**Supplementary Appendix**

This appendix has been provided by the authors to give readers additional information about their work.

Supplement to: ***High Immunogenicity of the Pneumococcal Conjugated Vaccine in Immunocompromised Adults with Inflammatory Bowel Diseases***

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Summary

[Supplement to Introduction 3](#_Toc527292784)

[Supplementary Table 1: Published Studies on Pneumococcal Immunization in Patients with IBD 3](#_Toc527292785)

[Supplement to Methods 5](#_Toc527292786)

[Supplementary Table 2: Inclusion and Exclusion Criteria for Study Enrollment. 5](#_Toc527292787)

[Supplementary Table 3: Post-Licensure Cut-Off Values Used to Predict Seroprotection Against Invasive Pneumococcal Disease. 6](#_Toc527292788)

[Supplementary Table 4: Toxicity Grading Scale for Local and Systemic Adverse Events. 7](#_Toc527292789)

[Supplementary Table 5: Minimal Wash-Out Delay Needed Between Last Dose of Immunosuppressive Treatment and Inclusion To Be Considered as Non-Immunocompromized. 8](#_Toc527292790)

[Supplement to Results 9](#_Toc527292791)

[Supplementary Table 6: Cumulative IBD Patient Exposure to PCV13 by Age, Gender and Disease Type. 9](#_Toc527292792)

[Supplementary Figure 1: Baseline Immunity Against 13 Pneumococcal Serotypes Evaluated with ELISA and OPA in 306 Adult IBD Patients. 10](#_Toc527292793)

[Supplementary Table 7: Evolution of *Streptococcus pneumoniae* Serotype-Specific OPA Titers Before and After PCV13 Administration in IBD Adult Patients. 11](#_Toc527292794)

[Supplementary Figure 2: Reverse Cumulative Curve of Serotype-Specific OPA Responses to PCV13 in IBD Patients. 13](#_Toc527292795)

[Supplementary Table 8: Cumulative Summary of Adverse Events. 15](#_Toc527292796)

[Narrative Report of Relevant Side-Effects 16](#_Toc527292797)

[Change in disease activity 16](#_Toc527292798)

[Serious adverse events unrelated to IBD 17](#_Toc527292799)

[References 18](#_Toc527292800)

# Supplement to Introduction

## Supplementary Table 1: Published Studies on Pneumococcal Immunization in Patients with IBD

|  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Reference** | **Number of patients and study type** | **Patient age, gender, disease type** | **Treatment** | **Intervention** | **Method of vaccine response measurment and seroconversion cut-off used** | **Seroconversion rate** | **Safety data** | **Supplementary data** |
| **Melmed et al.**2010 1USA | 45 patients19 healthy controls(prospective study) | Mean age 40.0 yo (5-ASA) and 36.5 yo (Anti-TNF)28 CD, 14 UC, 1 IC29 male (64%) | 5-ASA or no treatment (n=25)Anti-TNF + IM (n=20)Healthy control (n=19) | PPSV23(Pneumovax®, Merck, Whitehouse Station, NJ) | Serotype-specific ELISA for 5 serotypesTwo-fold increase in IgG antibody titer(or >1 μg /L post-vaccination titer) for 3/5 serotypes, 4 weeks after vaccination | 5-ASA or no treatment: 80% (20/25)Anti-TNF + IM:45% (9/20)Healthy controls: 84% (16/19) | Not available | Vaccine responses were higher in patients with 5-ASA compared to patients with Anti-TNF+IM (OR 4.6, 95 %CI 1.1-23.4). |
| **Dotan et al.**2012 2Israel & USA | 43 patients, only 28 patients analyzed for PPSV23 response(prospective study) | Mean age 33.1 yo (CD) and 35.6 yo (UC)31 CD, 12 UC25 male (58%) | All initiating thiopurine (n=43: 40 6MP, 3 AZA)Some co-medicated with steroids (n=11) | PPSV23(Pneumovax®, Merck, Whitehouse Station, NJ) just before initiating thiopurine therapy | Method NATwo-fold increase in IgG antibody titer for at least 4/14 serotypes, 3 weeks after vaccination | 21/28 (75%)  | Not available | Not available |
| **Fiorino et al.**2012 3Italy | 96 patients(prospective study) | Mean age 42.0 yo54 CD, 42 UC55 male (57%) | 5-ASA or no treatment (n=35)AZA (n=19)Anti-TNF (n=26)Anti-TNF + AZA (n=16) | PPSV23(Pneumovax®, Merck, Whitehouse Station, NJ) | Non serotype-specific ELISA commercial kit (VaccZyme™, Binding Site, Birmingham, UK)Two-fold increase in IgG antibody titer >3 weeks after vaccination | Overall: 74.0%(71/96)5-ASA or no treatment: 88.6% (31/35)Azathioprine: 78.9% (15/19)Anti-TNF: 57.7% (15/26)Anti-TNF + azathioprine: 62.5% (10/16) | 1 local reaction (redness) and 1 systemic reaction (fever) | Patients with infliximab (+/- azathioprine) had a decreased likelihood of responding to vaccination (OR 0.17, 95% CI 0.04–0.64, and OR 0.21, 95% CI 0.05–0.91, respectively) and significantly lower response rates to vaccination compared with the group on 5-ASA (P < 0.05). Azathioprine alone did not influence the response rate to vaccination (P=0.43) |
| **Lee et al.**2014 4Korea | 197 patients(prospective study) | Mean age 32.4 yoAll CD131 male (67%) | 5-ASA only (n=37)IM (n=70)Anti-TNF (n=40)Anti-TNF + IM(n=50) | PPSV23 (Prodiax-23®, MSD Korea, Seoul, Korea) | Non serotype-specific ELISA commercial kit (VaccZyme™, Binding Site, Birmingham, UK)Two-fold increase in IgG antibody titer 4 weeks after vaccination | Overall: 67.5%(133/197)5-ASA: 78.4% (29/37)IM: 78.6% (55/70)Anti-TNF: 50.0% (20/40) Anti-TNF+IM: 58.0% (29/50)  | Local reaction 6%Systemic reaction 3%1 patient with significant change in disease activity 1 month after vaccination | Female patients (OR 2.3, 95%CI 1.2-4.6; P=0.015) and patients with Anti-TNF treatment (OR 2.6, 95%CI 1.01-6.6, P=0.048) associated with non-serological response to the vaccine (after adjustment for age, disease activity and duration, duration of immunosuppression therapy) |
| **Kantso et al.**2015 5Denmark | 151 patients(prospective RCT) | Mean age 44 yoAll CD66 male (44%) | No treatment (n=69: 34 PCV13 and 35 PPV23)IM (n=56 (48 AZA, 8 6MP):27 PCV13 and 29 PPV23)Anti-TNF+IM (n=26: 13 PCV13 and 13 PPV23). | PPSV23 (n=77)(Pneumovax®, Merck, Whitehouse Station, NJ)OrPCV13 (n=74)(Prevenar13®, Pfizer) | Serotype-specific microsphere-based flow cytometric assays for 12 serotypes using in-house Luminex-based assay 6, measured 4 weeks after vaccinationCut-off not available | Not available, study aiming to compare antibody response between PPV23 and PCV13, no data on rate of seroprotection. | Not available | PCV13 induced a significantly higher antibody response than PPV23 for serotypes 4, 6B, 9V 18C, 19A, and 23F.Differences in vaccine responses among treatment group for serotypes 3, 6B, 7F, 9V, 18C, 19A, 19F, and 23F.  |
| **Banaszkiewicz et al.**2015 7Poland | 122 patients56 healthy controls(prospective study) | Median age 15.1 yo (inclusion criteria: 5-18 yo)72 CD, 50 UC74 male (60%) | 5-ASA or no treatment (n=28)IM (n=94; 12 anti-TNF, 80 AZA, 2 CYP)Healthy control (n=56) | PCV13 (Prevenar13®, Pfizer) | Serotype-specific ELISA for 13 serotypesTiter >0.35 mg/mL to all 13 serotypes 4-8 weeks after vaccination | Overall: 90% (66/73)CD: 93% (37/40)UC: 88% (29/33) Healthy controls:97% (28/29) | Local reaction 43% | Higher post-vaccination titer in patients without IM. No detail available. |

