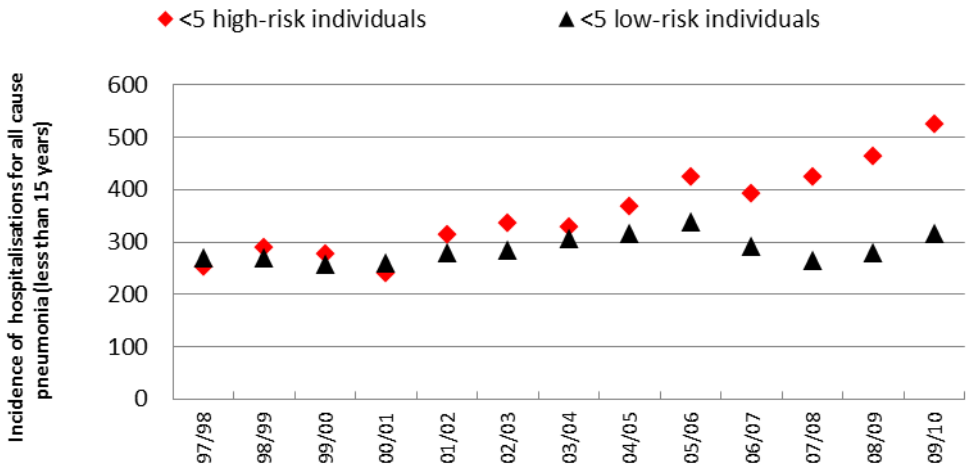
Appendix 1: Results of the interrupted time series analysis

Results of the segmented linear regression, which divides a time series into pre- and post-intervention portions. As the routine infant seven-valent pneumococcal conjugate vaccine programme was introduced in September 2006 with a campaign for those under the age of 2 years, we chose 2006-07 as the intersection between segments (i.e., the intervention). The graph displays the incidence of hospitalisation for all cause pneumonia before and after the introduction of the seven-valent pneumococcal conjugate vaccine, and Table 1 shows the results of the regression analysis. Over the time period there was a general trend for an increase in hospitalisations for pneumonia in children under 5 years of age in both high and low risk groups. In the low risk group the introduction of the seven-valent pneumococcal conjugate vaccine is associated with an immediate and significant reduction in incidence, while such a significant reduction was not observed in the high-risk group. Furthermore, during the post intervention period the incidence in the low risk group did not significantly change while in the high risk group an increase was observed (although also not significant p=0.07)



Appendix 1, Figure 1. Comparison in the incidence trend of hospitalized pneumonia in low-risk and high risk individuals (eligible for the 7-valent pneumococcal conjugate vaccine) before and after the introduction of 7-valent pneumococcal conjugate vaccine.

The expected annual incidence of hospitalisations for non-bacteraemic pneumonia Y_i, is modelled using multiple linear regression. The final model was:

$$Y_i = B_0 + B_1*T + B_2*D + B_3*P$$

Where T is time (in years) since the start of the observation period, D is a dummy variable indicating pre- or post-vaccination period (coded 0 prior to intervention, and

1 otherwise) and P is the time since vaccination, where time prior to vaccination is coded 0.

