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Infection Prevention by Vaccinations in Immunocompromised Patients

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Abbreviations

AD	Autoimmune Disease
Allo-HSCT	Allogeneic Hematopoietic Stem Cell Transplantation
AMC	Academic Medical Center
APC	Antigen Presenting Cell
AZA	Azathioprine
bIM	Biological Immunomodulator
cART	Combination Antiretroviral Therapy
CB	Cord Blood
CD	Crohn's Disease
CDC	Centers for Disease Control and Prevention
CI	Confidence Interval
CID	Chronic Inflammatory Disease
cIM	Conventional Immunomodulator
COPD	Chronic Obstructive Pulmonary Disease
DMARDs	Disease-Modifying AntiRheumatic Drugs
DTaP-IPV-Hib-HepB	Diphtheria, Pertussis, Tetanus, Polio, Haemophilus Influenza type B, and Hepatitis B
DTP	Diphtheria, Tetanus, Polio
EBMT	European Group for Blood and Marrow Transplantation
GMC	Geometric Mean Concentration
GVHD	Graft-Versus-Host Disease
Hep A	Hepatitis A
HIV	Human Immunodeficiency Virus
HOVON	Society of adult hematology-oncology in the Netherlands

HSCT	Hematopoietic Stem Cell Transplantation
IBD	Inflammatory Bowel Disease
ICCIT	Immunocompromised and Chronically Ill Traveller
ICP	ImmunoCompromised Patient
ICT	Immunocompromised Traveller
IDDM	Insulin Dependent Diabetes Mellitus
IPD	Invasive Pneumococcal Disease
IQR	Interquartile Range
ITP	Immune Thrombocytopenic Purpura
MA	Myelo-Ablative
MC	Median Concentration
MD	Mean Difference
MHC	Major Histocompatibility Complexes
MMR	Measles, Mumps and Rubella
Mo	Months
MSM	Men who have Sex with Men
MTX	Methotrexate
MUD	Matched Unrelated Donor
N/a	Not applicable
NR	Non-Response
NR	Not Reported
OR	Odds Ratio
ORS	Oral Rehydration Solution
PB	Pneumococcal Bacteraemia
PCV	Pneumococcal Conjugated Vaccine – Prevenar7 / 13

PPSV	Pneumococcal PolySaccharide Vaccine – Pneumovax23
PVL	Post-Vaccination Level
Py	Person years
RA	Rheumatoid Arthritis
RD	Rheumatic Diseases
RCT	Randomized Controlled Trial
RIST	Reduced-Intensity hematopoietic Stem cell Transplantation
SCR	Seroconversion Rate
SCT	Stem Cell Transplantation
SD	Standard Deviation
SIB	Sibling
SLE	Systemic Lupus Erythematosus
SOT	Solid Organ Transplantation
SpA	Spondylo-Arthritis
SR	Systematic Review
TD	Travellers' Diarrhoea
TF	Typhoid Fever
Th	T helper
TNF	Tumour Necrosis Factor
UC	Ulcerative Colitis
Wk	Weeks
VFR	Visiting Friends and Relatives
YF	Yellow Fever
Yr	Years

Chapter 1

General Introduction

General introduction

The concept of vaccination was first introduced by Edward Jenner in 1796. He immunised James Phipps, the son of his gardener, against smallpox by inoculating the eight-year-old boy with cowpox. His great contribution to science, however, was not the practice of inoculation, which had already been performed before; but the evidence that inoculation led to protection against smallpox which was proven by challenging the boy's immune system with small pox material without any signs of infection occurring (1). Since then, many vaccines have been developed, which had a major impact on infection prevention in human societies. To date, more than 20 vaccines exist and more than 20 vaccine candidates are under development (2).

Vaccinations are currently recommended for 1) small children; 2) travellers to countries that are endemic for certain infectious diseases; and 3) immunocompromised patients (ICPs), who are at increased risk of acquiring infections. Vaccinations are broadly divided into live-attenuated and inactivated vaccines. Live-attenuated vaccines are contra-indicated in ICPs, in children aged ≤ 6 months, and in the elderly, because of the risk of vaccine-associated viscerotropic or vaccine-associated neurologic disease. The childhood vaccination schedule includes the combined vaccination against diphtheria, pertussis, tetanus, polio, *Haemophilus influenzae* type b, and hepatitis B (DTaP-IPV-Hib-HepB), measles, mumps and rubella (MMR), and separate vaccinations against *Streptococcus pneumoniae* species, *Neisseria meningitidis* species, and human papillomavirus.

For travellers, vaccinations against diphtheria, polio, hepatitis A (HepA), hepB, typhoid fever, rabies, and yellow fever (YF) are most commonly recommended. Travellers to malaria-endemic areas are prescribed malaria chemoprophylaxis. However, recommendations depend on the visited country and specific risk factors in the individual traveller. For travelling ICPs, for example, specific recommendations exist because this group of patients is particularly vulnerable for infectious diseases. The "immunocompromised state" is caused by a broad spectrum of diseases, which have an impaired immune response to infections in common. For this reason, they are at increased risk of infectious diseases and their complications (3-5), which translates into an increased risk of morbidity and mortality in the immunocompromised population. However, precisely in this population, the post-vaccination immune response is expected to be hampered, leading to the clinical paradox that those who most need protection, are least likely to benefit from vaccinations (6-9).

Therefore, the most important deviations from the standard travel guidelines are the recommendation of the assessment of HepA and HepB antibody titres post-vaccination to check whether protection has been achieved; the prescription of on-demand antibiotics, to prevent travellers' diarrhoea and its complications; and the contra-indication of the live-attenuated yellow fever vaccine (10, 11).

For travelling as well as non-travelling ICPs, pneumococcal vaccination is recommended (12). Dependent on the immunocompromising condition, other

commonly recommended vaccinations are against HepB, *Haemophilus influenza*e type b, and *Neisseria meningitidis* species (12). Many of these vaccinations are currently included in the childhood vaccination schedule; however, these all have been introduced in the last 20 years, so that ICPs borne before that period are in need of these vaccinations.

In ICPs, infection prevention by vaccination and travel medicine advice can be paradoxical and complex, generating multiple questions from a scientific, but more importantly, from a clinical perspective. This thesis focuses on pneumococcal infection and vaccination. Furthermore, this thesis examines characteristics of pre-travel care for immunocompromised travellers and travel-related health problems, antibiotic use and medical care in this population during travelling.

Immune response to vaccination

A robust immune response of the immune system is fundamental to obtain protection after immunisation. When antigens are inoculated in the human body, antigen-presenting cells (APC) capture these antigens and migrate to the lymph nodes, while in the same time cutting the antigen in small fragments, which are then displayed on the cell surface by major histocompatibility complex (MHC) molecules. Fragments captured by MHC class I trigger CD8 T cell activation, whereas MHC class II molecules trigger a CD4 T cell activation. T helper (Th) 1 CD4 cells contribute to the elimination of intracellular pathogens by activation of, amongst other cells, CD8 T cells; the main function of Th2 CD4 cells is to eliminate extracellular pathogens by the production of certain interleukins. Essentially, both Th2 CD4 cells and TH1 CD4 cells activate B cells to differentiate into high affinity antibody-producing plasma cells and memory cells. The process from antigen exposure to producing high affinity antibodies takes 3-6 weeks (13).

To reach long-term protection after vaccination, the plasma cells need to produce significant antibody amounts, and, more importantly, they need to do this persistently. This persistence of antibody production depends on several factors, e.g. the nature of the antigen, vaccine schedules, age and the immune status of the vaccine recipient (13).

Immunocompromising conditions

The immunocompromising conditions addressed in this thesis comprise 1) immunosuppressive treatment due to an auto-immune disease or due to a solid-organ transplantation (SOT); 2) the immunocompromised status post-HSCT; and 3) infection with the human immunodeficiency virus (HIV).

Immunosuppressive treatment

Patients treated with immunosuppressive medications comprise two main groups: 1) patients with an autoimmune disease (AD), such as inflammatory bowel disease (IBD), or rheumatoid arthritis (RA), and 2) patients after a SOT. The main reasons for immunosuppressive treatment are to reduce inflammation in those with AD and to prevent SOT rejection. Although disease specific factors can also contribute to

immunosuppression in patients with an AD, we considered these of minor relevance and beyond the scope of this thesis.

Immunosuppressive medications can be categorized into four broad groups: glucocorticoids, conventional immunomodulators (cIMs), also often referred to as disease-modifying anti-rheumatic drugs (DMARDS), biological immunomodulators (bIMs) and medications that are mainly used in transplantation medicine. The immunosuppressive medications that are most relevant in relation to the content of this thesis are further detailed below.

Glucocorticoids

Glucocorticoids have a pivotal role in the anti-inflammatory feedback loop in the process of inflammation. Through their direct effects on gene expression, anti-inhibitory proteins are upregulated, while pro-inhibitory proteins are down-regulated; whereupon the synthesis of pro-inflammatory cytokines and proteins is reduced. As a result, the function and number of many immune cells, of which B and T lymphocytes are the most important, decrease (14).

Conventional immunomodulators

Mercaptopurine, its pro-drug azathioprine (AZA), and methotrexate (MTX) are the main medications in this group. Inhibition of cell proliferation is the most important characteristic of cIMs. AZA and mercaptopurine act, after incorporation into replicating DNA, by blocking DNA replication and purine synthesis, impacting mostly on proliferating cells, such as T and B cells, resulting in a severely impaired function. A second mechanism by which the number of T lymphocytes is reduced, is apoptosis of T lymphocytes by blocking CD28 co-stimulation, which normally is compulsory for T lymphocyte activation (15).

Although the mechanism of action of MTX is not completely understood, one of its effects is the inhibition of purine metabolism, which is the most important mechanism by which T and B cell activation is inhibited. Secondly, MTX inhibits an enzyme that participates in folate synthesis, normally required for DNA synthesis (16).