5-ASA: mesalazine; 6MP: mercaptopurine; anti-TNF: anti-tumor necrosis factor; AZA: azathioprine; CI: confidence interval; CD: Crohn’s disease; CYP: cyclosporine; IC: indeterminate colitis; IM: immunomodulating treatment (not anti-TNF); n: number; OR: odds ratio; PCV13: 13-valent pneumococcal conjugated vaccine; PPSV23: 23-valent pneumococcal polysacharidal vaccine; RCT: randomized controlled trial; UC: ulcerative colitis; yo: year-old.

# Supplement to Methods

## Supplementary Table 2: Inclusion and Exclusion Criteria for Study Enrollment.

|  |
| --- |
| Inclusion criteria |
| Patient with diagnosed inflammatory bowel disease (Crohn’s disease or ulcerative colitis) |
| Age >18 years-old |
| Followed in one of the participating centers |
| Informed consent signed |
| Exclusion criteria |
| Current relapse defined as:- Crohn’s Disease Activity Index score >150 for patients with Crohn’s disease 8- Modified Truelove & Witts Activity Index score >10 for patients with ulcerative colitis or indeterminate colitis 9 |
| Pregnant or planned pregnancy within the next month |
| Immunization with a pneumococcal vaccine (conjugated or polysaccharide) in the previous 5 years |
| Influenza vaccine in the previous 4 weeks |
| Previous severe systemic reaction to immunization (respiratory or circulative, not cutaneous) |
| Episode of fever in the last 24 hours |
| Participation to another interventional study using experimental immunomodulating treatment |

## Supplementary Table 3: Post-Licensure Cut-Off Values Used to Predict Seroprotection Against Invasive Pneumococcal Disease.

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **Serotype** | **ELISA** [ug/mL] | 95% CI | **OPA** | 95% CI |
| **1** | 0.78 | 0.47 - 1.68 | 4 | 4 – 8 |
| **3** | 2.83  | 1.16 - ∞ | 39 | 14 - ∞ |
| **4** | 0.35 | 0.20 - 1.17 | 70 | 52 - 329 |
| **5** | NA | NA | NA | NA |
| **6A** | 0.16 | 0.08 - 1.05 | 4 | 4 – 824 |
| **6B** | 0.16 | 0.08 - 2.54 | 97 | 4 - 1003 |
| **7F** | 0.87 | 0.40 - 1.80 | 769 | 373 – 1502 |
| **9V** | 0.62 | 0.19 - ∞ | 201 | 4 - ∞ |
| **14** | 0.46 | 0.25 - 1.12 | 4 | 4 – 92 |
| **18C** | 0.14 | 0.09 - 0.40 | 4 | 4 – 284 |
| **19A** | 1.00 | 0.60 - 2.47 | 48 | 15 – 234 |
| **19F** | 1.17 | 0.62 - 4.62 | 430 | 260 - 909 |
| **23F** | 0.20 | 0.08 - 1.50 | 231 | 4 – 890 |

Adapted from reference 10.

