against pneumococcal non-invasive community-acquired pneumonia: What is the evidence?

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ABSTRACT

Quantification of pneumococcal conjugate vaccines (PCVs) herd effects are mainly performed on invasive pneumococcal disease (IPD) but there is conflicting evidence regarding herd effects of PCVs on non-IPD pneumococcal community-acquired pneumonia. This review summarizes the available literature on herd effects of PCVs on non-IPD pneumococcal community-acquired pneumonia.

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Introduction

Herd effects induced by universal vaccination of children with pneumococcal conjugate vaccines (PCVs) contribute substantially to the cost-effectiveness of implementation of these vaccines in the national child immunization program.[1] Since the introduction of PCVs in children, indirect protection of unvaccinated populations against invasive pneumococcal disease (IPD) has been clearly demonstrated.[3-9] Despite a partial replacement by non-vaccine types, these studies have revealed a relevant decrease in the overall pneumococcal disease burden in all age groups. One could calculate from IPD surveillance data that for every single directly prevented episode of IPD in vaccinated children, there are several additional IPD episodes prevented in the unvaccinated adult population, particularly in elderly. (e.g.[2]) Obviously, the indirect effects are of major importance for policy makers to implement PCVs in the national child immunization programs. However, although herd effects are clearly present and their magnitude has been estimated for IPD, they are not clear for pneumococcal pneumonia in general. IPD, defined as isolation of Streptococcus pneumoniae from a normally sterile body fluid, is easy to study as long as blood cultures or other sterile cultures are routinely collected in patients with suspected pneumococcal infection and isolates are sent to a central lab for serotyping. Apart from that, it has a clear disease definition, which is not the case for non-IPD pneumococcal infection (i.e. infection caused by S. pneumoniae without isolation from a normally sterile body fluid).

Studies from the USA showed conflicting results regarding the effect of child vaccination with PCVs on pneumococcal pneumonia and all-cause pneumonia in elderly.[10-12] These studies relied on routinely collected coding data, could not distinguish IPD from non-invasive pneumococcal pneumonia, and lacked data on the serotype causing the disease. From a pathophysiological perspective it should be expected that herd effects occur in the same direction, yet, epidemiological studies could not demonstrate whether the magnitude of herd protection and replacement is the same for IPD and for non-IPD pneumococcal pneumonia. A cost-effectiveness analysis elegantly demonstrated that assumptions about herd effects for non-IPD pneumococcal pneumonia have large impact on the cost-effectiveness estimate.[13] This is because, in adults, only one in four pneumococcal pneumonia episodes yields S. pneumoniae from a sterile site and can thus be classified as IPD.[14] Although mortality and costs are lower in non-IPD pneumococcal pneumonia compared to IPD,(15) the three times higher frequency causes it to contribute substantially to cost-effectiveness estimates. The aim of the present paper is to review recent developments in estimating herd effects of child vaccination with PCVs on non-IPD pneumococcal pneumonia.

Respiratory tract cultures

Measurement of herd effects on non-IPD pneumococcal pneumonia is challenging because the conventional methods for serotyping (needed to disentangle herd protection and replacement) require the availability of an S. pneumoniae strain. Richter and colleagues therefore performed a study in which S. pneumoniae isolates from clinically relevant infectious disease episodes (as deemed by the sending laboratory) were collected from 43–45 hospitals during four one-year seasons between 1999 and 2011.[16] Both samples from normally sterile and non-sterile sites were included. 64–72% of the non-sterile samples were derived from the lower respiratory tract, followed by middle ear fluid (8-12%) and sinus (4-11%). With over a thousand non-invasive and over 400 invasive isolates per season under