Biological immunomodulators

Tumour Necrosis Factor (TNF)α blocking agents are the most commonly used bIMs in the treatment of auto-immune diseases. Many immune cells, such as T and B cells, but also non-immune cells and sometimes even tumour cells secrete TNFα, a pro-inflammatory cytokine. After release of TNFα from these cells, it induces the release of many pro-inflammatory cytokines through binding to TNFα-receptors on hematopoietic and non-hematopoietic cells. As a result, TNFα contributes to a robust inflammatory response and constitutes a major component of the innate immune system (17). Particularly the Th1 immune response targeting intracellular bacteria and certain viruses is dependent on TNFα (18). Since TNFα induces this cascade of pro-inflammatory processes, blocking of TNFα results in a reduction of migration of dendritic cells, inhibition of T cell activation and reduced memory cell survival (18, 19).

Human immunodeficiency virus infection

HIV predominantly infects CD4 T cells, and to some extent, other immune cells such as macrophages. As a result, infection with HIV leads to progressive depletion and dysfunction of the immune system (20). Other consequences of HIV are B cell dysfunction and consequently dysfunctions in antibody-production and immune memory. These are assumed to be caused by chronic immune activation. Although combination antiretroviral therapy (cART) reverses most immune cell damage, loss of and decrease in memory B cell function remains (21). Thus, cART does not totally recover the immune response to invasive pathogens and to vaccinations. Therefore, it is suggested that even patients on cART have a reduced immune response to vaccination and higher infection risk (22-24).

Hematopoietic stem cell transplantation

HSCT is the transplantation of multipotent hematopoietic stem cells derived from the bone marrow, peripheral blood or umbilical cord blood and is applied in the treatment of diseases such as leukaemia, multiple myeloma or myelofibrosis. In this thesis, we mainly focus on allogenic HSCT. In allogenic HSCT, the graft-versus-tumour effect, by which donor-derived stem cells attack malignant cells, has been shown to be pivotal. However, since these donor-derived stem cells can also attack healthy recipient tissue, graft-versus-host disease (GVHD) is a threatening adverse effect. Allogeneic HSCT can be either myelo-ablative (MA) or non-myelo-ablative (reduced-intensity stem cell transplantation or RIST); with the difference that in MA, the recipient's bone marrow and blood cell production is completely destroyed, whereas in RIST this destruction is incomplete. After both procedures, immunosuppressive medications are needed to prevent GVHD and to stimulate that donor stem cells take over the blood cell production (25).

Understandably, the immune system of HSCT recipients is impaired, particularly in the first months post-HSCT. The recovery period of the immune system differs per immune cell compartment; B-cells restore in 3-6 months post-HSCT with recovery of B cell functionality between 12-24 months. T-cells maturate in the thymus, which is the reason that restoration takes longer compared to B cell restoration, particularly in the elderly, in whom the thymus becomes less active with increasing age. In addition, cytokine production is impaired in HSCT recipients with a more extended period of reduced IFN-y and TNFα production compared to IL-2, IL-4 and IL-5 production (25).

Determinants of vaccine antibody responses

Many different types of vaccines exist. Each has a different working mechanism and consequent differences in immunogenicity and efficacy. The principal determinant for the peak antibody response is the nature of the vaccine antigen and its intrinsic immunogenicity (13). Other predominant determinants are whether a vaccine is live-attenuated or inactivated, and whether it is a conjugated or polysaccharide vaccine. Live-attenuated vaccines elicit a more sustained antibody response as compared to inactivated vaccines, supposedly because of antigen persistence within the host. Conjugate vaccines elicit the induction of a strong T cell dependent memory response.

By contrast, the response to polysaccharide vaccines is T cell independent, resulting in the production of high-affinity long-lived plasma cells, without the development of memory (13). Other determinants of immunogenicity are the antigen dose, the use of adjuvants and the vaccine schedule. Higher doses of inactivated vaccines elicit higher primary antibody responses but selection of high affinity plasma cells may be restricted due to reduced B-cell competition; adjuvants induce inflammation at the injection site, and increase cell-mediated antigen transport towards lymph nodes; a vaccine schedule with an interval of three weeks at minimum guarantees uninterrupted primary responses (13). In ICPs, the immunocompromising condition is a host-specific limitation of the immune response to vaccinations. In patients treated with cIMs, for example, proliferation of T and B cells post-vaccination is blocked. Furthermore, TNFα blocking agents reduce the immune response by their effects on migration of APCs, T cell activation, and memory cell survival (19).

In conclusion, the immune response to vaccination will thus be different per administered vaccine, per immunocompromising condition, and, because other undetermined factors may play a role as well, maybe even per individual.

Pneumococcal infection and vaccination

A second major subject in infection prevention by vaccinations in ICPs is the prevention of pneumococcal infections. Therefore, pneumococcal infection and vaccination in ICPs are the focus of section 2 of this thesis.

Streptococcus pneumoniae is a gram-positive, extra-cellular diplococcus, first isolated in 1881 by Louis Pasteur and George Sternberg (26). The bacteria, which belong to the natural upper respiratory tract flora, can become pathogenic under certain circumstances, of which both the host status and the pathogenic repertoire of the strain play a key role. Of the 96 different serotypes identified to date, serotypes 8, 3, 12F, 22F, 19A, 9N, 15A, 10A, 33F and 11A (in order of frequency) are the 10 serotypes most commonly found in isolates of patients with IPD (27).

Infection by *S. pneumoniae* is a serious public health issue; being the leading cause of bacterial respiratory tract infections and accounting for up to 400,000 hospitalisations each year in the USA (28). The case-fatality rate varies between 5-7%, but is even higher in certain subgroups (28). Particularly ICPs are at increased risk of pneumococcal infection (29-31). Therefore, guidelines recommend pneumococcal vaccination in ICPs (12). Polysaccharide pneumococcal vaccine has been recommended since 1984. In 2012 a new vaccination schedule was introduced, in which the 13-valent pneumococcal conjugated vaccine (PCV) is administered first, followed by the 23-valent pneumococcal polysaccharide vaccine (PPSV) two months later (12). Allogenic HSCT recipients follow a different immunisation schedule, with three PCV vaccinations on a monthly base starting up to 1-year post-HSCT, followed by one PPSV vaccination 3-6 months after the last PCV (32, 33). This schedule resembles the childhood vaccination scheme.

PCV differs from PPSV by its covalent binding of polysaccharides to the diphtheria toxoid CRM197. Theoretically, PCV therefore provokes a more robust immune response through the recruitment of Th2 CD4 cells eliciting the production of memory B cells than PPSV. In contrast, PPSV consists of purified polysaccharides only, evoking a less robust T cell-independent B cell response (34, 35). Except for serotype 6A, all the serotypes covered by PCV (serotypes 1, 3, 4, 5, 6A, 6B 7F, 9V, 14, 18C, 19A, 19F and 23F) are also covered by PPSV (serotypes 1, 2, 3, 4, 5,6B, 7F, 8, 9N, 9V, 10A, 11A, 12F, 14, 15B, 18C, 19A, 19F, 20, 22F, 23F, and 33F). Furthermore, PPSV includes ten additional serotypes. The serotypes in both vaccines are the most frequently isolated serotypes in clinical disease known to date (27). The rationale for the current vaccination schedule is that PPSV broadens the smaller spectrum of PCV and boosts the immune response to the serotypes present in both vaccines (36, 37).

However, immunogenicity (and efficacy) data of the currently recommended schedule is scarce, and in patients receiving immunosuppressive treatment, for example, studies primarily focused on single-vaccine type regimens (6, 8, 38). Therefore, a solid scientific base of current recommendations is lacking. As a result, at least in the Netherlands, pneumococcal vaccination guidelines are incomplete. Worldwide, pneumococcal vaccination coverage in ICPs is low - with the risk of unnecessary high mortality rates, hospitalisations, and health care costs (31, 39, 40). Furthermore, no consensus has yet been reached on the indication of post-vaccination antibody titre measurements, which are therefore currently not generally recommended in pneumococcal vaccination guidelines (12, 32).

Travel medicine for immunocompromised travellers

Despite the mentioned challenges in vaccine immunology in ICPs, pneumococcal vaccination is of foremost importance for (travelling and non-travelling) ICPs. However, vaccinations are probably most often administered in the context of pre-travel management. Section 2 of this thesis therefore involves travel medicine for travelling ICPs.

Novel (immunosuppressive) therapies are constantly developed, improving survival and quality of life of ICPs. Correspondingly, recent figures showed an increased number of travelling ICPs (41, 42). However, ICPs are vulnerable travellers and at risk of contracting infections during travelling (43-46). In immunocompetent travellers, already up to 50% experience some sort of health problem during travelling (45-48). Acute diarrhoea is a very frequent travel-related complaint with an increased risk of complications in ICPs (45, 49). To prevent travelling ICPs from severe complications of gastrointestinal infection, on-demand antibiotics are prescribed which are to be used in case of diarrhoea and fever (10, 43, 50, 51).

Other pre-travel measures that are specifically targeted to travelling ICPs include:

1) The assessment of post-vaccination antibody titre measurements after hepatitis A and B vaccination (52-54);

2) The routine administration of immunoglobulins as part of the post-exposure treatment for rabies, regardless of pre-exposure vaccinations (11, 55);

3) The contra-indication of vaccination with life-attenuated vaccines such as yellow fever vaccination (10, 32), sometimes leading to a negative travel advice, if never administered previously.

As shown, ICPs comprise a specific, vulnerable group of travellers; not comparable to immunocompetent travellers. However, travel medicine in ICPs is an under-studied area; guidelines are therefore often not specified for ICPs and existing recommendations for ICPs are rather based on expert-opinion than on evidence from the literature.

Objectives and Outline of this thesis

Objective

The objective of this thesis is to contribute to the improvement of vaccination schedules and pre-travel care advice for ICPs. A particular focus of this thesis is on the need for, and the evaluation of, the level of protection by pneumococcal vaccination in ICPs.