ELISA: enzyme-linked immunosorbent assay; NA: not available; OPA: opsonophagocytic assay

## Supplementary Table 4: Toxicity Grading Scale for Local and Systemic Adverse Events.

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| **Local reaction** | **Grade 0**None | **Grade 1**Mild | **Grade 2**Moderate | **Grade 3**Severe | **Grade 4**Potentially life-threatening |
| 1a | 1b |
| **Redness** | None | < 2.5 cm | 2.5 - 5 cm | 5.1 - 10 cm | >10 cm | Necrosis or exfoliative dermatitis |
| **Induration** | None | < 2.5 cm and does not interfere with activity | 2.5 - 5 cm and does not interfere with activity | 5.1 - 10 cm or interferes with activity | >10 cm or prevents daily activity | Necrosis  |
| **Pain** | None | Does not interfere with activity | Limitation of arm movement and/or interferes with activity | Prevents daily activity | Emergency room visit or hospitalization |
| **Systemic reaction** | **Grade 0**None | **Grade 1**Mild | **Grade 2**Moderate | **Grade 3**Severe | **Grade 4**Potentially life-threatening |
| 1a | 1b |
| **Fever** | None | 37.5-37.9 °C | 38.0-39.0°C | 39.1-40.0°C | >40°C for ≥24 hours | Death |
| **Anorexia** | None | No interference with activity | Some interference with activity | Significant, prevents daily activity | Medical consultation and/or hospitalization |
| **Fatigue** | None | No interference with activity | Some interference with activity | Significant, prevents daily activity | Medical consultation and/or hospitalization |
| **Headache** | None | No interference with activity | Some interference with activity | Significant, prevents daily activity | Medical consultation and/or hospitalization |
| **Nausea, vomiting** | None | No interference with activity | Some interference with activity not requiring medical intervention | Significant, prevents daily activity and requires medical intervention | Medical consultation and/or hospitalization |
| **Diarrhea** | None | No interference with activity | Some interference with activity not requiring medical intervention | Significant, prevents daily activity and requires medical intervention | Medical consultation and/or hospitalization |
| **Arthralgia** | None | No interference with activity | Some interference with activity | Significant, prevents daily activity | Medical consultation and/or hospitalization |
| **Myalgia** | None | No interference with activity | Some interference with activity | Significant, prevents daily activity | Medical consultation and/or hospitalization |

## Supplementary Table 5: Minimal Wash-Out Delay Needed Between Last Dose of Immunosuppressive Treatment and Inclusion To Be Considered as Non-Immunocompromized.

|  |  |
| --- | --- |
| **Molecule** | **Delay** |
| Systemic steroids (>2 week at >20mg/day) | 1 month |
| Azathioprine6-mercaptopurineCyclosporine AMycophenolate mofetilCyclophosphamideTacrolimus | 3 months |
| Methotrexate | 3 months |
| Anti-TNF or other biologics | 3 months |

# Supplement to Results

## Supplementary Table 6: Cumulative IBD Patient Exposure to PCV13 by Age, Gender and Disease Type.

|  |  |  |
| --- | --- | --- |
|  | **Number of subjects** |  |
| **Age at inclusion** [year] | **Crohn’s disease** | **Ulcerative colitis** | **Total** |
| Male | Female | Male | Female |  |
| **18-20** | 5 | 6 | 0 | 3 | **14** |
| **21-30** | 26 | 31 | 9 | 5 | **71** |
| **31-40** | 16 | 19 | 9 | 11 | **55** |
| **41-50** | 29 | 27 | 12 | 11 | **79** |
| **51-60** | 17 | 15 | 9 | 12 | **53** |
| **61-70** | 7 | 9 | 5 | 3 | **24** |
| **71-80** | 2 | 2 | 1 | 3 | **8** |
| **81-90** | 1 | 0 | 0 | 0 | **1** |
| **91-100** | 0 | 1 | 0 | 0 | **1** |
| **Total** | 103 | 110 | 45 | 48 | **306** |

## Supplementary Figure 1: Baseline Immunity Against 13 Pneumococcal Serotypes Evaluated with ELISA and OPA in 306 Adult IBD Patients.



Anti-TNF: anti-tumor necrosis factor immunosuppressive treatment; ELISA: enzyme linked immunosorbent assay; IBD: inflammatory bowel disease; IgG: immunoglobulin G; OPA: opsonophagocytic assay; PCV13: 13-valent pneumococcal conjugated vaccine.

Cut-off for seroprotection were defined as OPA titers >8 and ELISA titers >0.35ug/mL. Post-licensure cut-offs (as proposed by Andrew et al 10) are also shown (orange lines).

## Supplementary Table 7: Evolution of *Streptococcus pneumoniae* Serotype-Specific OPA Titers Before and After PCV13 Administration in IBD Adult Patients.

