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# Immunization of HIV-infected adults in the UK with Haemophilus influenzae b/meningococcal C glycoconjugate and pneumococcal polysaccharide vaccines

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## Abstract

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**Conclusions** In a UK adult HIV-infected population, Hib/MenC-TT induced similar IgG responses to HIV-uninfected adults, while PPV induced comparatively poor responses. Lack of association with CD4 count or viral load supports early immunization. Further studies are required to guide vaccination policy in HIV-infected patients.

# Immunization of HIV-infected adults in the UK with *Haemophilus influenzae* b/ meningococcal C glycoconjugate and pneumococcal polysaccharide vaccines

Running title: Bacterial immunization in HIV infection

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**Conclusions** In a UK adult HIV-infected population, Hib/MenC-TT induced similar IgG responses to HIV-uninfected adults, while PPV induced comparatively poor responses. Lack of association with CD4 count or viral load supports early immunization. Further studies are required to guide vaccination policy in HIV-infected patients.

**Key words** HIV; vaccines; bacteria; pneumococcus; *Haemophilus influenzae* b; meningococcus

## Introduction

There is an increased risk of disease and death due to vaccine-preventable infections among HIV-infected individuals compared with the general population. Incidence and mortality from bacterial pneumonia are both greatly increased among HIV-infected subjects and inversely correlate with CD4 count.[1] Pneumococcus and *Haemophilus influenzae* are most commonly isolated.[1] HIV-infected subjects are also at increased risk of invasive disease from these pathogens, despite a fall in incidence with use of highly-active antiretroviral therapy (HAART)[2] and implementation of childhood vaccination against pneumococcus.[3] HIV-infected individuals are also at a higher risk of meningococcal disease than those living without HIV.4

Multiple observational studies have shown that 23-valent polysaccharide pneumococcal vaccine (PPV, Pneumovax®) protects against all-cause pneumonia[5,6] and pneumococcal disease[7-9] in HIV-infected individuals. Where this has been examined in relation to CD4 count, findings vary with some studies indicating a benefit at all CD4 counts[9] while others detect a benefit only with CD4 counts above a certain threshold.[8] The only randomized placebo-controlled trial of PPV in HIV-infected subjects was conducted in Uganda and found an increase in all-cause pneumonia in the vaccine arm.[10]

The British HIV Association (BHIVA) national guidelines recommend a decreased threshold for offering HIV-infected subjects vaccination.[11] However, the basis for many of these guidelines is empirical, owing to the lack of controlled studies investigating the impact of vaccination in HIV-infected subjects. BHIVA recommends PPV for all HIV-infected adults and *Haemophilus influenzae* b (Hib) and meningococcal vaccines may be considered when HIV-infected adults are scheduled to receive other vaccines. The guidelines acknowledge patients may have reduced response to vaccination and that higher doses may be required. Also, the duration of responses may be shortened requiring booster doses. Patients attending the University Hospital Birmingham adult

HIV outpatient clinic are routinely offered Hepatitis B and annual influenza vaccinations. From September 2009, patients were offered PPV and a combined *Haemophilus influenzae* b and meningococcal C polysaccharide-tetanus toxoid glycoconjugate vaccine (Hib/MenC-TT, Menitorix®).

To better understand the effect of HIV infection on responses to these vaccines, vaccine-specific antibodies were measured before and after immunization, and compared with those in a cohort of HIV-uninfected adults.

## Methods

### Study design

The study was conducted at the University Hospitals Birmingham NHS Foundation Trust (UHBFT). HIV-infected patients commence HAART in accordance with national guidelines. At the time of the study, HAART most commonly consisted of a non-nucleoside reverse transcriptase inhibitor backbone of tenofovir and emtricitabine, with efavirenz as third agent. The study was part of a larger ongoing study, the AIR Study (Assessment of Immune Responses to Routine Immunisations in HIV-infected Adults, ISRCTN95588307) which began in September 2009, with HIV-infected adults offered enrolment and immunization with BHIVA-recommended vaccines, and serum antibody responses monitored before and four to six weeks after immunization. Clinic attendees declining the study are also offered the vaccinations. To reduce bias among the HIV-infected and -uninfected participant groups, HIV-uninfected participants were enrolled from UHBFT genitourinary medicine clinic attendees testing negative for HIV infection.

The study was conducted between September 2009 and December 2010, with AIR Study participants offered PPV (Merck, one 0.5 ml dose) and Hib/MenC-TT (GlaxoSmithKline, one 0.5 ml dose) vaccines at the same time. Inclusion criteria were consented AIR Study participants, proven HIV infection or absence of HIV infection (for control group) and age over 18 years. Individuals who had previously been vaccinated with pneumococcal, MenC or Hib vaccines were excluded. Demographic data, including age, sex and ethnic group, were collected.