We aimed to study:

- The incidence of invasive pneumococcal disease (IPD) in subgroups of ICPs;

- The immunogenicity of pneumococcal vaccination in patients with auto-immune disease;

- The immunogenicity of current pneumococcal vaccination schedules in cohorts of patients with inflammatory bowel disease and allogenic HSCT-recipients;

- The characteristics of pre-travel care, and the frequency of travellers' diarrhoea and travel-related complaints in ICTs.

Outline

The first section of this thesis focuses on pneumococcal infection and vaccination in ICPs. First, to provide support for current pneumococcal vaccination recommendations in ICPs, the incidence of IPD in subgroups of ICPs was evaluated (Chapter 2). Second, the immunogenicity of pneumococcal vaccination in patients with AD was studied (Chapter 3). Since, few studies exist on pneumococcal vaccine immunogenicity, Chapter 4, 5 comprise prospective cohorts in which immunogenicity of current pneumococcal vaccination schedules in patients with IBD (Chapter 4), and in allogeneic HSCT-recipients (Chapter 5) were studied.

In the second section, travel medicine in ICPs was studied. **Chapter 6** describes characteristics of pre-travel care for immunocompromised and chronically ill travellers. Travel destination and duration, and rates of vaccination, post-vaccination antibody titre measurements and prescription of on-demand antibiotics were analysed and described. In **Chapter 7,** ICPs were compared with sex- and age-matched

immunocompetent travellers with regard to the frequency of travellers' diarrhoea and other travel-related complaints; antibiotics use; use of medical care; and risk behaviours.
In the fourth and last section of this thesis, conclusions drawn from this thesis are summarized (**Chapter 8** and **9**).

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Section 1

Pneumococcal Infections and Vaccination in Immunocompromised Patients

Chapter 2

Incidence of invasive pneumococcal disease in immunocompromised patients: A systematic review and meta-analysis.

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Abstract

BACKGROUND: Invasive pneumococcal disease (IPD) is associated with high morbidity and mortality, with immunocompromised patients (ICPs) at particular risk. Therefore, guidelines recommend pneumococcal vaccination for these patients. However, guidelines are scarcely underpinned with references to incidence studies of IPD in this population. This, potentially results in unawareness of the importance of vaccination and low vaccination rates. The objective of this systematic review and meta-analysis was to assess the incidence of IPD in ICPs.

METHODS: We systematically searched PubMed and Embase to identify studies in English published before December 6th 2017 that included terms related to 'incidence', 'rate', 'pneumococcal', 'pneumoniae', 'meningitis', 'septicemia', or 'bacteremia'. We focused on patients with HIV, transplantation and chronic inflammatory diseases.

RESULTS: We included 45 studies in the systematic review reporting an incidence or rate of IPD, defined as isolation of *Streptococcus pneumoniae* from a normally sterile site. Random effects meta-analysis of 38 studies showed a pooled IPD incidence of 331/100,000 person years in patients with HIV in the late-antiretroviral treatment era in non-African countries, and 318/100,000 in African countries; 696 and 812/100,000 in patients who underwent an autologous or allogeneic stem cell transplantation, respectively; 465/100,000 in patients with a solid organ transplantation; and 65/100,000 in patients with chronic inflammatory diseases. In healthy control cohorts, the pooled incidence was 10/100,000.

DISCUSSION: ICPs are at increased risk of contracting IPD, especially those with HIV, and those who underwent transplantation. Based on our findings, we recommend pneumococcal vaccination in immunocompromised patients. Prospero registration: ID: CRD42016048438

KEYWORDS: Invasive pneumococcal disease; immunocompromised; human immunodeficiency; chronic inflammatory diseases; transplantation; incidence rate

Introduction

Streptococcus pneumoniae can cause uncomplicated upper and lower respiratory tract infections including pneumonia. However, invasive pneumococcal disease (IPD) is a more serious manifestation of infection by *S. pneumoniae* and is characterized by pneumonia with bacteremia, meningitis or bacteremia (1, 2). Morbidity and mortality of invasive pneumococcal disease (IPD) are high worldwide [1-4]. Most vulnerable patient groups are patients who are immunocompromised due to HIV infection, or immunosuppressive treatment for solid or bone marrow transplantation, and chronic inflammatory diseases. These patients are at risk of contracting IPD at home but also when travelling abroad. Although patients with (functional) asplenia and cancer are also at risk of IPD, we decided not to include these patient groups in this systematic review because of the high heterogeneity in these groups. International guidelines recommend pneumococcal vaccination in these groups, as reviewed by Lopez et al (5). However, these guidelines lack solid references to incidence studies of IPD in these patient groups (6-14), and instead mainly refer to studies on immunogenicity and safety of vaccination (6-10). As a result, the relevance of pneumococcal vaccination in immunocompromised patients is often questioned, with physicians hesitant to advise their patients on pneumococcal vaccination (15, 16). Accordingly, worldwide pneumococcal vaccination rates in immunocompromised patients are low (15-20).

The objective of this systematic review (SR) and meta-analysis was to assess the incidence of IPD in several groups of immunocompromised patients and to provide support for current guidelines. In addition, we describe the case fatality rates associated with IPD. The data obtained may provide a better rationale for pneumococcal vaccination for subgroups of immunocompromised patients.

Methods

We followed PRISMA guidelines and registered the protocol for this SR and meta-analysis with the PROSPERO systematic protocol registry (www.crd.york.ac.uk/prospero/; ID: CRD42016048438) (Supplementary File 1).

Population and Search Strategy

We conducted a literature search in Pubmed and Embase (Ovid) on December 6th 2017 that included terms related to ‘incidence’, ‘rate’, ‘pneumococcal’, ‘pneumoniae’, ‘meningitis’, ‘septicemia’, or ‘bacteremia’ (see Supplementary File 2 for search term details) and included cohort and surveillance studies, and randomized controlled trials (RCTs) reporting incidence rates of IPD in general, or pneumococcal meningitis or pneumococcal bacteremia/septicemia in particular, in adult patients with the following immunocompromised conditions: 1) chronic inflammatory diseases (CID), often treated with immunosuppressive therapy, including Crohn’s disease (CD), ulcerative colitis (UC), rheumatoid diseases (RD), systemic lupus erythematosus (SLE), 2) solid organ transplantation (SOT), 3) autologous or allogeneic stem cell transplantation (SCT) or 4) HIV-infection. We compared IPD incidence rates (incidence rates of pneumococcal meningitis and pneumococcal bacteremia/septicemia, respectively) in these patient groups to incidence rates of healthy control cohorts, evaluated in the included studies.

Study Selection

Inclusion criteria were a reported incidence rate of IPD in general, or pneumococcal meningitis or pneumococcal bacteremia/septicemia in particular, defined by isolation of *S. pneumoniae* from a normally sterile site (e.g. blood or cerebrospinal fluid) in patients with a medical history of SCT, HIV, CID or SOT. Additional inclusion criteria for the meta-analysis were:

- A reported incidence rate AND a reported number of IPDs;
- For studies on HIV: a reported incidence rate and a reported number of IPDs for one of the below mentioned eras (i.e. studies with overlapping study periods were excluded for the meta-analysis);
- For SCT patients: a reported incidence and IPD number for autologous and allogeneic SCT patients separately.

We excluded duplicates studies; studies written in other languages than English; studies that included isolation of *S. pneumoniae* from non-sterile sites in their definition of IPD; studies focusing on risk ratios, on colonization of *S. pneumoniae,* on serotypes of *S. pneumoniae,* on *S. pneumoniae* resistance patterns or on recurrent *S. pneumoniae* infections; studies in animals; studies specifically focusing on children (age < 18 years); case reports or case series; review articles; and studies of which the full text was not available.

Two authors (FL and MvA) independently selected articles meeting inclusion criteria based on title, abstract or keywords. Discrepancies were resolved by consensus. In case of remaining discerning views, last author GJdB was consulted. Subsequently, one author (MvA) read and analyzed selected studies for eligibility. Citations and reference lists from review articles found in the initial search were checked to ensure that no studies were missed.

Data Extraction

Two authors (FL and MvA) developed a data extraction sheet, which was reviewed by a third author (GJdB). One author (MvA) extracted study details, two authors (FL and GJdB) reviewed extracted study details. In the data extraction sheet we included the following study data (see Supplementary File 3): author, publication year, country, study design, enrolment start- and end date, total duration of follow up years, immunocompromising condition, CD4 count in case of HIV, information on pneumococcal vaccination status and relevant medications if available, incidence of IPD, case fatality rate, and factors associated with IPD incidence analyzed in a multiple regression model. We calculated the incidence rate and confidence interval (CI) if these were not provided in the original study, based on the number of infections and total follow-up years (21-24). We contacted authors in case of insufficient information provided in the article.

Critical Appraisal

We applied the Critical Appraisal Tool for prevalence studies developed by The Joanna Briggs Institute. This Critical Appraisal Tool provides a checklist that covers nine domains: appropriateness of sample frame, recruitment of participants, adequacy of sample size, description of study subjects and setting, coverage of identified samples, valid methods for identification of the condition, a standardized and reliable measurement of the condition, appropriateness of the statistical analysis, and adequacy of the response rate.

We modified this critical appraisal tool on three domains (Supplementary File 4): we removed the last domain (adequacy of the response rate), since a large part of included studies in this SR were surveillance studies for which this domain could not be used. We modified the domain 'valid methods for identification of the condition' to 'identification of *S. pneumoniae'*, and the domain 'a standardized and reliable measurement of the condition' to 'definition of *S. pneumoniae',* because our SR focused on IPD instead of a 'certain condition'.

We used the following formula to calculate the sample size for the incidence rate:

Rate/standard error^2 (s.e.) (25). Based on reported incidence rates for IPD (see this study), we estimated an incidence of around 500/100,000 person years (py) in the studied population, equal to 0.005/py. We intended to estimate the incidence within ± 0.002/py. So that, if an incidence of e.g. 300/100,000 py is reported, we can conclude that the true incidence is between 100 and 500 py. This means that the 95% CI should be no wider than ± 0.002, yielding a s.e. of 0.001 (because the CI is defined as ± 2 standard errors.