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
|  | **Serotype-specific OPA titer**Median titer (IQR) | **OPA ratio:** **after/before**Geometric mean (95% CI) | **Patients with OPA titer ≥8**% patient (95% CI) | **Patients with OPA titer ≥ post-licensure cut-off**% patient (95% Cl) |
| **Before PCV13** | **After PCV13** | p | **Before PCV13** | **After PCV13** | p | **Before PCV13** | **After PCV13** | p |
| **Serotype 1 Overall** | **4 (4-4)** | **102 (23-298)** | **\*\*\*** | **12.2 (10.1-14.9)** | **21.6 (17.1-26.6)** | **84.1 (79.5-88.1)** | **\*\*\*** | **100 (98.8-100)** | **100 (98.8-100)** | **-** |
| No immunosupressive treatment | 4 (4-4) | 183 (89-504) | \*\*\* | 25.6 (17.2-38.1) | 22.7 (13.3-34.7) | 95.2 (86.7-99.0) | \*\*\* | 100 (94.6-100) | 100 (94.3-100) | - |
| Immunosuppression (no anti-TNF) | 4 (4-4) | 184 (52-412) | \*\*\* | 21.4 (15.0-30.5) | 16.5 (9.3-26.1) | 90.1 (81.5-95.6) | \*\*\* | 100 (95.8-100) | 100 (95.5-100) | - |
| Immunosuppression with anti-TNF | 4 (4-5) | 50 (10-176) | \*\*\* | 6.7 (5.2-8.7) | 23.9 (17.4-31.4) | 76.3 (68.7-82.8) | \*\*\* | 100 (97.6-100) | 100 (97.6-100) | - |
| **Serotype 3 Overall**  | **4 (4-22)** | **50 (12-114)** | **\*\*\*** | **4.1 (3.5-4.8)** | **36.9 (31.5-42.6)** | **77.6 (72.3-82.2)** | **\*\*\*** | **16.7 (12.7-21.3)** | **54.4 (48.5-60.2)** | **\*\*\*** |
| No immunosupressive treatment | 5 (4-25) | 74 (30-166) | \*\*\* | 6.8 (4.9-9.4) | 42.4 (30.3-55.2) | 92.1 (82.4-97.4) | \*\*\* | 16.7 (8.6-27.9) | 66.7 (53.7-78) | \*\*\* |
| Immunosuppression (no anti-TNF) | 4 (4-19) | 70 (21-151) | \*\*\* | 6.3 (4.6-8.6) | 35.3 (25.2-46.4) | 86.3 (76.7-92.9) | \*\*\* | 12.9 (6.6-22.0) | 63.7 (52.2-74.2) | \*\*\* |
| Immunosuppression with anti-TNF | 4 (4-26) | 29 (4-79) | \*\*\* | 2.7 (2.2-3.2) | 35.5 (28.0-43.6) | 66.9 (58.8-74.3) | \*\*\* | 18.7 (12.9-25.8) | 44.4 (36.3-52.7) | \*\*\* |
| **Serotype 4 Overall**  | **4 (4-437)** | **2598 (937-5568)** | **\*\*\*** | **61.9 (43.3-88.3)** | **34.1 (28.5-39.9)** | **94.2 (90.8-96.7)** | **\*\*\*** | **29.0 (23.8-34.7)** | **91.3 (87.4-94.4)** | **\*\*\*** |
| No immunosupressive treatment | 4 (4-410) | 3287 (1190-6332) | \*\*\* | 108.4 (48.3-243.3) | 30.5 (19.2-43.9) | 98.3 (91.1-100) | \*\*\* | 30.5 (19.2-43.9) | 96.7 (88.5-99.6) | \*\*\* |
| Immunosuppression (no anti-TNF) | 4 (4-389) | 2959 (1255-6252) | \*\*\* | 110.2 (56.6-214.5) | 31.2 (21.1-42.7) | 97.4 (90.9-99.7) | \*\*\* | 28.6 (18.8-40.0) | 97.4 (90.9-99.7) | \*\*\* |
| Immunosuppression with anti-TNF | 4 (4-632) | 1783 (661-3476) | \*\*\* | 35.9 (22.1-58.5) | 37.1 (29.1-45.5) | 90.7 (84.6-95.0) | \*\*\* | 28.7 (21.4-36.8) | 85.7 (78.8-91.1) | \*\*\* |
| **Serotype 5 Overall**  | **4 (4-4)** | **58 (12-252)** | **\*\*\*** | **9.8 (8.0-11.9)** | **18.6 (14.4-23.4)** | **81.7 (76.8-85.9)** | **\*\*\*** | **18.6 (14.4-23.4)** | **81.7 (76.8-85.9)** | **\*\*\*** |
| No immunosupressive treatment | 4 (4-4) | 105 (21-334) | \*\*\* | 14.6 (9.6-22.4) | 13.6 (6.4-24.3) | 85.5 (74.2-93.1) | \*\*\* | 13.6 (6.4-24.3) | 85.5 (74.2-93.1) | \*\*\* |
| Immunosuppression (no anti-TNF) | 4 (4-6) | 129 (23-468) | \*\*\* | 18.1 (12.1-27.1) | 22.4 (14.0-32.7) | 92.6 (84.6-97.2) | \*\*\* | 22.4 (14-32.7) | 92.6 (84.6-97.2) | \*\*\* |
| Immunosuppression with anti-TNF | 4 (4-4) | 27 (7-117) | \*\*\* | 6.0 (4.6-7.7) | 18.7 (12.9-25.8) | 74.3 (66.6-81.1) | \*\*\* | 18.7 (12.9-25.8) | 74.3 (66.6-81.1) | \*\*\* |
| **Serotype 6A Overall**  | **4 (4-144)** | **3102 (1375-7115)** | **\*\*\*** | **122.6 (88.0-170.9)** | **29.6 (24.4-35.3)** | **95.1 (92.0-97.3)** | **\*\*\*** | **100 (98.7-100)** | **100 (98.7-100)** | **-** |