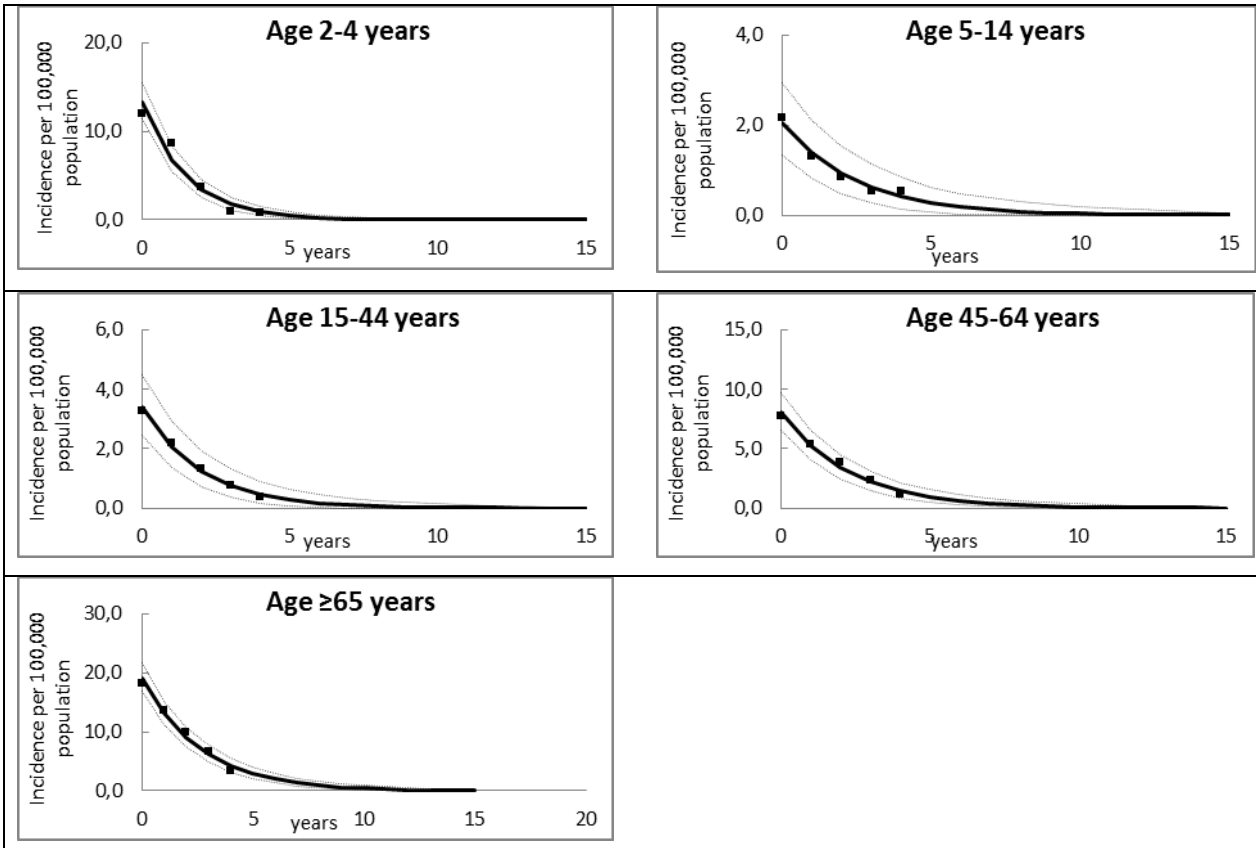
Appendix 1 Table 1, showing the outcome of the model for seven-valent pneumococcal conjugate vaccine eligible children (less than 5 years of age)				
	Coefficients	*Standard Error*	*t Statistics*	*P-value*
Low risk children (<5 years of age)				
Intercept, B_0	240.78	11.89	20.25	**<0.01**
Overall trend <5 years, B_1	9.10	2.11	4.31	**<0.01**
Change in level after vacc, <5 years, B_2	-56.81	22.43	-2.53	**0.03**
Difference in trend post- intervention <5 years, B_3	-0.41	7.62	-0.05	0.96
High risk children (<5 years of age)				
Intercept, B_0	221.58	19.10	11.60	**<0.01**
Overall trend <5 years, B_1	18.51	3.39	5.45	**0.00**
Change in level after vacc, <5 years, B_2	-47.95	36.04	-1.33	0.22
Difference in trend post- intervention <5 years, B_3	25.68	12.24	2.10	0.07

The incidence and case fatality ratio of non-bacteraemic pneumonia are shown in table 2.