### Investigations

HIV antibody testing (Abbott) and HIV-1 viral load measurement (Abbott) were performed. Participants were venesected for IgG screening before vaccination and four to six weeks post-vaccination. IgG antibody levels to 19 vaccine antigens: 12 PnPS (serotypes 1, 3, 4, 5, 6B, 7F, 9V, 14, 18C, 19A, 19F and 23F), four Men PS (serogroups A, C, W and Y), Hib PS, tetanus toxoid (TT)

and diphtheria toxoid (DT), were measured in serum using a 19-plex fluorescence microbead assay [12]. The recommended post-vaccination threshold for protective IgG antibody levels against Hib and Men C are 1.0 and 2.0 µg/ml respectively,[12] while two levels have been proposed for Pn serotypes: 1.3 µg/ml by the American Association of Asthma Allergy and Immunology (AAAAI) for the prevention of colonization and infection,[13,14] and 0.35 µg/ml by the WHO, used primarily as the correlate of protection for assessment of vaccine responses in infants.[15] Unless otherwise stated, 1.3 µg/ml was used as the threshold level. For tetanus and diphtheria, long-term protective levels are 0.1 IU/ml.[12] CD4 counting was performed by TruCount assay (Becton Dickinson). HIV-infected participants were stratified into four groups by CD4 count, <350, 350-490, 500-690 and ≥700 cells/µl.

**Statistical Analysis**

IgG antibody levels were initially treated as continuous variables, and compared across HIV status, use of HAART, as well as categories of CD4 count and viral load. Due to the level of skew in the IgG antibody levels, and truncated of some levels by the limits of measurement of the assay, a non-parametric analytical approach was employed. Comparisons between groups were performed using Mann-Whitney and Kruskal-Wallis tests, as appropriate, with the data summarized using medians and quartiles. The data were also analyzed treating the IgG antibody levels as a binary variable, specifying whether patients were above stated thresholds for each antigen, with comparisons across groups made using Fisher's exact test.

For both versions of the dependent variable, three sets of comparisons were made: pre-and post-vaccine IgG antibody levels, fold change in IgG levels and proportion of previously unprotected patients reaching threshold IgG levels post-vaccination. Since for each set of analyses, 19 antigens were considered, the effect of multiple comparisons on the type one error rate needed to be accounted for. Therefore, the critical p-value was Bonferroni-corrected for 57 comparisons (19

antigens by 3 outcomes). Hence $p<0.0009$ was considered significant throughout. All analyses were performed using IBM SPSS 19, with graphics produced using Graph-Pad Prism.

**Ethical Approval**

The study was approved by the North Staffordshire Research Ethics Committee of the National Research Ethics Service, REC reference 09/H1204/53. All participants gave informed written consent before taking part.

## Results

*Patient Population*

Of 263 HIV-infected and 119 HIV-uninfected individuals enrolled into the AIR study, respectively 211 and 73 received PPV and Hib/MenC-TT at the same time, completed post-vaccination follow-up and were included in the analysis (S Fig. 1). No vaccine-related serious adverse events were reported following immunization. Ineligibility to receive PPV owing to prior vaccination was common in the HIV-infected group, while declining PPV led to a loss of subjects from the control group. Median age (35 and 40, p=0.10) and gender ratio (55% and 64% male, p=0.16) were similar between both groups (S Table 1). Among the HIV-infected subjects, 83% (176) were receiving HAART and 73% (128) of these had VL<50 copies/ml. Median CD4 count was 500 cells/µl (inter-quartile range, IQR 350-630 cells/µl) and stratification by CD4 count gave four subgroups of around 50 subjects. For the 62 HIV-infected participants with detectable viral load (>50 copies/ml), the median was 5,060 copies/ml (IQR 482-51,933 copies/ml). There was a small amount of missing data, namely 10 MenY measurements and one MenA and Pn1 measurement, in the HIV-negative group. These values were excluded from their respective analyses, with all available data included in the other analyses.

*Low prevaccination specific antibody levels, particularly among HIV-infected participants*

Median specific IgG levels in HIV-infected and HIV-uninfected groups against the 19 bacterial target antigens were below their respective thresholds, except for TT in both groups and PnPS 14 in the HIV-infected group (Table 1 and 2, Fig. 1). Levels were significantly lower in the HIV-infected group compared with the HIV-uninfected group for Hib, MenC, TT, DT and PnPS 7F (p<0.001 for all comparisons). There was no statistically-significant difference for the other eleven PnPS tested.

*Equivalent response to Hib/MenC-TT among HIV-infected and HIV-uninfected individuals*

Both HIV-infected and HIV-uninfected subjects mounted IgG antibody responses to the Hib/MenC conjugate vaccine with median fold increases of 9.28 and 34.08, and 5.70 and 13.22 respectively. Median post-vaccination IgG antibody levels for the HIV-infected group (3.74 and 2.88) were not statistically different from those for the HIV-uninfected group (4.85 and 4.56) (Table 1). Threshold antibody levels against Hib and MenC were achieved in 68% (108/160) and 56% (106/188) of HIV-infected, and 77% (30/39) and 65% (37/57) of HIV-uninfected subjects with levels previously-below the threshold (Table 3).

*Poor response to PPV among HIV-infected individuals*

Vaccination with PPV induced a median four-fold or greater increase in IgG antibody levels for four Pn serotypes (1, 5, 7F, and 18C) among HIV-uninfected subjects, while a four-fold increase was only achieved for Pn serotype 5 in the HIV-infected group. Median post-vaccination levels reached the 1.3 μg/ml threshold for ten of twelve Pn serotypes in the HIV-uninfected group, but only five Pn serotypes in the HIV-infected group. Significantly higher median post-vaccination IgG antibody levels were found in the HIV-uninfected compared with HIV-infected group for PnPS1, 7F, 18C and 23F ($p<0.001$ for all comparisons). Response to Pn3 was universally poor with less than a two-fold median increase in both groups (Table 2). The proportion of individuals previously below the 1.3 μg/ml threshold who attained 1.3 μg/ml post-vaccination ranged from 13% (Pn13) to 75% (Pn7F) for the HIV-uninfected groups, and from 12% (Pn4) to 44% (Pn7F) in the HIV-infected group (Table 4). When the less-stringent WHO Pn IgG threshold of 0.35 μg/ml was used, these proportions increased to 35% and 75% for HIV-uninfected group and 30% to 78% for the HIV-infected group (S Table 2).