| No immunosupressive treatment | 4 (4-4) | 4443 (1456-8768) | \*\*\* | 241.1 (123.0-472.9) | 22.2 (12.7-34.5) | 95.2 (86.7-99.0) | \*\*\* | 100 (94.3-100) | 100 (94.3-100) | - |
| Immunosuppression (no anti-TNF) | 4 (4-108) | 3664 (1762-8831) | \*\*\* | 157.5 (83.1-298.4) | 30.9 (21.1-42.1) | 94.9 (87.5-98.6) | \*\*\* | 100 (95.5-100) | 100 (95.4-100) | - |
| Immunosuppression with anti-TNF | 4 (4-335) | 2231 (1251-4815) | \*\*\* | 78.8 (49.1-126.5) | 32.2 (24.6-40.5) | 95.2 (90.4-98.1) | \*\*\* | 100 (97.5-100) | 100 (97.5-100) | - |
| **Serotype 6B Overall**  | **455 (4-1765)** | **4644 (2221-8626)** | **\*\*\*** | **23.4 (16.4-33.5)** | **62 (55.8-67.9)** | **96.7 (93.8-98.5)** | **\*\*\*** | **58.6 (52.3-64.6)** | **96.0 (92.9-98.0)** | **\*\*\*** |
| No immunosupressive treatment | 77 (4-1064) | 5844 (2702-8435) | \*\*\* | 64.7 (28.6-146.2) | 51.7 (38.2-65.0) | 98.2 (90.3-100) | \*\*\* | 50.0 (36.6-63.4) | 98.2 (90.3-100) | \*\*\* |
| Immunosuppression (no anti-TNF) | 487 (4-1219) | 6808 (2952-11645) | \*\*\* | 26.3 (13.8-50.2) | 65.8 (53.7-76.5) | 96.2 (89.2-99.2) | \*\*\* | 58.9 (46.8-70.3) | 93.6 (85.7-97.9) | \*\*\* |
| Immunosuppression with anti-TNF | 787 (4-2684) | 3895 (1888-7855) | \*\*\* | 14.5 (8.8-23.8) | 64.4 (55.6-72.5) | 96.4 (91.8-98.8) | \*\*\* | 62.1 (53.3-70.4) | 96.4 (91.8-98.8) | \*\*\* |
| **Serotype 7F Overall**  | **29 (4-472)** | **1338 (623-2764)** | **\*\*\*** | **22.6 (16.6-30.6)** | **54.9 (49-60.6)** | **95.2 (92.1-97.3)** | **\*\*\*** | **16.8 (12.8-21.6)** | **69.4 (63.8-74.7)** | **\*\*\*** |
| No immunosupressive treatment | 4 (4-225) | 2182 (1198-3536) | \*\*\* | 57.1 (29.1-112.0) | 47.7 (35.1-60.5) | 100 (94.2-100) | \*\*\* | 15.4 (7.6-26.5) | 79.0 (66.8-88.3) | \*\*\* |
| Immunosuppression (no anti-TNF) | 132 (4-410) | 1589 (715-3442) | \*\*\* | 25.2 (14.3-44.7) | 60.0 (48.8-70.5) | 97.5 (91.4-99.7) | \*\*\* | 10.6 (5.0-19.2) | 72.8 (61.8-82.1) | \*\*\* |
| Immunosuppression with anti-TNF | 19 (4-569) | 1187 (486-2114) | \*\*\* | 14.1 (9.3-21.5) | 55.1 (46.7-63.3) | 91.9 (86.3-95.7) | \*\*\* | 21.1 (14.8-28.6) | 63.5 (55.2-71.3) | \*\*\* |
| **Serotype 9V Overall**  | **7 (4-834)** | **1903 (642-4149)** | **\*\*\*** | **18.6 (13.2-26.3)** | **49.8 (43.6-56)** | **92.5 (88.7-95.4)** | **\*\*\*** | **40.4 (34.4-46.6)** | **85.4 (80.6-89.4)** | **\*\*\*** |
| No immunosupressive treatment | 7 (4-541) | 1980 (667-5421) | \*\*\* | 44.9 (21.0-95.9) | 48.2 (34.7-62) | 98.2 (90.6-100) | \*\*\* | 33.9 (21.8-47.8) | 91.2 (80.7-97.1) | \*\*\* |
| Immunosuppression (no anti-TNF) | 52 (4-618) | 1903 (791-5036) | \*\*\* | 24.6 (13.2-45.8) | 52.6 (40.9-64) | 98.7 (93.0-100) | \*\*\* | 41.0 (30.0-52.7) | 92.2 (83.8-97.1) | \*\*\* |
| Immunosuppression with anti-TNF | 6 (4-1268) | 1586 (562-3211) | \*\*\* | 10.8 (6.6-17.6) | 48.9 (40-57.7) | 86.5 (79.5-91.8) | \*\*\* | 42.7 (34.1-51.7) | 78.9 (71.0-85.5) | \*\*\* |
| **Serotype 14 Overall**  | **477 (4-1262)** | **1656 (859-3425)** | **\*\*\*** | **8.8 (6.5-12.1)** | **69.4 (63.6-74.7)** | **97.5 (95.0-99.0)** | **\*\*\*** | **100 (98.7-100)** | **100 (98.7-100)** | **-** |
| No immunosupressive treatment | 351 (4-1024) | 1836 (812-3673) | \*\*\* | 12.5 (6.9-22.6) | 64.5 (51.3-76.3) | 100 (94.2-100) | \*\*\* | 100 (94.2-100) | 100 (94.2-100) | - |
| Immunosuppression (no anti-TNF) | 205 (4-1056) | 1524 (717-5004) | \*\*\* | 13.3 (7.2-24.7) | 67.9 (56.4-78.1) | 96.3 (89.6-99.2) | \*\*\* | 100 (95.4-100) | 100 (95.5-100) | - |
| Immunosuppression with anti-TNF | 800 (4-1611) | 1847 (1052-3237) | \*\*\* | 5.7 (3.7-8.6) | 72.2 (64.2-79.4) | 97.1 (92.8-99.2) | \*\*\* | 100 (97.5-100) | 100 (97.4-100) | - |
| **Serotype 18C Overall**  | **28 (4-727)** | **1750 (667-4065)** | **\*\*\*** | **21.2 (15.6-28.7)** | **58 (52.1-63.7)** | **95.3 (92-97.4)** | **\*\*\*** | **100 (98.7-100)** | **100 (98.7-100)** | **-** |