Appendix 1, Table 2, showing the incidence, case fatality ratios of non- bacteraemic pneumonia.			
Age group	Incidence per 100,000 (2009/10)	Case fatality ratios	Share of pneumococcal non- bacteraemic pneumonia which are 13-valent pneumococcal conjugate vaccine serotypes
2-4	270	1.5%	Similar to invasive pneumococcal disease see Appendix 2
5-14	62	2.6%	Similar to invasive pneumococcal disease see Appendix 2
15-44	218	10.8%	Similar to invasive pneumococcal disease see Appendix 2
45-64	744	17.8%	Similar to invasive pneumococcal disease see Appendix 2
65+	2883	34.1%	Similar to invasive pneumococcal disease see Appendix 2

Appendix 2: Poisson regression model to predict the future reduction in VT invasive pneumococcal disease

To predict the future reduction in invasive pneumococcal disease due to vaccine serotypes we fitted Poisson regression models to the corrected number of incident culture confirmed invasive pneumococcal disease cases due to vaccine serotypes for the post seven-valent pneumococcal conjugate vaccine period to the total number of invasive pneumococcal disease cases in yr 0 including PCR positives. We assumed that the number of incident cases is a variable with a Poisson distribution that has a mean depending on the explanatory variable, time (after the introduction of the infant seven-valent pneumococcal conjugate vaccine programme). Numbers of cases were obtained from a recently published study by our group[1] and data regarding the population size were obtained from the Office for National Statistics[2]. The models were estimated using the maximum likelihood method, while exact confidence intervals were calculated using the standard chi-square intervals. We projected the estimates for a maximum of 15 years using the aforementioned Poisson model and projected estimates of the population. Results of the prediction model are displayed in Appendix Figure 1.



Appendix 2, Figure 1. Expected decrease (solid line) and 95% confidence intervals (dashed) in the incidence of invasive pneumococcal disease due to vaccine serotypes after the introduction of the seven-valent pneumococcal conjugate vaccine in England and Wales. Data points represents the number of cases corrected for underlying trends in case ascertainment pre (average 2000-2006) and the post-seven-valent pneumococcal conjugate vaccine vaccination incidence[1].

Appendix 3: Vaccine efficacy

Studies have shown that both antibody responses and opsonic activity in adults are as high or higher after vaccination with the pneumococcal conjugate vaccines than after vaccination with the 23-valent vaccination for the serotypes included in both vaccine formulations[3]. Also young age could be associated with a more pronounced immune response[4, 5]. Immunogenicity studies specifically focussing on high-risk individuals such as the frail elderly[6], HIV-infected[7, 8], and transplant recipients[9, 10] show no significant difference between vaccination with the 23-valent polysaccharide vaccine and the seven-valent pneumococcal conjugate vaccine , although studies focussing on other high-risk individuals e.g. survivors of a pneumococcal pneumonia, and allogeneic stem cell transplant recipients do suggest a (small) advantage of seven-valent pneumococcal conjugate vaccine over 23-valent polysaccharide vaccine[11, 12].

However, two clinical trials evaluating vaccine efficacy in high-risk groups show a favourable efficacy estimates for the pneumococcal conjugate vaccines. Both studies looked at HIV-infected individuals, one focussed on adults[13] while the other focussed on infants[14]. The first one included 496 adult Malawi patients, who had recovered from documented invasive pneumococcal disease, of which 88% were HIV-positive. The efficacy of the seven-valent pneumococcal conjugate vaccine against invasive pneumococcal disease after 2 doses during the entire follow-up period (median 1.2 years) in HIV-infected adults was estimated at 74% (95% confidence interval [CI], 30-90), but decreased after the first year from 85% to 25%. In contrast a study comparing the 23-valent polysaccharide vaccine with a placebo in HIV infected adults with similar clinical endpoints showed no clinical benefit of the 23-valent polysaccharide vaccine[15]. Another study performed in South Africa evaluated the efficacy of 3 doses of the 9-valent conjugated pneumococcal vaccine in both children with and without HIV infection[14]. The efficacy against the first episode of invasive pneumococcal disease among HIV-infected infants was 65% (95% CI, 24-86) compared to 83% (95% CI, 39-97) in children without HIV infection. Also in HIV-infected children the efficacy attenuated faster during 5 years of follow-ups 38.8% (95% CI, -7.8-65.2) compared with uninfected children 77.8% (95%CI 34.4-92.5)[16]. Furthermore, this trial also evaluated the efficacy against the first episode if radiological confirmed alveolar consolidation (note that this is a measure of all-cause pneumonia, not specific to the pneumococcus). In HIV infected children the point estimate was 13%(95% CI, -7-29), while in non infected children the efficacy was 20%.