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study, the investigators clearly demonstrated a decreasing proportion of PCV7 serotypes in both invasive and non-invasive isolates. PCV13 serotypes increased until the introduction of PCV13, after which they decreased slightly. The less steep decline in the proportion of PCV7 serotypes in non-invasive isolates (from 50.1% to 4.2%) compared to invasive isolates (from 64.0% to 3.8%) might suggest that herd effects are less strong or more delayed for non-invasive isolates. However, for several reasons, this cannot be firmly concluded. First, the non-sterile isolates were derived from respiratory samples, a third of these being from the upper respiratory tract. It is hard to distinguish infection from colonization, even in sputum samples, let alone in upper respiratory tract samples. Although colonization is a prerequisite for infection with S. pneumoniae, it has been demonstrated that colonization capacity does not go hand in hand with pathogenicity, i.e., some serotypes are better colonizers while others are more pathogenic.[17] If this is distinct for PCV7 and nonPCV7 serotypes, including colonizing strains will bias the results. Another difficulty is that all age groups were included in the study, including those that received PCV7. Nearly one quarter of isolates was derived from children under 5 years of age, impeding the study of mere herd effects. Finally, the lack of numerator data complicate inference on the direction and magnitude of the effect, e.g., the change in serotype proportions could be caused by only an increase in the absolute number of non-PCV7 serotypes or by a decrease in the absolute number of PCV7 serotypes.

In a more recently published study Mendes and colleagues performed serotyping of 2,927 clinical S. pneumoniae isolates retrieved from non-sterile sites in adults patients.[18] These were derived between 2009 and 2012 from 50 hospitals located in the 9 US Census regions. Only patients presenting with a respiratory infection were included and 87% of the cultures were from the lower respiratory tract. During the observation period, PCV7 serotypes (i.e., those covered by the 7-valent PCV) were stable at around 5% of all samples available, PCV13 serotypes declined from 35.5% to 28.2%. Obviously, as the results were presented as proportion of all samples, nonPCV13 serotypes increased over the same period to add up to 100%. Compared to the previous study, this study confirmed that PCV7 serotypes keep circulating at low proportions of around 5%. However, also in this study, mixing of colonization with infection cannot be excluded and absolute effects could not be calculated.

Serotype specific urinary antigen tests

The study of serotype distributions for non-IPD pneumococcal pneumonia has long been hampered by the lack of a sensitive and specific test to diagnose non-IPD pneumococcal disease and, at the same time, determine the serotype. As explained, serotyping of pneumococcal isolates from respiratory samples yields difficulties for distinguishing infection from colonization, i.e., the test is not specific for infection. The development of serotype-specific urine antigen tests has paved the way for more accurate determination of herd effects for non-IPD pneumococcal pneumonia. These assays are based on the excretion of capsular polysaccharide in urine, which is low during colonization and increases in case of infection. To achieve specificity (i.e., to exclude colonization) the tests use a cutoff level to declare positivity. As a result, sensitivity of the test may be lost to some extent if there is overlap in the amount of capsular antigen excretion between colonized and infected patients. Two assays are currently available. The serotype-specific urinary antigen detection assay (UAD) was developed by Pfizer, USA, detects the 13 serotypes included in PCV13, and has an estimated sensitivity and specificity of 98% and 100%, respectively.[19] The Bio-Plex assay, developed by Bio-Rad, USA, is capable of detecting 14 pneumococcal serotypes (1, 3, 4, 5, 6A/C, 6B, 7F/A, 8, 9 V, 14, 18, 19A, 19F, and 23F), and has an estimated sensitivity and specificity of 79.3 and 99.3%, respectively.[20] Noteworthy, the sensitivity of these tests has been estimated using blood-culture positive (i.e., proven) cases while the specificity has been measured using cases with a confirmed alternative pathogen and/or confirmed absence of pneumonia. It is not possible to estimate the sensitivity and specificity for non-IPD pneumococcal CAP as there is no gold standard available. Four papers have used these tests to assess herd effects for non-IPD pneumococcal CAP. The papers will be discussed in order of publication.