| No immunosupressive treatment | 11 (4-441) | 2528 (1279-5450) | \*\*\* | 42.1 (20.0-88.7) | 50.8 (37.9-63.6) | 94.7 (85.4-98.9) | \*\*\* | 100 (94.3-100) | 100 (93.7-100) | - |
| Immunosuppression (no anti-TNF) | 28 (4-521) | 1833 (708-3696) | \*\*\* | 24.0 (13.6-42.4) | 58.7 (47.2-69.6) | 98.7 (93.0-100) | \*\*\* | 100 (95.5-100) | 100 (95.3-100) | - |
| Immunosuppression with anti-TNF | 33 (4-1211) | 1397 (608-4119) | \*\*\* | 15.0 (10.0-22.6) | 60.7 (52.4-68.5) | 93.6 (88.1-97.0) | \*\*\* | 100 (97.6-100) | 100 (97.4-100) | - |
| **Serotype 19A Overall**  | **20 (4-116)** | **766 (206-1597)** | **\*\*\*** | **20.0 (15.9-25.0)** | **64.3 (58.6-69.8)** | **96.9 (94.1-98.6)** | **\*\*\*** | **33.7 (28.3-39.4)** | **88.9 (84.6-92.2)** | **\*\*\*** |
| No immunosupressive treatment | 17 (4-123) | 1152 (458-2416) | \*\*\* | 39.3 (25.0-61.8) | 69.2 (56.6-80.1) | 100 (94.2-100) | \*\*\* | 30.8 (19.9-43.4) | 96.8 (88.8-99.6) | \*\*\* |
| Immunosuppression (no anti-TNF) | 18 (4-132) | 820 (224-2240) | \*\*\* | 24.9 (15.1-41.0) | 61.0 (49.6-71.6) | 97.4 (91.0-99.7) | \*\*\* | 37.8 (27.3-49.2) | 89.7 (80.8-95.5) | \*\*\* |
| Immunosuppression with anti-TNF | 23 (4-103) | 508 (160-1144) | \*\*\* | 13.4 (10.0-17.9) | 64.0 (55.8-71.7) | 95.2 (90.4-98.1) | \*\*\* | 32.7 (25.2-40.8) | 85.0 (78.2-90.4) | \*\*\* |
| **Serotype 19F Overall**  | **4 (4-90)** | **1046 (57-2926)** | **\*\*\*** | **21.1 (15.7-28.6)** | **43.8 (38-49.6)** | **88.7 (84.4-92.2)** | **\*\*\*** | **16.5 (12.5-21.2)** | **63.3 (57.3-69.0)** | **\*\*\*** |
| No immunosupressive treatment | 4 (4-45) | 1415 (248-3072) | \*\*\* | 36.6 (19.5-68.5) | 40.6 (28.5-53.6) | 93.0 (83.0-98.1) | \*\*\* | 9.4 (3.5-19.3) | 68.4 (54.8-80.1) | \*\*\* |
| Immunosuppression (no anti-TNF) | 6 (4-151) | 1495 (266-4074) | \*\*\* | 28.5 (15.5-52.4) | 48.8 (37.6-60.1) | 89.9 (81.0-95.5) | \*\*\* | 17.1 (9.7-27.0) | 72.2 (60.9-81.7) | \*\*\* |
| Immunosuppression with anti-TNF | 4 (4-134) | 574 (43-2195) | \*\*\* | 14.3 (9.5-21.5) | 42.4 (34.4-50.7) | 86.3 (79.5-91.6) | \*\*\* | 19.2 (13.3-26.4) | 56.1 (47.5-64.5) | \*\*\* |
| **Serotype 23F Overall**  | **4 (4-20)** | **654 (42-1715)** | **\*\*\*** | **23.4 (17.7-31.1)** | **32.2 (27-37.8)** | **81.4 (76.5-85.7)** | **\*\*\*** | **11.6 (8.2-15.8)** | **64.3 (58.5-69.8)** | **\*\*\*** |
| No immunosupressive treatment | 4 (4-37) | 1158 (165-2861) | \*\*\* | 35.7 (20.0-63.7) | 35.4 (23.9-48.2) | 87.3 (76.5-94.4) | \*\*\* | 10.8 (4.4-20.9) | 66.7 (53.7-78.0) | \*\*\* |
| Immunosuppression (no anti-TNF) | 4 (4-20) | 924 (186-1588) | \*\*\* | 28.4 (17.0-47.6) | 34.9 (24.8-46.2) | 83.7 (73.8-91.1) | \*\*\* | 13.3 (6.8-22.5) | 71.2 (60.0-80.8) | \*\*\* |
| Immunosuppression with anti-TNF | 4 (4-16) | 494 (13-1386) | \*\*\* | 17.7 (11.7-26.8) | 29.4 (22.3-37.3) | 77.7 (70.1-84.1) | \*\*\* | 11.1 (6.6-17.2) | 59.5 (51.1-67.4) | \*\*\* |
| **All serotypes Overall** | **4 (4-202)** | **1034 (123-3020)** | **\*\*\*** | **19.0 (17.5-20.7)** | **44% (19-69%)** | **94% (78-98%)** | **\*\*\*** | **49.0 (47.4-50.6)** | **84.1 (82.8-85.2)** | **\*\*\*** |
| No immunosupressive treatment | 4 (4-124) | 1248 (196-3766) | \*\*\* | 36.0 (30.1-43.2) | 42% (14-69%) | 95% (85-100%) | \*\*\* | 46.8 (43.4-50.3) | 88.3 (85.8-90.5) | \*\*\* |
| Immunosuppression (no anti-TNF) | 4 (4-218) | 1171 (197-3569) | \*\*\* | 26.5 (22.7-31.0) | 49% (16-68%) | 96% (84-99%) | \*\*\* | 49.0 (45.9-52.0) | 88.0 (85.9-90.0) | \*\*\* |
| Immunosuppression with anti-TNF | 4 (4-319) | 781 (55-2525) | \*\*\* | 12.2 (10.9-13.7) | 42% (19-72%) | 91% (67-97%) | \*\*\* | 50.0 (47.8-52.3) | 80.1 (78.2-81.9) | \*\*\* |