With an estimated incidence of 0.005/ py and a s.e. of 0.001, the required sample size would be ≥ 5,000 when applying the formula for a single rate (sample size = rate/s.e.^{2} = 0,005/0.001^2 = 5000) (25, 26). Accordingly, studies with a sample size < 5,000 persons lack power to accurately estimate the incidence.

Identification of *S. pneumoniae* was considered adequate if this was either by chart review with >1 reviewer or based on a regulatory audited laboratory surveillance. The statistical analysis was considered appropriate if the methods section of a study described the calculation of the incidence.

Outcome

Our primary outcome was the incidence of IPD, categorized by immunosuppressive condition and compared to the incidence in healthy cohorts in included studies. Our secondary outcome was the IPD case fatality rate.

Data Synthesis and Analysis

We used RevMan (version 5.3; Nordic Cochrane Centre) and R (i386 3.3.3) software for the meta-analysis of the IPD incidence rate in different patient groups. Most studies calculated more than one incidence rate for different years, or for different patient

categories, i.e. age, medication use or immunization against *S. pneumoniae.* Therefore, although we excluded duplicate studies, we included some studies in the meta-analysis more than once, albeit with extraction of different data sets. We analyzed the pooled IPD incidence rate for each patient group (HIV, SCT, SOT, CID) separately, and the pneumococcal meningitis incidence rate for patient groups collectively (irrespective of the underlying condition), because of few studies on this subject. We only analyzed the pooled pneumococcal bacteremia incidence rate in HIV patients, because no data were available for the other patient groups.

The introduction of combination antiretroviral therapy (cART) in 1996 had a substantial effect on the infection risk in HIV patients (27, 28). Therefore, we performed a sub-analysis of the IPD incidence in HIV patients for which we categorized studies into three eras: pre-, early, and late ART. The pre-ART era included studies carried out between 1985 and 1998. Because ART did not become available in all areas at the same time, we allowed studies up to year 1998 to be included in the pre-ART era. Studies performed from 1996 up to 2003 were allocated to the early-ART era, and studies from 2000 onwards to the advanced-ART era, because in that year combination treatment became available. The resulting overlap between 2000 and 2003 is due to publication of data on patients recruited in the period from 1996 to 2003. Furthermore, because differences between low/middle income countries as compared to affluent high-income countries potentially affects the incidence rate of IPD, we stratified studies on IPD in HIV patients to African and non-African countries.

The degree of statistical heterogeneity between studies was assessed by the Cochran's Q-test (29). We used a random effects model to estimate the weighted average of the IPD incidence and pneumococcal meningitis (29).

Patient and Public Involvement

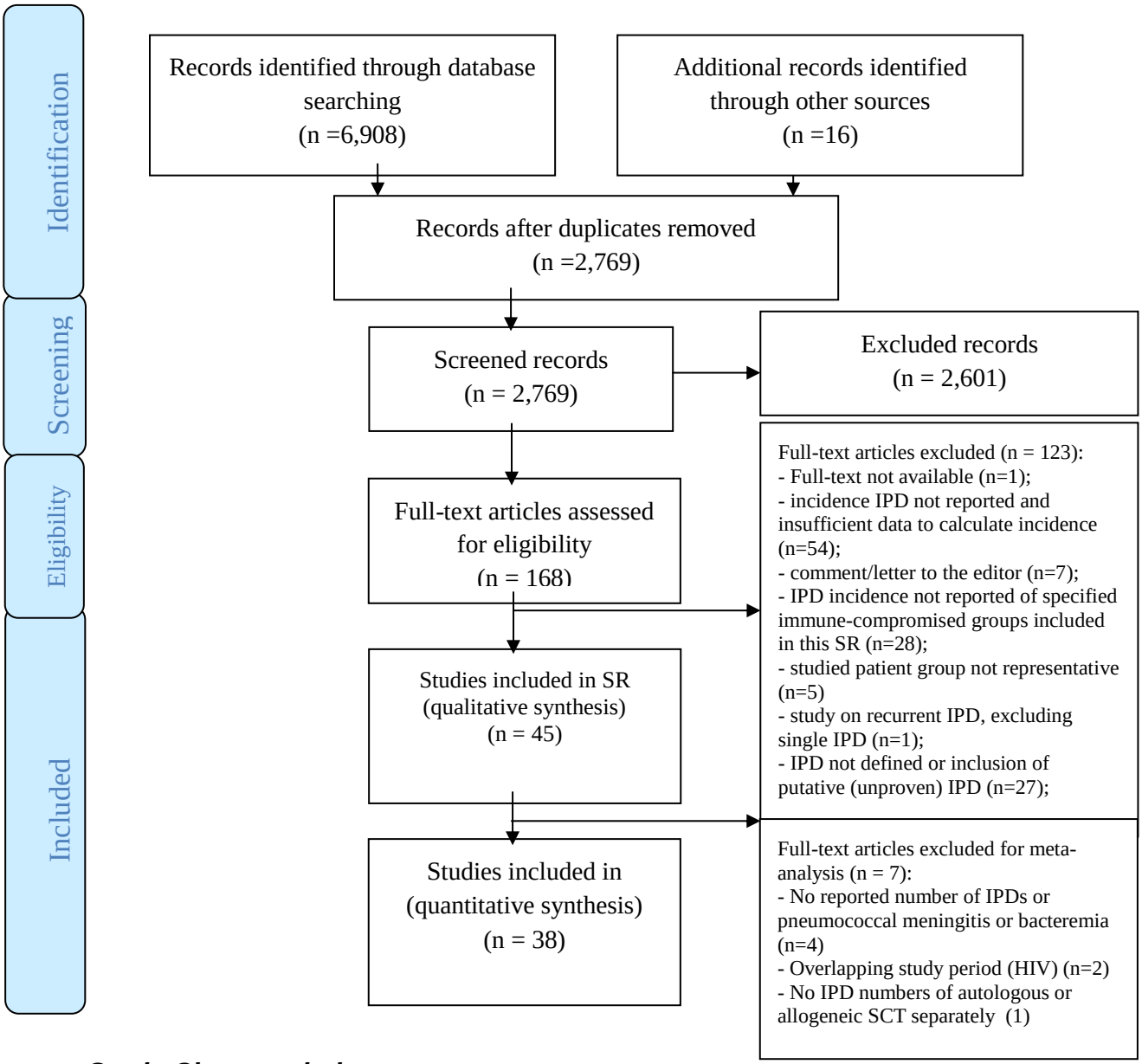
This systematic review and meta-analyses used conventional methods. As such, we did not involve patients in the design or conduct of our study. Patients were not invited to comment on the study design and were not consulted to develop patient relevant outcomes or interpret the results. Patients were not invited to contribute to the writing or editing of this document for readability or accuracy.

Results

Literature Search and Result

Figure 1 shows the study selection process reported according to PRISMA guidelines. We identified 6,908 articles through database searching, and we identified 16 additional articles by screening reference lists of reviewed articles. After removal of duplicates, we screened titles and abstracts of 2,769 articles. Ninety-eight articles were eligible for full-text screening. Finally, of the 45 articles in the SR, 38 were suitable for the meta-analysis (Figure 1).

Figure 1: Flow diagram of the selection process



Study Characteristics

Supplementary File 3A-F provides a summary sheet of all 45 included studies and incidence rates of IPD in the SR. Of 45 studies, 36 studies focused on IPD in general, and 9 focused on pneumococcal meningitis (4 studies) or pneumococcal bacteremia (5 studies).

Of the 36 studies on IPD in general, 27 included data on HIV, 5 on SCT, 5 on SOT, and 5 on patients with CID (Supplementary File 3A). Eighteen studies on IPD in general included a healthy control group or surveillance data on healthy individuals (Supplementary File 3B) (3, 21-23, 30-43). Of the 4 specific studies on pneumococcal meningitis, 2 focused on HIV, 1 on SCT, and 1 on SOT (Supplementary File 3C) (44-47). These studies provided two control cohorts with healthy individuals (Supplementary File 3D) (44-47). The incidence rate in the same cohort of healthy individuals was reported in all three studies of Van Veen et al. (45-47). Of the 5 studies

on pneumococcal bacteremia or septicemia, 4 focused on HIV patients and 2 on SOT (Supplementary File 3E) (48-52). One of these studies compared the incidence rate to the incidence rate in a healthy control cohort (Supplementary File 3F) (50, 51).

Calculated IPD incidence rates in included studies were derived from surveillance data in 19 studies, from study cohorts in 24 studies, and from an RCT in one study (Supplementary File 3A-F). The study design was not reported for one study (3).

Studies in patients with CID, or SCT/SOT were all performed in non-African countries, while 33 studies in HIV patients (27 studies on IPD in general, two specific studies on pneumococcal meningitis and four specific studies on pneumococcal bacteremia) comprised different geographical regions, of which 6 were performed in African countries and 27 in non-African countries (Supplementary File 3A-F).

Nineteen of the 27 studies on IPD in general in HIV patients involved data of the advanced-ART era (3, 24, 30, 31, 33, 35-37, 40-43, 53-59), 13 of the early-ART era (3, 31-35, 40, 53, 54, 56, 57, 60, 61), and 10 of the pre-ART era (31-33, 38-40, 53, 57, 62, 63). The study period of one of the two specific studies on the pneumococcal meningitis in HIV patients, encompassed all ART eras (pre-ART, early-ART, and advanced-ART) (44). The second study was performed in the advanced-ART era (47). Of the four specific studies on pneumococcal bacteremia in HIV patients, 2 were performed in the pre-ART-era (50, 52), 1 in both the early- and advanced-ART era (48), and 1 in the advanced-ART era (Supplementary File 3A) (51).

Critical Appraisal and Heterogeneity

Of the studies that met the eligibility criteria (n=45), we performed a critical appraisal assessment to analyze the risk of bias (Supplementary File 4). Scores ranged from 1 to 8.