Rodrigo and colleagues aimed to study the association between adults having contact with vaccinated or unvaccinated children and pneumococcal infections.[21] They prospectively included 1,130 adult patients with community-acquired pneumonia (CAP) from two hospitals in the UK between September 2008 and September 2011. A urine sample was collected in all patients to perform a BinaxNOW urinary pneumococcal antigen test (PUAT) and the Bio-Plex assay. A blood culture was drawn in 88% of patients and S. pneumoniae isolates were serotyped using conventional methods. Pneumococcal etiology was confirmed in 410 individuals, with a positive blood culture in 43 (10.3%) and a positive Bio-Plex assay in 274 (66.8%) individuals; the serotype was determined in 274. They found that patients having contact were at higher risk of having pneumococcal etiology, irrespective of the child vaccination status. Patients having contact with a PCV7 vaccinated child where less likely to have a PCV7 serotype as causing pathogen compared to patients that had contact with non-vaccinated child (OR 0.37, 95% CI 0.14-0.99). This was the first study to demonstrate that herd effects exist for non-IPD pneumococcal CAP through direct contact with vaccinated children. However, no comparison between IPD and non-IPD pneumococcal CAP was made, probably because of the limited number of bacteremia cases.

After another two years of recruitment for the same study, Rodrigo and colleagues reported trends in serotype specific incidences of pneumococcal pneumonia.[22] Of 2,229 patients with CAP, 653 (29.3%) had confirmed pneumococcal CAP: 407 with a positive PUAT, 411 with a positive Bio-Plex assay, and 87 with a positive blood culture. As in the previous publication, the proportion of pneumococcal pneumonia with bacteremia was low (13.3%) compared to a systematic review that found bacteremia in 25% of pneumococcal pneumonia patients.[14] As a result, the investigators were not able to compare trends for IPD and non-IPD pneumococcal CAP separately. Due to the overrepresentation of non-IPD pneumococcal CAP, they claim that trends will be largely due to this group of patients. Unfortunately, because of the lower sensitivity of the Bio-Plex assay, a positive PUAT with negative Bio-Plex assay and negative

blood culture could not be considered as being a non-Bio-Plex serotype. Therefore, the investigators had to exclude patients with negative Bio-Plex and negative or missing blood culture from the analysis, resulting in the availability of 436 (66.8%) of the pneumococcal CAP patients for the time trend analysis. A positive aspect of the study is that, because the size and demographics of the underlying population was known, it was possible to calculate incidences for the different serotypes. The incidence of CAP episodes due to PCV7 serotypes decreased from 11.1 per 100,000 in 2008–2009 to 1.6 per 100,000 in 2009–2010 and after that varied from 0.4 to 2.3. Additional PCV13 serotypes topped in 2009–2010 with 11.5 per 100,000 and then decreased slowly to 6.3 per 100,000 in 2012–2013. Importantly, PCV7 was introduced in 2006 in the UK, followed by PCV13 in April 2010, therefore, the investigators measured the late herd effects of PCV7 and the first effects of PCV13. Non-PCV13 serotypes were between 2.1 and 4.3 per 100,000 with no discernible time trend. However, due to the exclusion of Bio-Plex and blood culture negative cases, the incidences of the non-PCV13 will be largely underestimated. Moreover, the Bio-Plex assay only included the non-PCV13 serotype 8. Replacement effects could have been masked if they are less strong for serotype 8 compared to other non-PCV13 serotypes, as these rely on the less sensitive blood culture. Although the incidence of untyped pneumococcal CAP didn't change, the relative contribution increased (as can be calculated from the raw numbers). These will include PCV7 and PCV13 serotypes in unknown amounts (but probably decreasing throughout the study) and non-PCV13 serotypes. Therefore, the study cannot be used to quantify replacement effects.