*Large increase in antibody levels to TT, but low antibody levels to DT*

Median pre-vaccination IgG levels against TT were above the long-term protective level (0.1 IU/ml) for both HIV-infected and control groups, but below this level (0.1 IU/ml) for DT, with levels significantly higher among HIV-uninfected compared with HIV-infected participants ($p<0.001$, Table 1). A marked fold increase in median antibody levels to tetanus toxoid (3.58 and 3.45 for both HIV-infected and HIV-uninfected groups) was observed post-vaccination, while antibody levels to diphtheria toxoid remained unchanged.

*Influence of CD4 count and viral load on vaccine responses*

Among HIV-infected participants, there was a lack of significant association between pre-vaccination, post-vaccination or fold change in antibody levels, and CD4 count subgroup, full VL suppression or taking HAART (S. Table 3 and 4). The closest association was between fully-suppressed VL and fold change in antibody to TT (4.27 compared with 2.48 for VL≥50, $p=0.002$). To investigate the effect of optimal response to HAART on vaccine response, we compared subjects with both CD4 ≥500 cells/μl and fully-suppressed VL with all other HIV-infected subjects (S. Table 5 and 6). Again, there was little difference between the two HIV-infected groups divided in this way. However, borderline significance was reached for fold change increase of the three vaccine components of Hib/MenC-TT (TT 4.58 and 3.24, $p=0.007$; MenC 59.25 and 29.22, $p=0.026$; Hib 18.75 and 7.70, $p=0.099$).

## Discussion

The main conclusions of the study are that, although HIV-infected adults have relatively low antibody levels against encapsulated bacteria, they achieve similar levels of immunity to HIV-uninfected individuals through vaccination with glycoconjugates against Hib and MenC. In contrast, vaccination with pneumococcal polysaccharide results in poor responses compared with HIV-uninfected individuals. In general, there was a lack of association between response to vaccination and CD4 count, VL or HAART. An unanticipated finding was a boost in post-vaccination antibody levels to TT, likely due to the TT carrier component of the Hib/MenC vaccine, but overall low antibody levels to DT.

Previous studies of vaccine immunogenicity in HIV-infected individuals have tended to focus on one vaccine. Lack of consistency between findings from various vaccine studies emphasizes the importance of conducting such work in the population of interest and studies of vaccine immunogenicity among HIV-infected adult cohorts in the UK are currently lacking. A study from 1995, investigating response to PPV and Hib-$CRM_{197}$ among 20 recent HIV-seroconverters and 15 HIV-uninfected individuals found similar responses in both groups[16]. Conclusions from other studies with PPV have been mixed, with some investigators finding a strong response among HIV-infected adults,[17,18] while others reported a poor response.[19,20] Where response was compared with CD4 count, some studies found no correlation with antibody response,[18,20] while others reported low CD4 count being associated with a poor response.[19,21] A lack of effect of HAART on antibody response to PPV has been described.[21] A recent study found no serological benefit from delaying administration of PPV in newly-diagnosed HIV-infected adults until after 6-12 months of HAART.[22]

Fewer studies have been conducted on responses to Hib conjugate vaccines. These have generally reported a good response compared with controls, though not among individuals with low CD4

counts.[23-25] In our study, all subgroups of HIV-infected subjects responded to the three components of Hib/MenC-TT, although individuals with CD4 counts >500 cells/μl and fully suppressed VL had borderline larger responses to all three components of this vaccine compared with all other HIV-infected individuals. The relatively small numbers in our study may have prevented us from detecting such differences as being significant, though no such borderline significant differences were detected for responses to PPV. It is intuitive that T-dependent antibody responses to Hib/MenC-TT should benefit from CD4 T-cell reconstitution more than the T-independent responses of PPV. Nevertheless, the lack of clear association between response to vaccination and CD4 count and viral load, all support a policy of early vaccination once diagnosis of HIV infection has been made. These findings indicate the need for further functional studies of $CD4^+$ T cells and B cells, which are dysfunctional in HIV infection,[26] in order to better understand immune reconstitution in HIV infection beyond what can be discerned from the CD4 count alone.