We took into account factors that could potentially introduce bias. First, regarding the recruitment procedure; in fifteen studies, patients lost to follow-up were not taken into account, because HIV patients were recruited from an outpatient clinic and then followed up (24, 33, 35, 37, 44, 48, 49, 51, 53, 54, 57, 58, 60-62).

Second, identification of *S. pneumoniae* (chart review or audited laboratory surveillance) was a potential source of bias because inaccurate identification can lead to an underestimation. Nine studies did not fulfil the criteria for this item (see method section) (3, 23, 41, 44-47, 51, 52, 59, 61, 64). An additional three studies did not report how *S. pneumoniae* was identified (chart review or laboratory result-based) (24, 54). Finally, since the incidence rate of IPD does not follow a Poisson distribution, a small sample size results in a less precise estimate of the incidence rate, which can be either very small or very high (see sample size calculation in the Methods section). Studies scored low on the item ‘statistical analysis’ if studies did not describe the method of calculation of the incidence rate.

Next, we determined statistical heterogeneity which showed substantial-to-considerable heterogeneity between studies (see Figure 2A-H). As a result of the substantial level of heterogeneity, we calculated the pooled incidence rates in a random effects model (see Methods section) (29). Exclusion of studies with a high bias score (likely to introduce bias), or selection based on study design i.e. cohort or surveillance, did not reduce heterogeneity. Therefore, we decided to include all studies, independent of bias risk score.

Finally, because funnel plots on publication by result were largely symmetric, we judged publication bias as limited.

Pooled Incidence Rates of IPD

Healthy Individuals

The pooled incidence of IPD in healthy individuals was 10/100,000 py (95% CI 7.8-13.8) (Figure 2A) (n=14). Two studies of Kumar et al. (21, 22) comprised the same healthy control group, and were therefore included only once.

HIV Infected Individuals

In non-African countries, the pooled incidence rate decreased from 746/100,000 py (95% CI 588.7-946.0) (n=5) in the pre-ART, to 490/100,000 py (95% CI 406.3-591.7) (n=7) in the early-ART, to 331/100,000 py (95% CI 241.9-452.8) (9 studies) in the advanced-ART era. The pooled incidence of IPD in African countries in the pre-ART era (2 studies) was almost three times as high as the incidence in non-African countries (5 studies) in the same era: 2,465/100,000 py (95% CI 1896.5-3180.5) (n=2). In the advanced-ART era the pooled incidence available from one African country (South-Africa) was 318 (95% CI 258.6-392.1) (Figure 2B-C). Most studies lacked information on the (mean) CD4 count, ART, immunosuppressive treatment, and coverage of pneumococcal vaccination, so that a sub-analysis on these data was not feasible.

Stem Cell Transplantation

The pooled incidence rate of IPD in allogeneic SCT recipients was higher compared to the rate in autologous SCT recipients: 812/100,000 (95% CI 555.6-1185.6) (n=3) compared to 696 (95% 243.5-1987.3) (n=2) (Figure 2D). One study by Moreno et al. (65) reported a very high incidence rate, 2,213/100,000 py (CI 553.5-9948.6), which is probably due to the relatively short follow-up time (2 years), limited patient numbers, and the Poisson distribution of occurrence of IPD.

Solid Organ Transplantation

The pooled incidence in SOT recipients was 414/100,000 (95% CI 98.7-1731.9) (Figure 2E) (n=3) [21, 65, 66]. Kumar et al. (21) did not provide enough information to include incidence rates of separate organ transplantation groups. Amber et al. (66) reported a much higher incidence rate compared to the other studies. As in the study of Moreno et al. (65), this study had a short follow-up period and a limited number of patients.

Chronic Inflammatory Disease

The pooled IPD incidence rate in the population with CID was 65/100,000 py (95% CI 36.8-114.2) (n=5) (Figure 2F). One study reported separate incidence rates for a group of patients with SLE, Sjögren's syndrome or polymyositis/dermatomyositis, and for a group of patients with chronic obstructive pulmonary disease (COPD), asthma, CU, CD or RA (40). Studies on patients with SLE reported a remarkably higher incidence rate than studies on patients with other CID [3, 23, 64].

Pneumococcal Meningitis

The pooled incidence rate of pneumococcal meningitis in the different immunocompromised groups was 14/100,000 py (95% CI 5.5-33.9) (n=4), compared to a pooled incidence of pneumococcal meningitis of 0.8/100,000 py (95% CI 0.51-1.12) in two healthy control groups (Figure 2G). As expected, the incidence rates of pneumococcal meningitis were lower than of IPD in general.

Pneumococcal Bacteremia

The pooled incidence rate of pneumococcal bacteremia in patients with HIV was 391/100,000 (95% CI 347.6-440.3) (n=4). This was compared to an incidence rate of 24/100,000 (95% CI 21.4-27.1) in one healthy control group (Figure 2H), which is higher than the incidence rate of IPD in general in healthy cohorts (10/100,000). However, only one study conducted in South Africa provided a control cohort on pneumococcal bacteremia.

Case Fatality Rate

Seventeen of 36 studies reported an IPD case fatality rate with a range of 0-28.6% (3, 11, 21, 22, 31, 33, 37, 38, 40, 50, 54, 56-58, 60, 62, 67, 68). In HIV patients, the case fatality rate ranged from 0-25.6%, in SCT recipients from 10.3-20%, in SOT recipients from 12.2-28.6%, and in patients with a CID from 0-10%, this, compared to a case fatality rate in healthy groups with a range 1.5-14% (Supplementary File 3A, B) (11, 21, 22, 40, 54, 62, 69).

Figure 2A: Forest plot of incidence per 100,000 py of IPD in healthy control cohorts/surveillance data

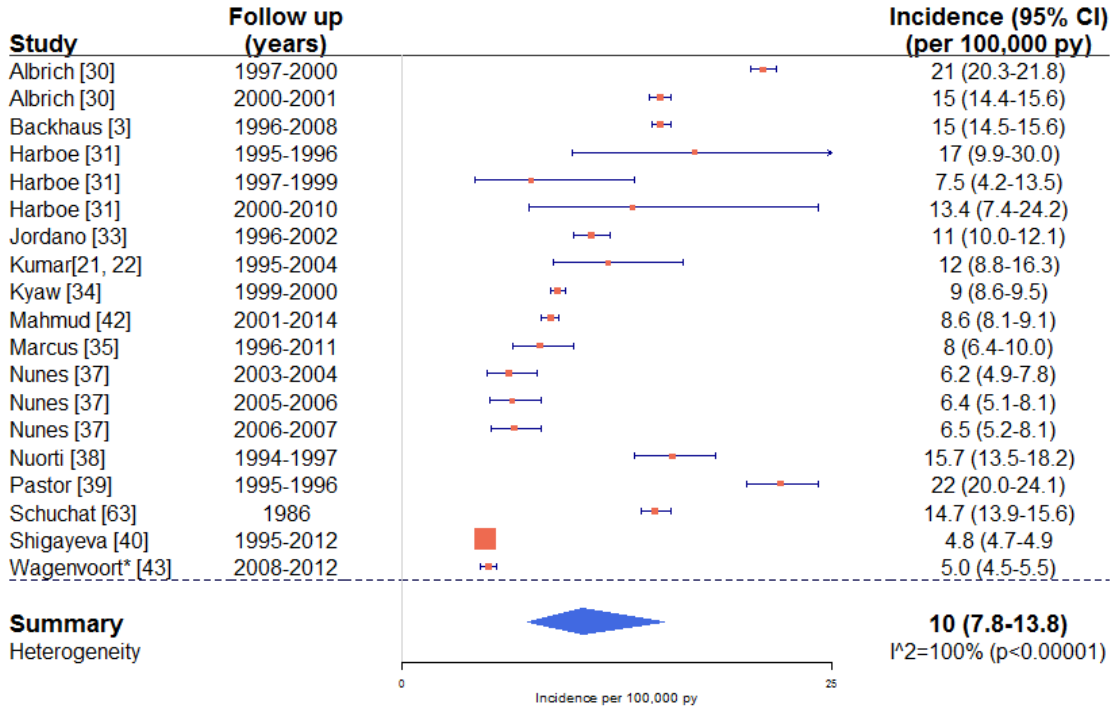
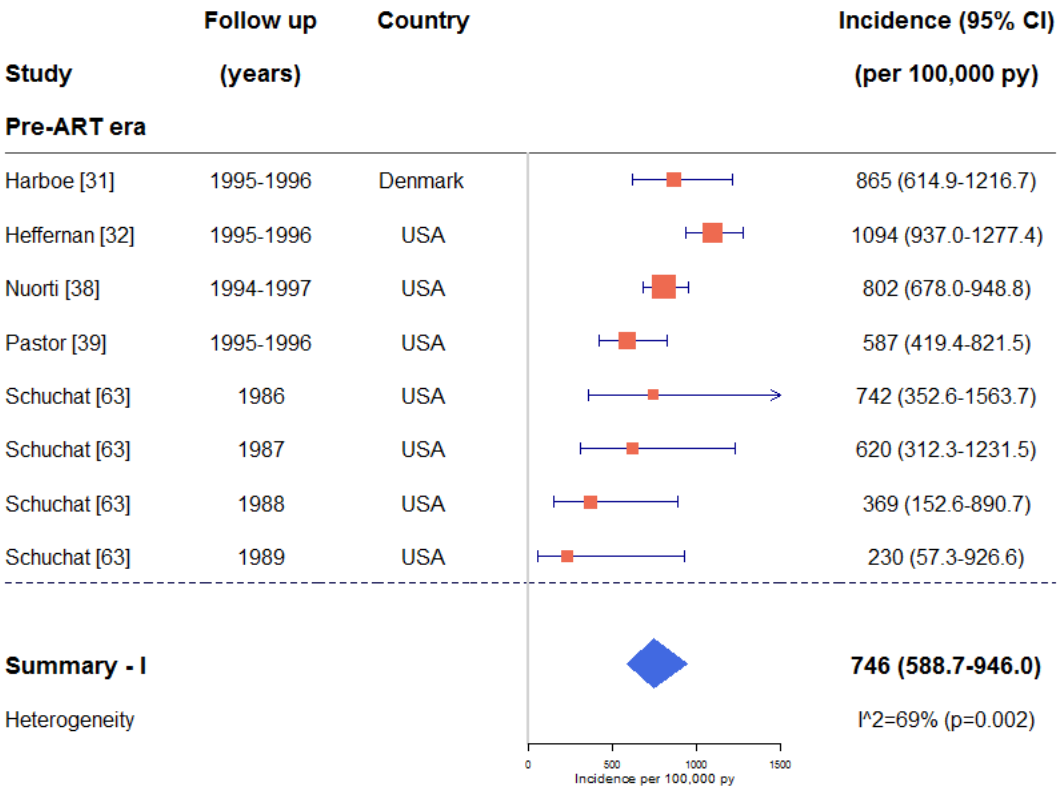
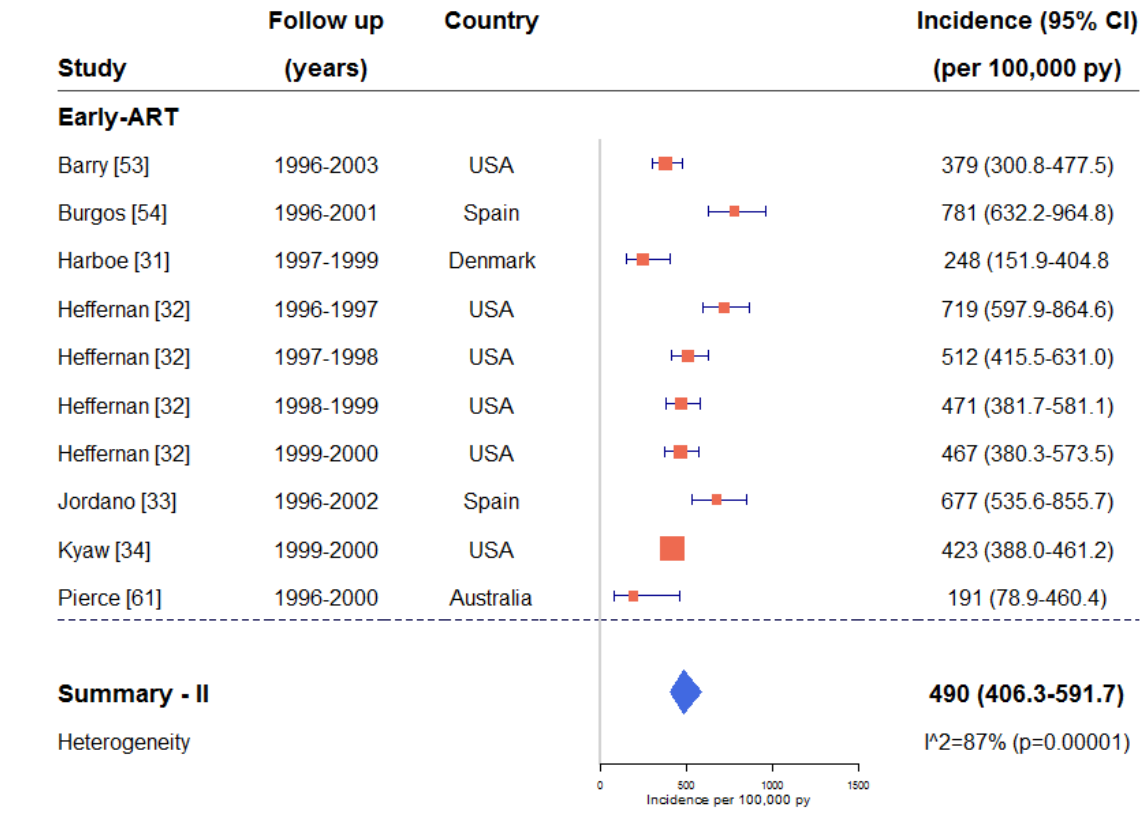