In conclusion, immunogenicity data for conjugated pneumococcal vaccines show generally better results than the 23-valent polysaccharide vaccine in non-immunosupressed adults, while in adults with specific underlying conditions no or only small advantages are observed for the seven-valent pneumococcal conjugate vaccine over the 23-valent polysaccharide vacccine . Nevertheless, a clinical trial showed that conjugated pneumococcal vaccine is effective in HIV-infected adults, while the 23-valent polysaccharide vaccine failed to demonstrate efficacy in a similar study. Also, the nine valent pneumococcal vaccine was shown to be effective in HIV-infected infants, although the vaccine efficacy was lower compared to those without HIV infection. It is however uncertain if these efficacy estimates will also apply for developed countries in which the invasive pneumococcal disease incidence is lower and HAART therapy is generally available[3]. Furthermore, it should be noted that these studies used multiple doses of the conjugated vaccine.

Appendix 4: Elicitation of vaccine efficacy estimates

We performed a formal elicitation of expert opinions on vaccine related parameters to construct a probability distribution that represent the experts' knowledge and uncertainty. The aim of the elicitation were to estimate efficacy and the level of waning immunity after vaccination with the13-valent pneumococcal conjugate vaccine in both high-risk immunocompromised and high-risk immunocompetent individuals aged less than 65 years or more than 65 years of age after one (one dose was used in the base case analysis) or two doses of the vaccine

The level of waning immunity was calculated by letting the experts estimate the vaccine efficacy during the first and third year after vaccination. Based on the difference in vaccine efficacy between these years the annual waning rate was calculated assuming an exponential decay of immunity.

A questionnaire covering these areas was designed using an iterative process involving trials on three test subjects and modifications to the questionnaire based on test subject feedback. We recruited five experts of the Pneumococcal Subcommittee of the Joint Committee on Vaccination and Immunisation to undertake the elicitation process, as it is known that there is little additional benefit in combining expert judgments from more than 4 or 5 experts[17]. The experts were provided with background information on the question topics, the aims of the study, and the questionnaire by email.

Probability distributions were elicited using the quartile/probability technique, where each expert separately specified their median, lower, and upper quartile estimate[17]. After the initial elicitation, distributions were fitted to the estimations and experts were given the opportunity to revise their estimations if they thought this was necessary after comparing their estimate with those of the other experts. Subsequently, the obtained experts distributions were combined mathematically using the method of (linear) opinion pooling. A beta distribution was chosen to fit to the experts' responses as this distribution is defined on the interval (0,1) and therefore suitable for quantifying uncertainty in probabilities. To obtain the distributions we used the Sheffield Elicitation Framework (SHELF, v2.0 www.tonyohagan.co.uk/shelf/).