The enhanced response to glycoconjugate MenC/Hib vaccination compared with that to PPV suggests that a similar strategy may overcome the lack of immunogenicity when vaccinating with pneumococcal conjugate vaccine (PCV). However, these different polysaccharide antigens may not be recognized in the same way by the immune system. HIV-infected children mount poor antibody responses to Pn PS even after systemic pneumococcal illness,[27] suggesting that these polysaccharides are inherently non-immunogenic, particularly to an immune system compromised by HIV infection. Immunogenicity studies in settings where patients have access to HAART have found a higher antibody response to PCV than PPV.[28,29] A 9-valent PCV has been shown to protect HIV-infected South Africa children against pneumonia and invasive pneumococcal disease.[30] To date, the only randomized placebo-controlled trial of PCV in HIV-infected adults, from Malawi, showed enhanced protection against recurrent pneumococcal infection.[31] Vaccination with PCV for HIV-infected adults was recommended in the US by the Advisory Committee on Immunization Practices in 2012.[32] Meanwhile in the UK, in 2013 the Joint Advisory Committee on Vaccination

and Immunisation advised against the introduction of PCV in the UK[33] on grounds of lack of cost effectiveness.[34]

The large proportions of HIV-infected individuals in our study who failed to exceed threshold antibody levels post-vaccination, particularly with PPV, suggests that single vaccine doses against encapsulated bacteria are insufficient in this population. Furthermore, even with HAART, maintenance of antibody responses to PPV over a 5-year period is a problem for HIV-infected adults, particularly where CD4 counts are low.[35] Mixed vaccination regimes with conjugated and unconjugated pneumococcal polysaccharide vaccines have been tested. Vaccination with a PCV7-PCV7-PPV schedule has been shown to establish memory in HIV-infected children, as judged by the response to a subsequent booster vaccination five years later.[36] Similar benefits have been found in HIV-infected adults revaccinated with PPV after 5 years on HAART,[37] although there is the risk that multiple doses of polysaccharide vaccines will result in hyporesponsiveness.[38] A recent study using three doses of PCV13 in HIV-infected adults previously vaccinated with PPV found a rise in pneumococcal antibody concentrations after each immunization compared with prevaccination levels before, but overall levels after each dose were similar.[39] One dose of MenC/Hib conjugate vaccines failed to induce threshold antibody levels in approximately a third of HIV-infected subjects previously below these thresholds, indicating the need to investigate the use of multiple doses of this vaccine too.

The low levels of antibodies to DT in HIV-infected individuals are a cause for concern as they identify a potential risk of diphtheria outbreak among HIV-infected adults. A possible solution is to vaccinate with glycoconjugates that use DT or $CRM_{197}$ (non-toxic recombinant form of diphtheria toxin) as carrier protein, thereby providing a diphtheria booster. Although there were no serious adverse events, it is important to be vigilant for episodes of clinical pneumonia among HIV-infected subjects, particularly following the increased number of cases of pneumonia in the Ugandan PPV

316 trial.[10] In addition to the use of fixed vaccine doses without booster vaccinations, limitations of our
317 study include the lack of clean matching between ethnic background of HIV-infected and HIV-
318 uninfected groups which could introduce a potential source of bias in the results. Uncertainty also
319 comes from a recent study of PCV13 in infants that questions our current understanding of
320 correlates of protection for pneumococcal vaccines.[40] Serotype-specific correlates of protection
321 were found to range widely for IgG levels and opsonophagocytic antibody titers, with an overall
322 aggregate correlate of protection of 0.98 μg/ml IgG against the 13 serotypes of PCV13 (range: 0.14
323 μg/ml for Pn18C to 2.83 μg/ml for Pn3).
324
325 The main unanswered clinical question from the study and subject for future research is how to
326 robustly induce sustained protective antibody levels against encapsulated bacteria among HIV-
327 infected adults in high-income countries such as the UK. While use of pneumococcal
328 glycoconjugate vaccine is an obvious step, differences in quantity of vaccine used and dosing
329 schedule may also be important. The lack of improved vaccine responses at high CD4 counts
330 indicates that physicians should remain vigilant for clinical presentations of bacterial pneumonia
331 and invasive disease, even in HIV-infected patients who have apparently normal immunity or
332 reconstituted immunity on HAART.

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## Figure legends

1. **Vaccine-specific antibody levels pre- and post-vaccination with PPV and Hib/MenC-TT**

   Each point represents one subject. Solid horizontal lines indicate medians. Dotted horizontal lines indicate thresholds for protective post-vaccination antibody responses. Pn pneumococcal; Men meningococcal; Hib *Haemophilus influenzae* b; TT tetanus toxoid; DT diphtheria toxoid

**Table 1. Median IgG antibody levels to meningococcal and Hib capsular polysaccharides, tetanus and diphtheria toxoid in study participants according to HIV status**