Pletz and colleagues included 358 patients from CAPNETZ, a German prospective multicenter cohort study, with non-IPD pneumococcal CAP with unknown serotype. They were selected by having a positive PUAT and negative cultures (with at least a blood culture obtained). The serotype specific UAD was performed on frozen urine samples.[23] Serotype distributions were compared between two groups, those presenting between 2001 and 2006 and those presenting between 2007 and 2011. In Germany, PCV7 was introduced in 2007 and was replaced by PCV13 in 2010, therefore, the study assessed the effect of PCV7. The proportion of patients with PCV7 serotype pneumococcal CAP decreased from 31.3% to 14.8%. By year, the proportion of PCV7 serotypes decreased gradually from 34.1% in 2006 to 4.3% in 2011. PCV13 serotypes (including PCV7) were stable: 61.5% in the first and 59.7% in the second period, which was mainly caused by increasing proportions of serotypes 1, 3, and 7F. Colloquially, the non-PCV13 proportion (i.e., with a negative UAD) also remained stable at 38.5% and 40.3%. As in the first two studies, no absolute effects are reported and no adequate comparison with IPD was possible due to the low number of bacteremic cases. Another limitation of the study is that they excluded all patients with positive sputum cultures but negative blood cultures, while these should be considered non-IPD pneumococcal CAP if the PUAT or serotype specific UAD is positive.

Finally, van Werkhoven and colleagues combined two study cohorts of CAP patients from the Netherlands conducted between 2008 and 2013.[24] The serotype specific UAD and PUAT was performed on urine samples and blood cultures were collected in 78–88% of CAP patients. Non-IPD pneumococcal CAP was defined as having a positive PUAT or UAD and not having a positive culture from a normally sterile body fluid. Patients with a positive PUAT and negative UAD were considered to be non-PCV13 serotype CAP. Because of the eligibility criteria in one study, the analysis was restricted to patients over 65 years of age. Time trends of the serotype distribution were compared with data from the Dutch national IPD surveillance, covering about 25% the Dutch population. A total of 270 non-IPD pneumococcal CAP episodes were included in the analysis. The proportion of non-IPD pneumococcal CAP episodes due to PCV7 decreased from 28% in 2008–2009 to 7% in 2012–2013. Additional serotypes included in PCV10 and PCV13 were stable, on average 19% and 29%, respectively. The proportion of non-PCV13 serotypes increased from 30% to 37%. In the Netherlands, PCV7 was introduced in 2006 and was replaced by PCV10 in 2011. No discernible effect of PCV10 was visible in the two years following its implementation. There was no difference in serotype trends between the national IPD data and non-IPD pneumococcal CAP data. Again, no incidences could be calculated, precluding firm conclusions about the contribution of herd protection and replacement to the observed proportions.

Discussion

What can we conclude from these studies? First of all, herd effects are present for non-IPD pneumococcal CAP, as demonstrated by these studies and as was to be expected. Second, there is an absolute reduction of serotypes covered by the vaccine administered to children, as demonstrated by the German study. Third, the speed and magnitude of the relative herd effects are similar for IPD and non-IPD pneumococcal CAP as revealed by the Dutch study. So, are we there yet? It is tempting to conclude that the effects are the same, as (so far) there is no signal that they are different. However, as shown in two extreme hypothetical scenarios, very different absolute effects can result in the same relative effect (Table 1). Stated differently, what we have seen in the studies so far could be equally explained by smaller and larger herd protection and replacement effects for non-IPD pneumococcal CAP compared to

Table 1. Putative scenarios that result in similar relative herd effects.