Anti-TNF: anti-tumor necrosis factor immunosuppressive treatment; IBD: inflammatory bowel disease; OPA: opsonophagocytic assay; PCV13: 13-valent pneumococcal conjugated vaccine.

Cut-off for seroprotection is defined as OPA titers >8 or > post-licensure cut-off value proposed by Andrew et al (Supplementary Table 2).10 OPA titers before and after PCV13 are compared using the paired non-parametric Wilcoxon signed-rank test. Percentages of seroprotection are compared using Pearson's chi-squared test (\*: *P* <.05; \*\*: *P*m<.01; \*\*\*: *P* <.001).

## Supplementary Figure 2: Reverse Cumulative Curve of Serotype-Specific OPA Responses to PCV13 in IBD Patients.





## Supplementary Table 8: Cumulative Summary of Adverse Events.

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
|  |  | **PCV13 in SIBDCS \*** | **EMA report 11** | **CAPITA study 12**% (95% CI) |
| **Metabolism and nutrition disorders** |  |  |  |
|  | Decreased appetite | 13% | Very common; >10% | 5.3 (3.9, 7.0) |
| **Nervous system disorders** |  |  |  |
|  | Headaches | 21% | Very common; >10% | 15.9 (13.6, 18.5) |
| **Gastrointestinal disorders** |  |  |  |
|  | Diarrhea | 13% | Very common; >10% | 5.7 (4.3, 7.5) |
|  | Nausea, vomiting | 9% | Vomiting: Common (>50 y) or Very common (18-59 y)Nausea: Uncommon; <1% | Vomiting: 0.3 (0.1, 1.0) |
| **Immune system disorders** |  |  |  |
|  | Hypersensitivity reaction | 0% | Uncommon; <1% | No data reported |
| **Skin and subcutaneous tissue disorders** |
|  | Rash | 2% | Very common; >10% | 3.3 (2.2, 4.7) |
| **General disorders** |  |  |  |
|  | Pyrexia | 6% | Very common (18-29 y)Common (>30 y) | 2.9 (1.9, 4.3) |
|  | Fatigue | 29% | Very common; >10% | 18.8 (16.3, 21.5) |
| **Administration site conditions** |  |  |  |
|  | Vaccination-site erythema | 10% | Very common; >10% | 4.9 (3.5, 6.5) |
|  | Vaccination-site induration/swelling | 19% | Very common; >10% | 6.8 (5.2, 8.6) |
|  | Vaccination-site pain/tenderness | 53% | Very common; >10% | 36.1 (33.0, 39.3) |
|  | Limitation of arm movement | 33% | Very common; >10% | 14.1 (11.9, 16.6) |
| **Musculoskeletal and connective tissue disorders** |  |
|  | Arthralgia | 20% | Very common; >10% | New pain: 7.4 (5.8, 9.4)Aggravated pain: 5.2 (3.8, 6.9) |
|  | Myalgia | 21% | Very common; >10% | New pain: 18.4 (15.9, 21.1)Aggravated pain: 9.1 (7.3, 11.2)  |

\* The percentage is calculated by dividing the number of patients who have reported the side-effect during the two months of follow-up by the total number of patients who have returned the side-effects diary card (234 patients).