| **Pre-Vaccine** | | **Hib** | **MenC** | **TT** | **DT** | **MenA** | **MenW** | **MenY** |
|---|---|---|---|---|---|---|---|---|
| **HIV Status** | ***HIV-*** | 0•94 (0•21-2•01) | 0•23 (0•06-1•73) | 1•60 (0•48-3•46) | 0•08 (0•03-0•21) | 1•77 (0•83-5•18) | 0•09 (0•03-0•22) | 0•50 (0•18-1•97) |
| | ***HIV+*** | 0•24 (0•07-0•92) | 0•06 (0•02-0•22) | 0•51 (0•15-1•56) | 0•02 (0•01-0•07) | 0•81 (0•38-2•32) | 0•04 (0•01-0•10) | 0•20 (0•06-0•48) |
| | ***p*** | ***<0•001**** | ***<0•001**** | ***<0•001**** | ***<0•001**** | ***<0•001**** | ***<0•001**** | ***<0•001**** |
| **Post-Vaccine** | | **Hib** | **MenC** | **TT** | **DT** | **MenA** | **MenW** | **MenY** |
| **HIV Status** | ***HIV-*** | 4•85 (1•99-13•72) | 4•56 (1•90-15•00) | 7•59 (3•18-10•00) | 0•11 (0•04-0•35) | 3•77 (1•39-7•98) | 0•17 (0•06-0•28) | 0•87 (0•42-2•16) |
| | ***HIV+*** | 3•74 (1•08-14•46) | 2•88 (0•90-8•94) | 2•94 (0•68-7•57) | 0•03 (0•01-0•08) | 1•47 (0•59-3•33) | 0•06 (0•02-0•17) | 0•31 (0•10-0•70) |
| | ***p*** | ***0•064*** | ***0•010****** | ***<0•001**** | ***<0•001**** | ***<0•001**** | ***<0•001**** | ***<0•001**** |
| **Fold Change** | | **Hib** | **MenC** | **TT** | **DT** | **MenA** | **MenW** | **MenY** |
| **HIV Status** | ***HIV-*** | 5•70 (1•67-21•25) | 13•22 (4•41-52•67) | 3•45 (1•82-6•92) | 1•10 (0•77-1•78) | 1•37 (0•97-2•23) | 1•24 (1•00-2•00) | 1•43 (1•09-2•19) |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| ***HIV+*** | 9•28 (2•68-34•00) | 34•08 (9•87-96•00) | 3•58 (1•63-8•62) | 1•00 (1•00-1•50) | 1•31 (1•00-2•04) | 1•25 (1•00-2•00) | 1•35 (1•00-2•20) |
| ***p*** | ***0•071*** | ***0•003**** | ***0•656*** | ***0•621*** | ***0•983*** | ***0•682*** | ***0•619*** |

*Data reported as: "Median (Quartiles)"*

*p-values from Mann-Whitney tests*

**Significant at p<0.05*

***Significant after Bonferroni correction for 57 comparisons (19 antibodies by 3 measures) at p<0.00088*

*Hib Haemophilus influenzae b; Men meningococcus; TT tetanus toxoid; DT diphtheria toxoid*

**Table 2. Median IgG antibody levels to pneumococcal polysaccharides in study participants according to HIV status**

| **Pre-Vaccine** | **Pn1** | **Pn3** | **Pn4** | **Pn5** | **Pn6B** | **Pn7F** | **Pn9V** | **Pn14** | **Pn18C** | **Pn19A** | **Pn19F** | **Pn23F** |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **HIV Status** ***HIV-*** | 0.24 (0•10-0•76) | 0•29 (0•10-1•78) | 0•14 (0•07-0•33) | 0•38 (0•19-1•06) | 0•36 (0•14-1•49) | 0•77 (0•39-1•49) | 0•52 (0•18-1•33) | 1•03 (0•32-3•94) | 0•44 (0•18-1•95) | 0•78 (0•25-2•71) | 0•63 (0•19-2•26) | 0•55 (0•22-1•60) |
| ***HIV+*** | 0•24 (0•08-0•67) | 0•24 (0•08-0•78) | 0•12 (0•04-0•35) | 0•24 (0•09-0•72) | 0•32 (0•10-1•12) | 0•35 (0•15-1•07) | 0•25 (0•10-0•70) | 1•51 (0•23-5•65) | 0•43 (0•08-1•52) | 0•66 (0•15-2•23) | 0•40 (0•14-1•38) | 0•31 (0•10-0•96) |
| ***p*** | ***0•782*** | ***0•446*** | ***0•398*** | ***0•015**** | ***0•600*** | ***<0•001**** | ***0•002**** | ***0•516*** | ***0•168*** | ***0•243*** | ***0•146*** | ***0•005**** |
| **Post-Vaccine** | **Pn1** | **Pn3** | **Pn4** | **Pn5** | **Pn6B** | **Pn7F** | **Pn9V** | **Pn14** | **Pn18C** | **Pn19A** | **Pn19F** | **Pn23F** |
| **HIV Status** ***HIV-*** | 2•74 (0•93-10•00) | 0•49 (0•16-3•93) | 0•36 (0•21-1•06) | 4•63 (0•58-10•00) | 1•67 (0•41-5•72) | 5•24 (2•43-10•00) | 1•89 (0•82-10•00) | 7•76 (1•22-10•00) | 5•96 (1•13-10•00) | 3•72 (1•00-8•50) | 2•19 (0•57-7•08) | 2•35 (0•79-6•69) |
| ***HIV+*** | 1•11 (0•46-3•55) | 0•53 (0•20-2•10) | 0•30 (0•10-0•79) | 1•34 (0•41-5•55) | 0•97 (0•25-3•20) | 1•51 (0•65-4•75) | 1•15 (0•35-3•82) | 5•12 (1•38-10•00) | 2•01 (0•29-9•48) | 2•19 (0•57-6•97) | 1•07 (0•30-4•32) | 1•08 (0•31-2•72) |
| ***p*** | ***<0•001**** | ***0•791*** | ***0•044**** | ***0•003**** | ***0•031**** | ***<0•001**** | ***0•002**** | ***0•255*** | ***<0•001**** | ***0•035**** | ***0•008**** | ***<0•001**** |
| **Fold Change** | **Pn1** | **Pn3** | **Pn4** | **Pn5** | **Pn6B** | **Pn7F** | **Pn9V** | **Pn14** | **Pn18C** | **Pn19A** | **Pn19F** | **Pn23F** |
| **HIV Status** ***HIV-*** | 8•01 (3•92-16•67) | 1•63 (1•00-3•95) | 2•65 (1•60-5•93) | 4•15 (2•07-12•88) | 2•20 (1•30-10•02) | 5•56 (2•15-11•88) | 2•81 (1•58-11•25) | 3•43 (1•27-8•19) | 5•47 (2•17-16•66) | 3•31 (1•29-6•22) | 2•94 (1•52-6•19) | 2•55 (1•80-8•91) |
| ***HIV+*** | 3•42 (1•54-10•32) | 1•79 (1•00-3•90) | 2•00 (1•24-4•08) | 4•00 (1•62-11•07) | 1•87 (1•18-4•69) | 3•50 (2•00-7•65) | 3•82 (1•57-8•29) | 1•99 (1•00-4•63) | 3•35 (1•56-7•30) | 2•00 (1•20-5•58) | 2•06 (1•29-4•82) | 2•40 (1•40-5•56) |
| ***p*** | ***<0•001**** | ***0•387*** | ***0•030**** | ***0•299*** | ***0•156*** | ***0•060*** | ***0•863*** | ***0•017**** | ***0•013**** | ***0•181*** | ***0•060*** | ***0•126*** |