Figure 2B: Forest plot of incidence per 100,000 py of IPD in HIV patients in non-African countries




Study
Follow up (years)
Country
Incidence (95% CI) (per 100,000 py)
Early-ART
Barry [53] 1996-2003 USA 379 (300.8-477.5)
Burgos [54] 1996-2001 Spain 781 (632.2-964.8)
Harboe [31] 1997-1999 Denmark 248 (151.9-404.8
Heffernan [32] 1996-1997 USA 719 (597.9-864.6)
Heffernan [32] 1997-1998 USA 512 (415.5-631.0)
Heffernan [32] 1998-1999 USA 471 (381.7-581.1)
Heffernan [32] 1999-2000 USA 467 (380.3-573.5)
Jordano [33] 1996-2002 Spain 677 (535.6-855.7)
Kyaw [34] 1999-2000 USA 423 (388.0-461.2)
Pierce [61] 1996-2000 Australia 191 (78.9-460.4)
Summary - II 490 (406.3-591.7)
Heterogeneity I^2=87% (p=0.00001)
0
500
1000
1500
Incidence per 100,000 py

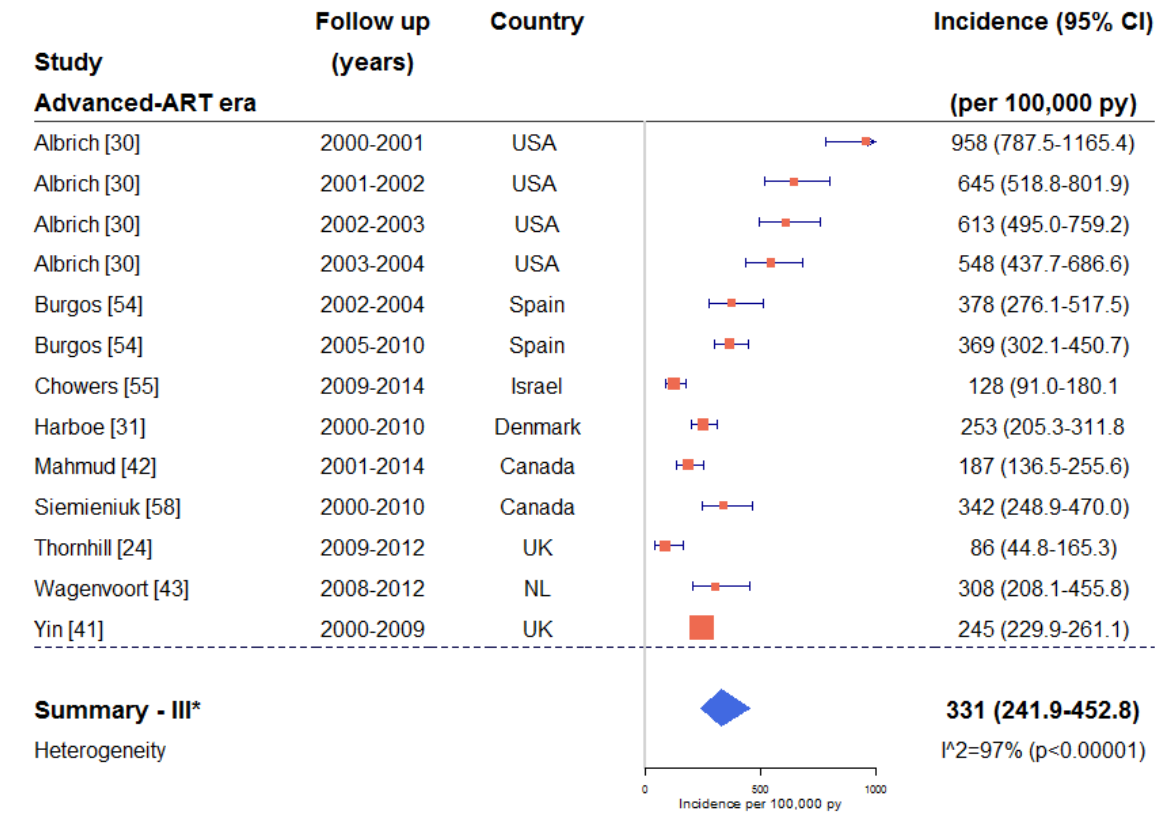

Study
Follow up (years)
Country
Incidence (95% CI) (per 100,000 py)
Advanced-ART era
Albrich [30] 2000-2001 USA 958 (787.5-1165.4)
Albrich [30] 2001-2002 USA 645 (518.8-801.9)
Albrich [30] 2002-2003 USA 613 (495.0-759.2)
Albrich [30] 2003-2004 USA 548 (437.7-686.6)
Burgos [54] 2002-2004 Spain 378 (276.1-517.5)
Burgos [54] 2005-2010 Spain 369 (302.1-450.7)
Chowers [55] 2009-2014 Israel 128 (91.0-180.1
Harboe [31] 2000-2010 Denmark 253 (205.3-311.8
Mahmud [42] 2001-2014 Canada 187 (136.5-255.6)
Siemieniuk [58] 2000-2010 Canada 342 (248.9-470.0)
Thornhill [24] 2009-2012 UK 86 (44.8-165.3)
Wagenvoort [43] 2008-2012 NL 308 (208.1-455.8)
Yin [41] 2000-2009 UK 245 (229.9-261.1)
Summary - III* 331 (241.9-452.8)
Heterogeneity I^2=97% (p<0.00001)
0
500
1000
Incidence per 100,000 py

Figure 2C: Forest plot of incidence per 100,000 py of IPD in HIV patients in African countries