Scenario 1: herd protection and replacement comparable to IPD effects*					
Year since PCV7 introduction	0	1	2	3	4
PCV7 absolute	100	80	60	40	20
Non-PCV7 absolute	100	110	120	130	140
PCV7 relative	50%	42%	33%	24%	13%
Scenario 2: there is modest herd protection and strong replacement*					
Year since PCV7 introduction	0	1	2	3	4
PCV7 absolute	100	90	80	70	60
Non-PCV7 absolute	100	124	160	227	420
PCV7 relative	50%	42%	33%	24%	13%
Scenario 3: there is strong herd protection and no replacement*					
Year since PCV7 introduction	0	1	2	3	4
PCV7 absolute	100	73	50	31	15
Non-PCV7 absolute	100	100	100	100	100
PCV7 relative	50%	42%	33%	24%	13%

*Hypothetical data

IPD. For this reason, it would have been valuable if the absolute effect estimates from the UK study were compared to national IPD surveillance data from the UK from the same time period, even though the comparison of non-PCV13 serotype trends would still be impeded by the large number of Bio-Plex assay negative cases.

In countries with existing IPD surveillance that are considering a change in the pneumococcal vaccination schedule, or that have recently changed, it would be valuable to set up a non-IPD pneumococcal CAP surveillance system as an additive to the IPD surveillance. Challenges to overcome in setting up this network are to collect (residual) urine samples in all CAP patients, to apply a clear case definition to routinely collected data, and to use the most specific and sensitive serotype specific urine test available. However, as the incidence of non-IPD pneumococcal CAP is three times larger compared to IPD, the surveillance network could be kept smaller compared to the IPD surveillance. Such a system will provide answers to the important remaining questions with regards to herd effects induced by PCV use in children, particularly for non-IPD pneumococcal CAP in adults.

Disclosure of potential conflicts of interest

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References

[1] McIntosh EDG, Conway P, Willingham J, Hollingsworth R, Lloyd A. Pneumococcal pneumonia in the UK—how herd immunity affects the cost-effectiveness of 7-valent pneumococcal conjugate vaccine (PCV). Vaccine [Internet] 2005 [cited 2016 Nov 8]; 23(14):1739-45. Available from: http://linkinghub.elsevier.com/retrieve/pii/S0264410X04007315; http://dx.doi.org/10.1016/j.vaccine.2004.08.051

[2] Knol MJ, Wagenvoort GHJ, Sanders EAM, Elberse K, Vlaminckx BJ, de Melker HE, van der Ende A. Invasive pneumococcal disease 3 years after introduction of 10-valent pneumococcal conjugate vaccine, the Netherlands. Emerg Infect Dis [Internet] 2015 [cited 2015 Oct 27]; 21(11):2040-4. Available from: http://www.ncbi.nlm.nih.gov/pubmed/26488415; http://dx.doi.org/10.3201/eid2111.140780

[3] Direct and indirect effects of routine vaccination of children with 7-valent pneumococcal conjugate vaccine on incidence of invasive pneumococcal disease–United States, 1998-2003. MMWR Morb Mortal Wkly Rep 2005; 54(1545–861X (Electronic)):893-7.

[4] Moore MR, Link-Gelles R, Schaffner W, Lynfield R, Lexau C, Bennett NM, Petit S, Zansky SM, Harrison LH, Reingold A, et al. Effect of use of 13-valent pneumococcal conjugate vaccine in children on invasive pneumococcal disease in children and adults in the USA: analysis of multisite, population-based surveillance. Lancet Infect Dis 2015; 15(3):301-9; PMID:25656600; http://dx.doi.org/10.1016/S1473-3099(14)71081-3

[5] Miller E, Andrews NJ, Waight PA, Slack MPE, George RC. Effectiveness of the new serotypes in the 13-valent pneumococcal conjugate vaccine. Vaccine 2011; 29(49):9127-31; PMID:21983361; http://dx.doi.org/10.1016/j.vaccine.2011.09.112

[6] Steens A, Bergsaker MAR, Aaberge IS, Rønning K, Vestrheim DF. Prompt effect of replacing the 7-valent pneumococcal conjugate vaccine with the 13-valent vaccine on the epidemiology of invasive pneumococcal disease in Norway. Vaccine 2013; 31(52):6232-8; PMID:24176490; http://dx.doi.org/10.1016/j.vaccine.2013.10.032