*Data reported as: "Median (Quartiles)"*

*p-values from Mann-Whitney tests*

**Significant at p<0.05*

***Significant after Bonferroni correction for 57 comparisons (19 antibodies by 3 measures) at p<0.00088*

*Pn pneumococcal*

17 **Table 3. Rates above nominal IgG protection levels against meningococcus, Hib, tetanus and diphtheria in study participants according to**

18 **HIV status**

| **Pre-Vaccine** | | **Hib** | **MenC** | **TT** | **DT** | **MenA** | **MenW** | **MenY** |
|---|---|---|---|---|---|---|---|---|
| **HIV Status** | ***HIV-*** | *34/73* | *16/73* | *70/73* | *34/73* | *32/73* | *3/73* | *18/73* |
| | | **47%** | **22%** | **96%** | **47%** | **44%** | **4%** | **25%** |
| | ***HIV+*** | *51/211* | *23/211* | *173/211* | *42/211* | *58/211* | *7/211* | *22/201* |
| | | **24%** | **11%** | **82%** | **20%** | **27%** | **3%** | **11%** |
| | ***p*** | ***<0•001**** | ***0•028**** | ***0•003**** | ***<0•001**** | ***0•013**** | ***0•721*** | ***0•007**** |
| **Post-Vaccine** | | **Hib** | **MenC** | **TT** | **DT** | **MenA** | **MenW** | **MenY** |
| **HIV Status** | ***HIV-*** | *64/73* | *53/73* | *72/73* | *40/73* | *48/73* | *3/73* | *21/73* |
| | | **88%** | **73%** | **99%** | **55%** | **66%** | **4%** | **29%** |
| | ***HIV+*** | *159/211* | *129/211* | *198/211* | *50/211* | *80/210* | *7/211* | *22/202* |
| | | **75%** | **61%** | **94%** | **24%** | **38%** | **3%** | **11%** |
| | ***p*** | ***0•031**** | ***0•090*** | ***0•126*** | ***<0•001**** | ***<0•001**** | ***0•721*** | ***0•001**** |
| **Absolute Increase** | | **Hib** | **MenC** | **TT** | **DT** | **MenA** | **MenW** | **MenY** |
| **HIV Status** | ***HIV-*** | *30/73* | *37/73* | *2/73* | *6/73* | *16/73* | *0/73* | *3/73* |
| | | **41%** | **51%** | **3%** | **8%** | **22%** | **0%** | **4%** |
| | ***HIV+*** | *108/211* | *106/211* | *25/211* | *8/211* | *22/210* | *0/211* | *0/201* |

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | | **51%** | **50%** | **12%** | **4%** | **11%** | **0%** | **0%** |
| | ***p*** | **-** | **-** | **-** | **-** | **-** | **-** | **-** |
| **Protection for Previously Unprotected Patients‡** | | **Hib** | **MenC** | **TT** | **DT** | **MenA** | **MenW** | **MenY** |
| **HIV Status** | ***HIV-*** | *30/39* | *37/57* | *2/3* | *10/39* | *16/41* | *0/73* | *4/55* |
| | | **77%** | **65%** | **67%** | **26%** | **39%** | **0%** | **7%** |
| | ***HIV+*** | *108/160* | *106/188* | *25/38* | *13/169* | *26/152* | *0/204* | *3/179* |
| | | **68%** | **56%** | **66%** | **8%** | **17%** | **0%** | **2%** |
| | ***p*** | ***0•333*** | ***0•285*** | ***1•000*** | ***0•003**** | ***0•005**** | ***1•000*** | ***0•055*** |

*Data reported as the numbers and proportions of patients with antibody levels above the protection thresholds (Hib=1 μ/ml, Men=2 μ/ml, DT/TT=0.1 IU/ml)*

*p-values from Fisher's Exact tests*

**Significant at p<0.05*

***Significant after Bonferroni correction for 57 comparisons (19 antibodies by 3 measures) at p<0.00088*

*#Patients with 8 Pn antibodies above the thresholds*

*‡The proportion of patients with antibody levels below the threshold pre-vaccine, who had levels above the thresholds post-vaccine*

*Hib Haemophilus influenzae b; Men meningococcus; TT tetanus toxoid; DT diphtheria toxoid*