* Cohort not receiving PPSV23
** Cohort receiving PPSV23

Figure 2D: Forest plot of incidence per 100,000 py of IPD in SCT recipients

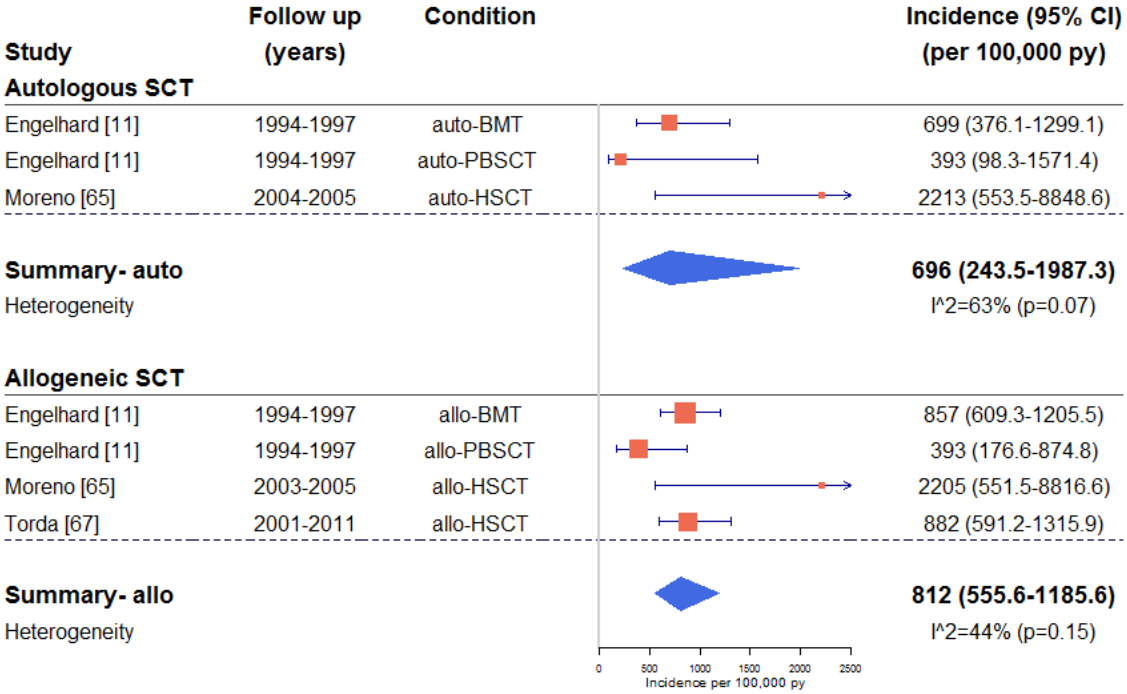
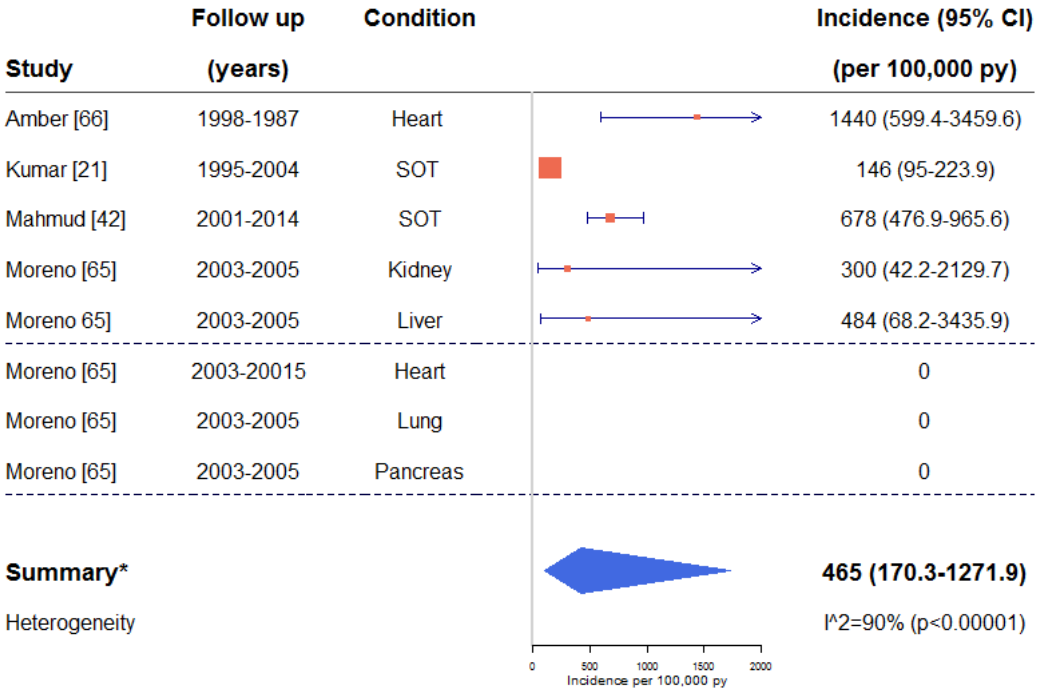


Figure 2E: Forest plot of incidence per 100,000 py of IPD in SOT recipients



* Studies with incidence of 0 not included in calculation of the pooled incidence

Figure 2F: Forest plot of incidence per 100,000 py of IPD in patients with CID

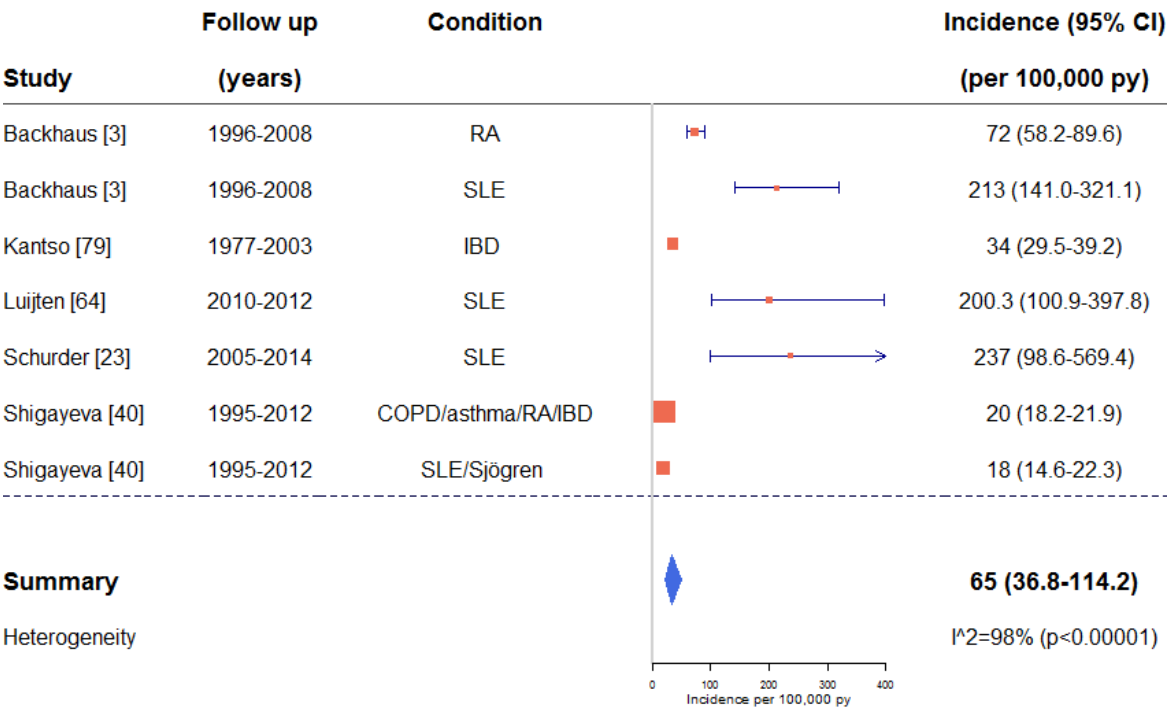


Figure 2G: Forest plot of incidence per 100,000 py of pneumococcal meningitis in immunocompromised and healthy groups