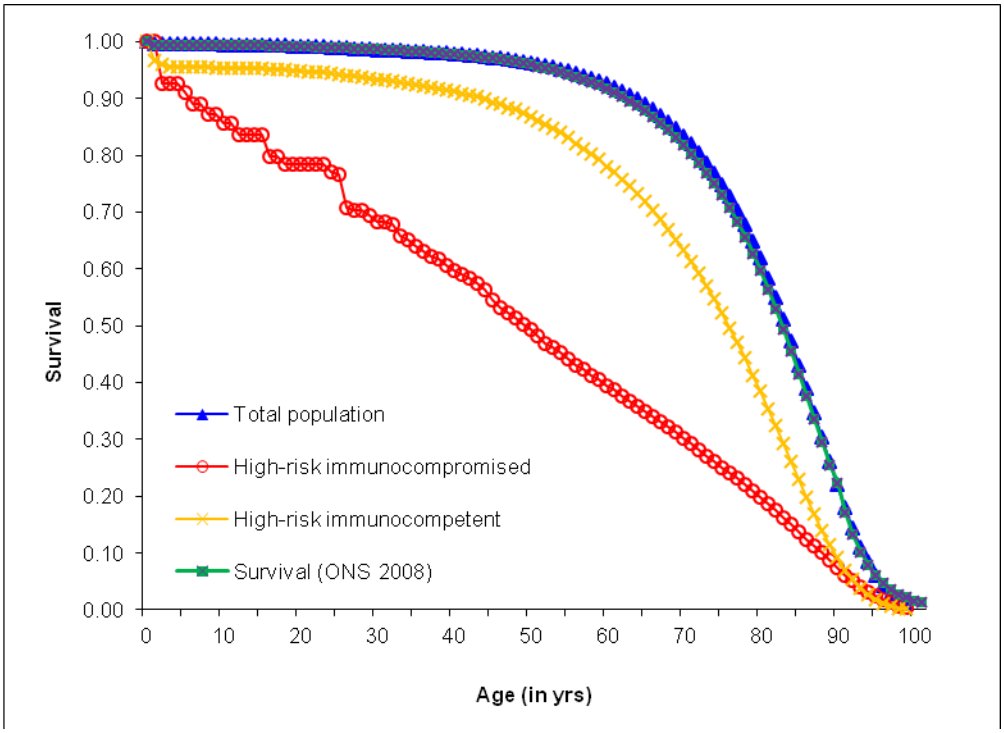
The result of the elicitation can be found in Table 1 of the main paper for the base-case analysis (after a single dose of the 13 valent pneumococcal conjugated vaccine) and the results after two doses of the 13 valent pneumococcal conjugated vaccine can be found in table 1.

Appendix 4, Table 1. Average vaccine efficacy after two doses of 13-valent pneumococcal conjugate vaccine during the first year of vaccination								
Type of disease	Invasive pneumococcal disease				Non-bacteraemic pneumococcal pneumonia			
Immunostatus	Immunocompetent		Immunocompromised		Immunocompetent		Immunocompromised	
Age (in years)	2-65	≥65	2-65	≥65	2-65	≥65	2-65	≥65
Vaccine efficacy$	85%	74%	68%	54%	56%	46%	41%	32%

$ Efficacy estimates do not apply for serotype 3 (see method section) [16]

Appendix 5: Life expectancy among high-risk groups

The Figure below shows the survival curves for the high-risk immunocompromised population, high-risk immunocompent, the general population based on the RCGP data collected for the years 2005 to 2010. These data were used to calculate different background life expectancies. The Royal College of General Practitioners (RCGP) data was validated by comparing the calculated survival curves with the survival curve of the general population based on mortality data obtained from the Office for National Statistics (ONS) for the year 2008[2].



Appendix 5, Figure 1. Survival curves for individuals at different risk of developing invasive pneumococcal disease and the general population. Data taken from Royal College of General Practitioners database and compared with the survival curve for the general population obtained from the Office for National Statistics[2].

Appendix 6: Used ICD-10 codes to identify possible acute pneumococcal disease

A40.3	Septicaemia due to Strep Pneumoniae
A40.8	Other streptococcal septicaemia
A40.9	Strep. Septicaemia non specified
A41.9	Septicaemia, unspecified
A49.1	Streptococcal unspecified
A49.9	Bacterial infection, unspecified
B95.3	Step pneum as the cause of disease classified in other chapters
B95.4/B95.5	Streptococcus as the cause of disease classified in other chapters
G00.1	Pneumococcal meningitis
G00.8	Other bacterial meningitis
G00.9	Bacterial meningitis unspecified
G04.2	Bacterial meningoencephalitis and meningomyelitis not elsewhere classified
G04.8	Other encephalitis, myelitis and encephalomyelitis
G04.9	Encephalitis, myelitis and encephalomyelitis, unspecified
G05.0	Encephalitis, myelitis and encephalomyelitis in bacterial diseases classified elsewhere
I33.0	Acute and subacute infective endocarditis
J00	Acute Nasopharyngitis
J01	Acute sinusitis
J02.0	Acute pharyngitis Streptococcal
J02.9	Acute pharyngitis, unspecified
J03.0	Streptococcal tonsillitis
J03.9	Tonsillits unspecified
J04	Acute Laryngitis and tracheitis
J05	Acute obstructive laryngitis
J06	Acute upper respiratory infections of multiple and unspecified sites
J13	Pneumonia due to Streptococcus pneumoniae
J15.9	Bacterial pneumonia, unspecified
J18	Pneumonia, organism unspecified
J20.2	Acute Bronchitis due to streptococcus
J20.9	Acute bronchitis, unspecified
J21.8	Acute Bronchiolitis other specified
J21.9	Acute Bronchiolitis, unspecified
J22	Unspecified acute lower respiratory infection
J86	Pyothorax
M00.1	Pneumococcal arthritis and polyarthritis
M00.2	Other streptococcal arthritis and polyarthritis