In the EMA report  **11**, the frequency is defined as: very common (≥10%), common (1-10%), uncommon (<1%).

The results from the CAPITA study are included in the EMA report. This randomized, double-blind, placebo-controlled trial involves **84,496 adults aged 65 years or older**, and evaluates the efficacy of PCV13 in preventing pneumonia.

# Narrative Report of Relevant Side-Effects

## Change in disease activity

* **Subject LA025**: 75-year-old female with Crohn’s disease treated with infliximab who consulted her gastroenterologist on June 18, 2015 (21 days after PCV13 administration) complaining of increasing diarrhea, anorexia, vomiting, as well as headache and fatigue. Her doctor diagnosed a relapse of Crohn’s disease; the patient was hospitalized and received a double injection of infliximab 800 mg on June 25, 2015 (5 days earlier than initially planned).
* **Subject LA044**: 55-year-old female with ulcerative colitis disease treated with golimumab 50 mg. On March 07, 2015 (1 day after PCV13 administration), she complained of anorexia, fatigue, headache, arthralgia, myalgia and fever (38.8°C, 1 day duration), as well as abdominal pain and diarrhea. Her physician diagnosed an ulcerative colitis relapse and increased the subsequent dose of golimumab to 100 mg, which she received as planned on April 02, 2015. Of note, this patient usually has these same complaints during the week that precedes her regular treatment.
* **Subject LA075**: 65-year-old male with ulcerative colitis disease treated with golimumab 100 mg and sulfasalazine. On April 15, 2015 (7 days after PCV13 administration), he complained about arthralgia of both hands and knees with redness and swelling, as well as bloody diarrhea. His rheumatologist started again methotrexate 15 mg injections once a week. Of note, these arthralgias were known to both the patient and his rheumatologist prior to study inclusion. Methotrexate treatment was indicated, but the patient had decided on his own to stop the injections 2.5 months before study inclusion.
* **Subject LA178**: 78-year-old female with ulcerative colitis disease treated with vedolizumab. She complained of abdominal pain and bloody diarrhea approximately 3 days after PCV13 administration. She consulted on September 09, 2015 and received vedolizumab a few days before the expected date.
* **Subject GE002**: 42-year-old male with Crohn’s disease treated with infliximab. On April 10, 2014 (day of the PCV13 vaccination), he complained about unusual diarrhea that lasted for 8 weeks. Of note, he received infiximab treatment on the same day as the vaccine administration as his treatment interval was being adapted at that time (shortened from every 8 weeks to every 6 weeks).
* **Subject GE025**: 32-year-old male with Crohn’s disease since 2006, treated with azathioprine until 2010, and stopped thereafter because of complete remission. He complained of anorexia, tiredness, nausea, abdominal pain and increased diarrhea 1 week after PCV13 administration. First, he consulted his gastroenterologist on November 17, 2014. Subsequently, on November 24, 2014, he received an iron infusion for the correction of known anemia. On January 07, 2015 (73 days after PCV13 administration), he developed a large size peri-anal abscess requiring hospitalization for emergent drainage. He also began corticotherapy on the same day and infliximab treatment was started on January 28, 2015.
* **Subject GE042**: 20-year-old female with Crohn’s disease treated with infliximab and adalimumab. On August 3, 2015 (21 days after PCV13 administration), she complained of anorexia, fatigue and an increasing frequency of diarrhea. She consulted her gastroenterologist who consequently increased her treatment.
* **Subject GE056**: 28-year-old male with Crohn’s disease treated with azathioprine. On June 06, 2015 (10 days after PCV13 administration), he complained of an increasing frequency of diarrhea, abdominal pain and fatigue and consulted his gastroenterologist on June 17, 2015. An increase in Crohn’s disease activity was diagnosed and the patient was treated with corticotherapy.
* **Subject BE016**: 24-year-old female with Crohn’s disease treated with infliximab. She was known to have an anal fistula since March 2013. On September 21, 2015 (70 days after PCV13 administration), she consulted for a peri-anal abscess. She was hospitalized and had surgical drainage of the abscess on September 22, 2015.
* **Subject BE024**: 18-year-old male with Crohn’s disease treated with adalimumab since June 2015. On September 04, 2015 (49 days after PCV13 administration), he complained of fever that lasted for 10 days. He was hospitalized during 12 days for severe ileal stenosis and recovered completely after surgery.

## Serious adverse events unrelated to IBD

* **Subject LA147**: 68-year-old male with Crohn’s disease treated with methotrexate and certolizumab pegol. Between August 26, 2015 and September 3, 2015 (63 days after PCV13 administration), he was hospitalized for *Legionella* pneumonia during which he received intravenous macrolide treatment and fully recovered.
* **Subject LA180**: 27-year-old female with ulcerative colitis disease treated with 6-mercaptopurin and 5-ASA. On September 15, 2015 (20 days after PCV13 administration), she complained of a cough and tiredness and consulted her general practitioner who gave her a 3-day course of antibiotics for the treatment of a possible bacterial pneumonia of unknown etiology.
* **Subject LA051**: 39-year-old male with Crohn’s disease since 2010 and treated with infliximab since 2012. On March 1, 2015 (2 days after PCV13 administration), he complained of abdominal pain, cough, fever and dyspnea. His general practitioner prescribed an inhalation of budesonide and formoterol, codeine 50 mg/day, as well as cefuroxim 1 g/day during 7 days for a possible bronchitis and sinusitis.

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