[7] Harboe ZB, Dalby T, Weinberger DM, Benfield T, Mølbak K, Slotved HC, Suppli CH, Konradsen HB, Valentiner-Branth P. Impact of 13-valent pneumococcal conjugate vaccination in invasive pneumococcal disease incidence and mortality. Clin Infect Dis 2014; 59(8):1066-73; PMID:25034421; http://dx.doi.org/10.1093/cid/ciu524

[8] Regev-Yochay G, Paran Y, Bishara J, Oren I, Chowers M, Tziba Y, Istomin V, Weinberger M, Miron D, Temper V, et al. Early impact of PCV7/PCV13 sequential introduction to the national pediatric immunization plan, on adult invasive pneumococcal disease: A nationwide surveillance study. Vaccine 2015; 33(9):1135-42; PMID:25613717; http://dx.doi.org/10.1016/j.vaccine.2015.01.030

[9] National Institute for Health and Welfare Finland. Incidence of invasive pneumococcal disease in Finland [Internet]. 2014. Available from: https://www.thl.fi/en/web/thlfi-en/topics/information-packages/incidence-of-invasive-pneumococcal-disease-in-finland.

[10] Grijalva CG, Nuorti JP, Arbogast PG, Martin SW, Edwards KM, Griffin MR. Decline in pneumonia admissions after routine childhood immunisation with pneumococcal conjugate vaccine in the USA: a time-series analysis. Lancet 2007; 369(9568):1179-86; PMID:17416262; http://dx.doi.org/10.1016/S0140-6736(07)60564-9

[11] Nelson JC, Jackson M, Yu O, Whitney CG, Bounds L, Bittner R, Zavitkovsky A, Jackson LA. Impact of the introduction of pneumococcal conjugate vaccine on rates of community acquired pneumonia in children and adults. Vaccine 2008; 26(38):4947-54; PMID:18662735; http://dx.doi.org/10.1016/j.vaccine.2008.07.016

[12] Simonsen L, Taylor RJ, Schuck-Paim C, Lustig R, Haber M, Klugman KP. Effect of 13-valent pneumococcal conjugate vaccine on admissions to hospital 2 years after its introduction in the USA: a time series analysis. Lancet Respir Med [Internet] 2014 [cited 2015 Jan 5]; 2(5):387-94. Available from: http://www.ncbi.nlm.nih.gov/pubmed/24815804; http://dx.doi.org/10.1016/S2213-2600(14)70032-3

[13] Smith KJ, Wateska AR, Nowalk MP, Raymund M, Nuorti JP, Zimmerman RK. Cost-effectiveness of adult vaccination strategies using pneumococcal conjugate vaccine compared with pneumococcal polysaccharide vaccine. JAMA 2012; 307(1538–3598 (Electronic)):804-12; PMID:22357831

[14] Said MA, Johnson HL, Nonyane BAS, Deloria-Knoll M, O'Brien KL, Andreo F, Andreo F, Beovic B, Blanco S, Boersma WG. Estimating the burden of pneumococcal pneumonia among adults: a systematic review and meta-analysis of diagnostic techniques. PLoS One [Internet] 2013 [cited 2014 Nov 27]; 8(4):e60273. Available from: http://www.pubmedcentral.nih.gov/articlerender.fcgi?artid=3615022&tool=pmcentrez&rendertype=abstract; http://dx.doi.org/10.1371/journal.pone.0060273

[15] Mangen M-JJ, Rozenbaum MH, Huijts SM, van Werkhoven CH, Postma DF, Atwood M, van Deursen AM, van der Ende A, Grobbee DE, Sanders EA. Cost-effectiveness of adult pneumococcal conjugate vaccination in the Netherlands. Eur Respir J [Internet] 2015 [cited 2015 Jul 21]; Available from: http://www.ncbi.nlm.nih.gov/pubmed/26160871.