Appendix 7: Annual vaccine coverage of 23-valent vaccination

Appendix 7, table 1.Proportion of patients annually vaccinated by risk groups with the 23 valent pneumococcal polysaccharide as measured in the 2009 data extract from Generals Practitioners Practices' IT systems.			
Age group (years)	2-15	16-65	65 +
One or more Risk Group(s)	4.1%	1.5%	7.2%

Appendix 8: Age group specific incidence of invasive pneumococcal disease

Appendix 8, table 1. Invasive pneumococcal disease incidence per 100,000 population per risk- and age-group for the epidemiological year 2009-10.

	Age groups				
Risk type	**2-4y**	**5-14y**	**15-44y**	**45-64y**	**≥65y**
Any risk group	109.4	37.5	24.7	57.5	43.5
splenic dysfunction	44.2	15.2	7.4	17.2	10.8
Chronic Respiratory Disease	118.8	40.8	54.5	127.1	83.0
Chronic Heart Disease	38.7	13.3	22.5	52.4	48.9
Chronic Kidney Disease	110.1	37.8	21.2	49.5	14.0
Chronic Liver Disease	277.6	95.3	108.1	252.0	116.9
Diabetes	35.5	12.2	14.9	34.7	38.0
Immunocompromised	384.2	131.9	55.6	129.5	190.6
HIV Infection	945.7	324.7	198.9	463.4	86.2

Appendix 9 Definition of the risk groups in ICD-10 codes

Overview of the used ICD-10 codes to identify risk group. Where possible the lowest specificity was used; e.g. only a letter includes all codes in the corresponding chapter.

Risk group	**Used ICD codes**
Chronic respiratory disease	J40,J41,J42,J43,J44,J47,J6,J7,J80,J81,J82,J83,J84,Q30,J31,Q32,Q 33Q34,Q35,Q36,Q37
Chronic heart disease	I05,I06,I07,I08,I09,I11,I12,I13,I20,I21,I22,I25,I27,I28,I3,I40,I41,I42,I43 ,I44,I45,I47,I48,I49,I50,I51,I52,Q2
Chronic kidney disease	N00,N01,N02,N03,N04,N05,N07,N08,N11,N12,N14,N15,N16,N18,N1 9,N25,Q60,Q61
Chronic liver disease	K70,K71,K72,K73,K74,K75,K76,K77,P78.8,Q44
Diabetes	E10,E11,E12,E13,E14,E24,G59.0,G63.2,G73.0,G99.0,N08.3,O24, P70.0,P70.1,P70.2
Immunosuppression	Malignancies affecting the immune system: C81,C82,C83,C84,C85,C88,C90,C91,C92,C93,C94, C95,C96 HIV: B20,B21,B22,B23,B24 Transplantations: Z94,Z85 (Bone marrow transplants: Z94.8) Conditions affecting the immune system: D56.1,D57.8,D57.0,D57.D61,D70,D71,D72,D73,D76,D80,D81,D82D 83,D84, 1,K90.0
Asplenia or dysfunction of the spleen	D73,D56.1,D57.8,D57.0,D57.1,K90.0
Individuals with cochlear implants	Z96.1
Individuals with cerebrospinal fluid leaks	G96.0

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