27 **Table 4. Rates above nominal IgG protection levels against pneumococcus, in study participants according to HIV status**

| **Pre-Vaccine** | **Pn1** | **Pn3** | **Pn4** | **Pn5** | **Pn6B** | **Pn7F** | **Pn9V** | **Pn14** | **Pn18C** | **Pn19A** | **Pn19F** | **Pn23F** | **8 Pn's[#]** |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **HIV Status** ***HIV-*** | *15/73* | *20/73* | *2/73* | *14/73* | *20/73* | *22/73* | *19/73* | *33/73* | *21/73* | *30/73* | *23/73* | *21/73* | *9/73* |
| | **21%** | **27%** | **3%** | **19%** | **27%** | **30%** | **26%** | **45%** | **29%** | **41%** | **32%** | **29%** | **12%** |
| ***HIV+*** | *37/211* | *42/211* | *12/211* | *32/211* | *47/211* | *42/211* | *36/211* | *113/211* | *60/211* | *74/211* | *54/211* | *39/211* | *15/211* |
| | **18%** | **20%** | **6%** | **15%** | **22%** | **20%** | **17%** | **54%** | **28%** | **35%** | **26%** | **18%** | **7%** |
| ***p*** | ***0.600*** | ***0•191*** | ***0•530*** | ***0•462*** | ***0•424*** | ***0•076*** | ***0•121*** | ***0•225*** | ***1•000*** | ***0•398*** | ***0•360*** | ***0•069*** | ***0•220*** |

| **Post-Vaccine** | **Pn1** | **Pn3** | **Pn4** | **Pn5** | **Pn6B** | **Pn7F** | **Pn9V** | **Pn14** | **Pn18C** | **Pn19A** | **Pn19F** | **Pn23F** | **8 Pn's[#]** |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **HIV Status** ***HIV-*** | *48/73* | *26/73* | *16/73* | *47/73* | *40/73* | *60/73* | *48/73* | *54/73* | *53/73* | *51/73* | *45/73* | *46/73* | *39/73* |
| | **66%** | **36%** | **22%** | **64%** | **55%** | **82%** | **66%** | **74%** | **73%** | **70%** | **62%** | **63%** | **53%** |
| ***HIV+*** | *99/210* | *68/211* | *35/211* | *108/211* | *92/211* | *115/211* | *97/211* | *159/211* | *117/211* | *131/211* | *94/211* | *91/211* | *69/211* |
| | **47%** | **32%** | **17%** | **51%** | **44%** | **55%** | **46%** | **75%** | **55%** | **62%** | **45%** | **43%** | **33%** |
| ***p*** | ***0•007**** | ***0•665*** | ***0•376*** | ***0•057*** | ***0•104*** | ***<0•001*** | ***0•004**** | ***0•876*** | ***0•012**** | ***0•259*** | ***0•014**** | ***0•004**** | ***0•002**** |

| **Absolute Increase** | **Pn1** | **Pn3** | **Pn4** | **Pn5** | **Pn6B** | **Pn7F** | **Pn9V** | **Pn14** | **Pn18C** | **Pn19A** | **Pn19F** | **Pn23F** | **8 Pn's[#]** |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **HIV Status** ***HIV-*** | *33/73* | *6/73* | *14/73* | *33/73* | *20/73* | *38/73* | *29/73* | *21/73* | *32/73* | *21/73* | *22/73* | *25/73* | *30/73* |
| | **45%** | **8%** | **19%** | **45%** | **27%** | **52%** | **40%** | **29%** | **44%** | **29%** | **30%** | **34%** | **41%** |
| ***HIV+*** | *62/210* | *26/211* | *23/211* | *76/211* | *45/211* | *73/211* | *61/211* | *46/211* | *57/211* | *57/211* | *40/211* | *52/211* | *54/211* |
| | **30%** | **12%** | **11%** | **36%** | **21%** | **35%** | **29%** | **22%** | **27%** | **27%** | **19%** | **25%** | **26%** |

| | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | ***p*** | - | - | - | - | - | - | - | - | - | - | - | - | - |
| **Protection for Previously Unprotected Patients‡** | | **Pn1** | **Pn3** | **Pn4** | **Pn5** | **Pn6B** | **Pn7F** | **Pn9V** | **Pn14** | **Pn18C** | **Pn19A** | **Pn19F** | **Pn23F** | **8 Pn's#** |
| **HIV Status** | ***HIV-*** | *33/58* | *7/53* | *14/71* | *33/59* | *21/53* | *38/51* | *30/54* | *21/40* | *32/52* | *22/42* | *22/50* | *26/52* | *30/64* |
| | | **57%** | **13%** | **20%** | **56%** | **40%** | **75%** | **56%** | **53%** | **62%** | **51%** | **44%** | **50%** | **47%** |
| | ***HIV+*** | *64/173* | *28/169* | *24/199* | *76/179* | *46/164* | *74/169* | *61/175* | *46/98* | *57/151* | *57/137* | *42/157* | *55/172* | *54/196* |
| | | **37%** | **17%** | **12%** | **43%** | **28%** | **44%** | **35%** | **47%** | **38%** | **42%** | **27%** | **32%** | **28%** |
| | ***p*** | ***0•009**** | ***0•669*** | ***0•116*** | ***0•097*** | ***0•126*** | ***<0•001*** | ***0•010**** | ***0•578*** | ***0•004**** | ***0•294*** | ***0•034**** | ***0•021**** | ***0•005**** |