[16] Richter SS, Heilmann KP, Dohrn CL, Riahi F, Diekema DJ, Doern G V. Pneumococcal serotypes before and after introduction of conjugate vaccines, United States, 1999-2011(1.). Emerg Infect Dis [Internet] 2013 [cited 2016 Oct 14]; 19(7):1074-83. Available from: http://www.ncbi.nlm.nih.gov/pubmed/23763847; http://dx.doi.org/10.3201/eid1907.121830

[17] van Hoek AJ, Sheppard CL, Andrews NJ, Waight PA, Slack MPE, Harrison TG, Ladhani SN, Miller E. Pneumococcal carriage in children and adults two years after introduction of the thirteen valent pneumococcal conjugate vaccine in England. Vaccine [Internet] 2014 [cited 2015 Mar 2]; 32(34):4349-55. Available from: http://www.ncbi.nlm.nih.gov/pubmed/24657717; http://dx.doi.org/10.1016/j.vaccine.2014.03.017

[18] Mendes RE, Hollingsworth RC, Costello A, Jones RN, Isturiz RE, Hewlett D, Farrell DJ. Non-invasive Streptococcus pneumoniae serotypes recovered from hospitalized adult patients in the United States (2009-2012). Antimicrob Agents Chemother 2015;59(9):5595-601; http://dx.doi.org/10.1128/AAC.00182-15

[19] Huijts SM, Pride MW, Vos JMI, Jansen KU, Webber C, Gruber W, Boersma WG, Snijders D, Kluytmans JA, van der Lee I, et al. Diagnostic accuracy of a serotype-specific antigen test in community-acquired pneumonia. Eur Respir J [Internet] 2013 [cited 2014 Oct 7];

42(5):1283-90. Available from: http://www.ncbi.nlm.nih.gov/pubmed/23397295; http://dx.doi.org/10.1183/09031936.00137412

[20] Sheppard CL, Harrison TG, Smith MD, George RC. Development of a sensitive, multiplexed immunoassay using xMAP beads for detection of serotype-specific streptococcus pneumoniae antigen in urine samples. J Med Microbiol 2011;60(Pt 1):49-55; http://dx.doi.org/10.1099/jmm.0.023150-0

[21] Rodrigo C, Bewick T, Sheppard C, Greenwood S, Macgregor V, Trotter C, Slack M, George R, Lim WS. Pneumococcal serotypes in adult non-invasive and invasive pneumonia in relation to child contact and child vaccination status. Thorax [Internet] 2014 Feb [cited 2014 Sep 25]; 69(2):168-73. Available from: http://www.ncbi.nlm.nih.gov/pubmed/24048505; http://dx.doi.org/10.1136/thoraxjnl-2013-203987

[22] Rodrigo C, Bewick T, Sheppard C, Greenwood S, Mckeever TM, Trotter CL, Slack M, George R, Lim WS. Impact of infant 13-valent pneumococcal conjugate vaccine on serotypes in adult pneumonia. Eur Respir J [Internet] 2015 [cited 2015 Mar 23]; Available from: http://www.ncbi.nlm.nih.gov/pubmed/25792633.

[23] Pletz MW, Ewig S, Rohde G, Schuette H, Rupp J, Welte T, Suttorp N, Forstner C; CAPNETZ Study Group. Impact of pneumococcal vaccination in children on serotype distribution in adult community-acquired pneumonia using the serotype-specific multiplex urinary antigen detection assay. Vaccine 2016; 34(20):2342-8; PMID:27016653; http://dx.doi.org/10.1016/j.vaccine.2016.03.052

[24] van Werkhoven CH, Hollingsworth RC, Huijts SM, Bolkenbaas M, Webber C, Patterson S, Sanders EA, Bonten MJ. Pneumococcal conjugate vaccine herd effects on non-invasive pneumococcal pneumonia in elderly. Vaccine 2016; 34(28):3275-82; PMID:27171754; http://dx.doi.org/10.1016/j.vaccine.2016.05.002