*Data reported as the numbers and proportions of patients with antibody levels above the protection thresholds (Pn=1.3 μ/ml)*

*p-values from Fisher's Exact tests*

**Significant at p<0.05*

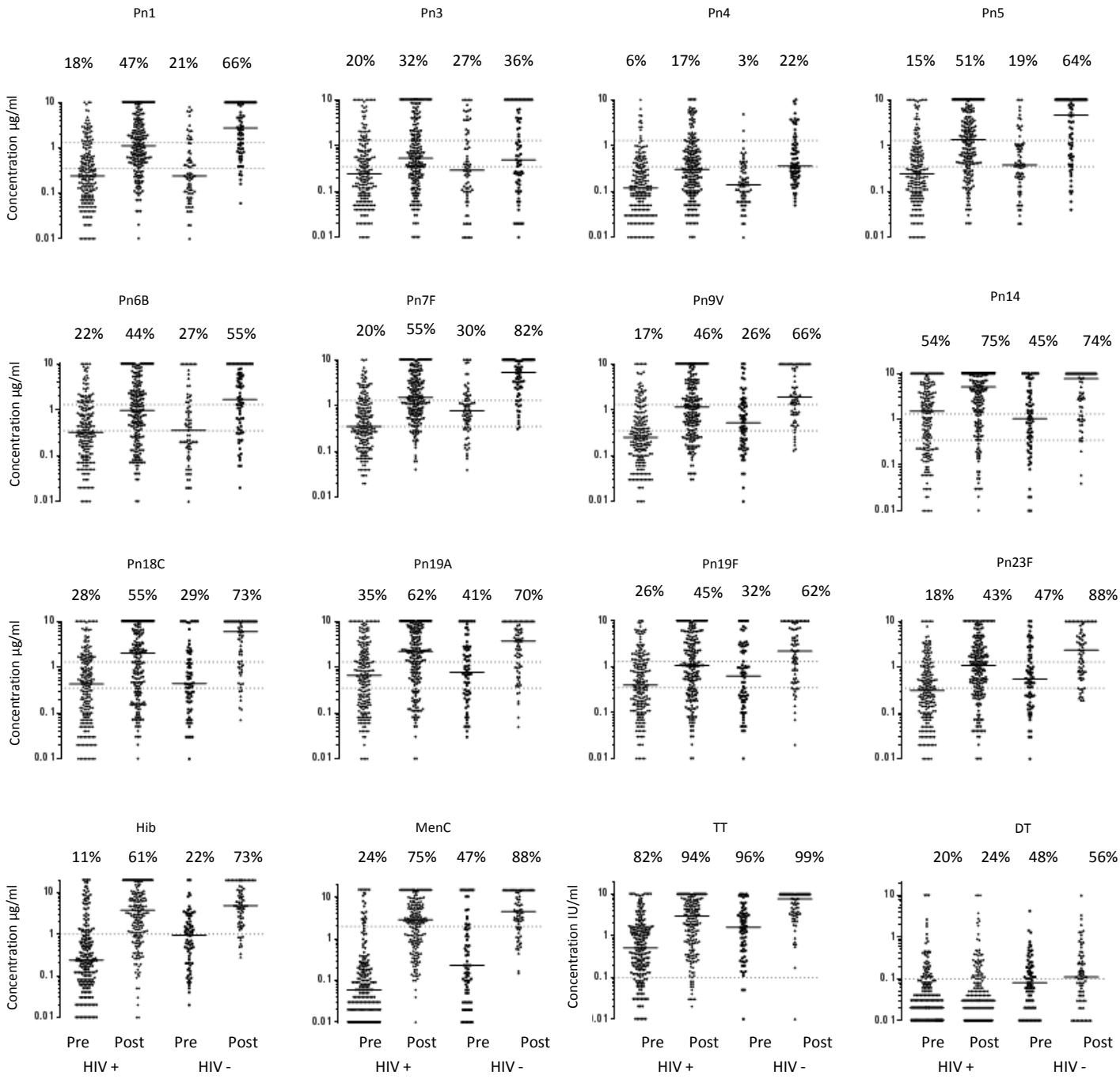
***Significant after Bonferroni correction for 57 comparisons (19 antibodies by 3 measures) at p<0.00088*

*#Patients with 8 Pn antibodies above the thresholds*

*‡The proportion of patients with antibody levels below the threshold pre-vaccine, who had levels above the thresholds post-vaccine*

*Pn pneumococcal*

Figure 1


Pn1
18% 47% 21% 66%
Pn3
20% 32% 27% 36%
Pn4
6% 17% 3% 22%
Pn5
15% 51% 19% 64%
Pn6B
22% 44% 27% 55%
Pn7F
20% 55% 30% 82%
Pn9V
17% 46% 26% 66%
Pn14
54% 75% 45% 74%
Pn18C
28% 55% 29% 73%
Pn19A
35% 62% 41% 70%
Pn19F
26% 45% 32% 62%
Pn23F
18% 43% 47% 88%
Hib
11% 61% 22% 73%
MenC
24% 75% 47% 88%
TT
82% 94% 96% 99%
DT
20% 24% 48% 56%
Concentration µg/ml
Concentration IU/ml
10
1
0.1
0.01
Pre Post Pre Post
HIV + HIV -

S Tables
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S Fig 1
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