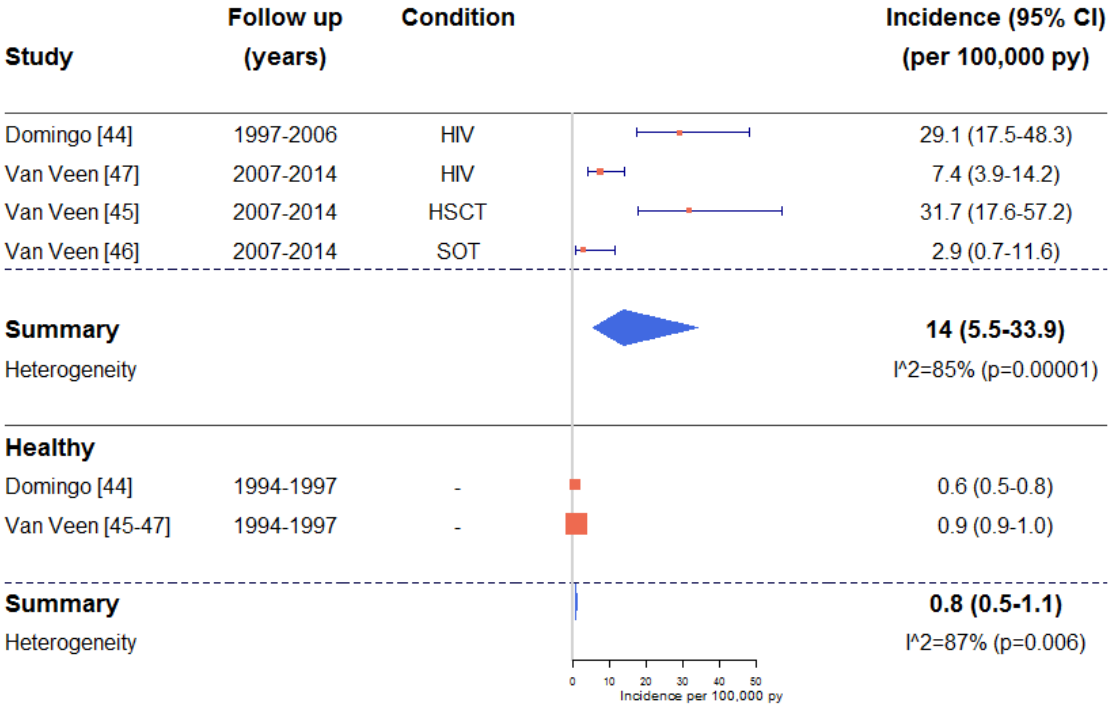
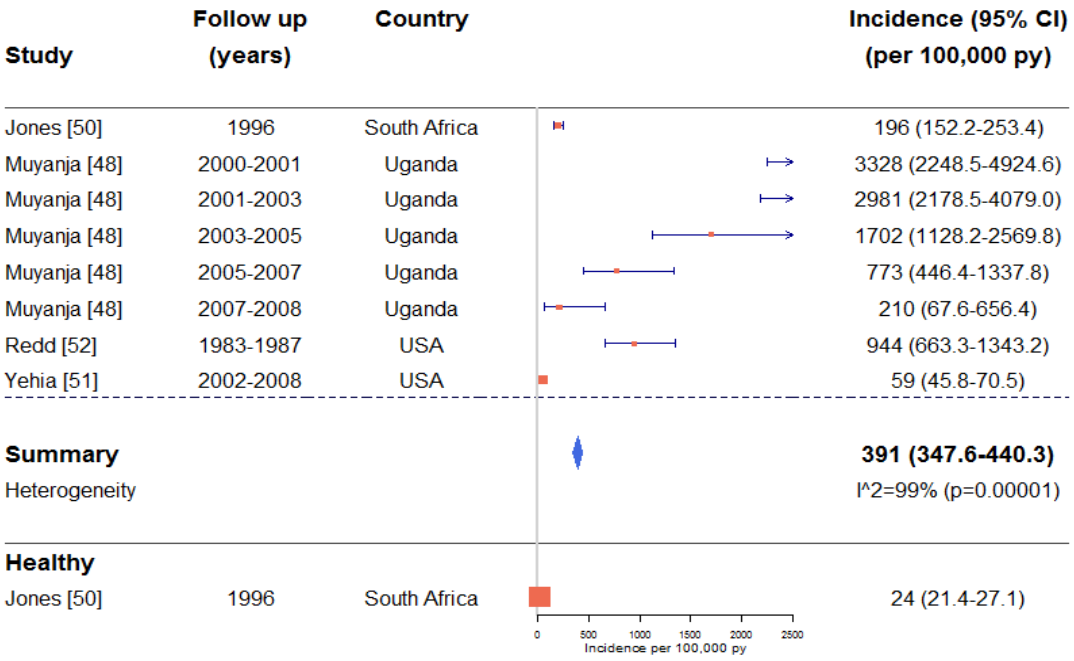


Figure 2H: Forest plot of incidence per 100,000 py of pneumococcal bacteremia in HIV and healthy groups



Legend: ⟶ CI continues beyond scale of the forest plot

Discussion

This SR and meta-analysis provides a comprehensive overview on the incidence rates of IPD in different groups of immunocompromised patients (HIV, CID, SOT, and SCT). The highest incidence rates occurred in patients with HIV (mainly in the pre-ART era), and patients with a medical history of a SCT or a SOT. We found a remarkably lower incidence rate in patients with CID, but compared to the incidence in healthy individuals, the incidence rate was still approximately six-fold higher.

Vaccination Recommendations

Currently, international guidelines recommend pneumococcal vaccination for immunocompromised patients (reviewed by Lopez et al. (5)). In order to subscribe to the rationale for vaccination in these groups, several criteria are relevant and should be taken into account. The frequency at which an infection occurs (incidence rate), the severity of the disease, and the mortality rate are fundamental aspects to substantiate vaccination recommendations.

Therefore, the demonstrated high incidence rates of IPD in HIV patients and SCT/SOT recipients stress the importance of pneumococcal vaccination in these populations. Moreover, since we only included studies evaluating IPD, defined by the isolation of *S. pneumoniae* from a normally sterile site, the incidence rates reported may be an underestimation of the total burden of pneumococcal infections in the immunocompromised population, because IPD is not always confirmed by culture.

Current pneumococcal vaccination guidelines for ICPs recommend the 13-valent conjugate vaccine (PCV13) followed by the 23-valent pneumococcal polysaccharide vaccine (PPSV23) two months later. Although different vaccination schedule have been studied, albeit scarcely, a consensus has not yet been reached to change the recommendation for this schedule. Therefore, we recommend to adhere to this schedule until more research on the immunogenicity and/or efficacy of different vaccination schedules has been performed and a new consensus will be reached.

Furthermore, we recommend this vaccination schedule for travelling and non-travelling ICPs. However, for travelling ICPs protection by vaccination might be even more important because, in the case of contracting an IPD, access to appropriate health care facilities in the visiting country might be less accessible due to travel distance or availability. We furthermore recommend assessing antibody titers to check whether protection has been reached in terms of sufficient antibody titers post-vaccination. This recommendation is further supported by a recent study in travelers by Van Aalst et al. (70) that showed that antibody titers were not assessed in up to 25% and 45% of travelling ICPs with an indication for a hepatitis A or B antibody titer.

Patients with an HIV infection are at risk for pneumococcal infections (31, 33, 35, 71), and therefore pneumococcal vaccination is internationally recommended in HIV patients. Early studies showed that adequate ART substantially lowers the IPD risk (31, 48, 72-74). This is supported by studies that found lower CD4 counts and a high viral load to be associated with a higher incidence of IPD (44, 53, 58, 75). However,

susceptibility for pneumococcal infections persists also under adequate viral suppression and is related to persistent humoral immune defects in these patients as reviewed by Moir and Fauci (76).

We observed a clear decline in IPD incidence rate following the introduction of ART, which is indirectly suggestive of a partly protective effect of cART against IPD. However, in the advanced-ART era the observed incidence (331/100.000 py) is still substantially higher compared to healthy individuals (10/100,000). However, because the advanced cART era also comprises patients not on cART with low CD4 counts, the actual incidence rate in stable virally suppressed HIV patients on cART is probably lower than the reported incidence rates here. Yet, given the large difference in IPD incidence (10/100,000 py in healthy controls vs. 331/100,000 py in HIV patients in the advanced cART era), these data support the current recommendations on pneumococcal vaccination (5).

Incidence rates in transplantation patients were very high with the highest incidence rates in patients who underwent an allogeneic SCT, followed by patients with an autologous SCT and patients with a SOT. The higher IPD incidence rates after allogeneic SCT is explained by the longer immunologic recovery period (1-2 years) compared autologous SCT. Furthermore, after allogeneic SCT immunosuppressive therapy is required to prevent graft-versus-host disease, which suppresses the immune system even more (77). Incidence rates in SOT patients were lower than in SCT patients, but still much higher compared to patients with CID. Both patients with SOT and CID are treated with immunosuppressive drugs. However, in contrast to CID patients who are often treated with immunosuppressive monotherapy periodically, patients with a SOT need to take combination immunosuppressive therapy for life (78).

With regard to patients with CID, we analyzed incidence rates of the total cohort of different CIDs, although etiology and immunocompromised status differed. The pooled IPD incidence rate was much lower than the incidence in the other immunocompromised patient groups. However, only few studies were conducted on CID patients. Furthermore, immunosuppressive therapy was either not reported, or was only received by a proportion of patients; and precisely immunosuppressive therapy is the most important driver of the immunocompromised status and the increased risk of infection and which is the main reason to recommend pneumococcal vaccination (79). In the study of Kantso et al. (80) 4.7% of UC, and 12.8% of CD patients ever used azathioprine, 11.2% and 13.7% ever used systemic steroids, and 3.5% and 11% ever used anti-TNFα inhibitors, respectively. In the studies of Schurder et al. (23) and Luijten et al. (64), who reported a much higher IPD incidence in SLE patients, the number of patients using immunosuppressive drugs was significantly higher.

However, in SLE patients, a higher rate of medication induced immunosuppression is not the only explanation, for the increased IPD incidence. The increased susceptibility for infections is also related to disease specific factors, such as lymfopenia, asplenia

(81). In the present analysis, it was not possible to discriminate between the effects of medication versus SLE induced immunosuppression, because the majority of patients received immunosuppressive medication.

An important limitation in the assessment of IPD incidence in patients with CID is the fact that the sample sizes in the included studies were small (Supplementary File 3), resulting in a less precise estimate. However, although the scientific evidence base for pneumococcal vaccination in patients with CID remains thin to date, we would advise to comply with current guidelines (5). The most important argument for this advice is that we consider the IPD incidence likely to be underestimated for patients who receive immunosuppressive therapy, which emphasizes the need for more research on this topic, specifically for patients stratified to different immunosuppressive regimens.

Further Research

Further research is therefore needed to investigate the IPD incidence rate in specific patient categories in order to identify patients at highest risk, who would benefit most from pneumococcal vaccination. Conversely, for patients at lower risk this vaccination may be expendable.

IPD incidence rates in immunocompromised populations have, to our knowledge, not been comprehensively analyzed before. The data presented here could also be used in mathematical models to evaluate cost-effectiveness of the pneumococcal vaccination.

Limitations

Our study has several limitations. First, we aimed to review the rationale for guideline recommendations regarding pneumococcal vaccination. However, we limited our focus to IPD incidence rates, while studies providing a risk ratio might need evaluation as well (82).

Second, we observed high heterogeneity between studies, which means that there are probably more underlying factors associated with IPD. For instance, included studies did often not provide information on vaccination status, CD4 count (HIV), viral load (HIV) or relevant medication that could have influenced the results. With regard to the vaccination status, one could speculate that an increase in vaccination coverage among patients with HIV played a role in the decreasing IPD incidence in the advanced-ART era or that the high IPD incidences in ICPs are due to vaccination failure. This warrants further research.

Third, we only included studies published in English. Exclusion of non-English studies may have led to an underestimation of IPD incidence.

More reasons for limited generalizability were that HIV patients were recruited from outpatient clinics in a number of studies (24, 33, 35, 37, 44, 48, 49, 51, 53, 54, 57, 58, 60-62). This may have resulted in a lower estimated incidence in these studies because patients who are lost to follow up do probably not take their medications, needed to control the HIV and decrease the infection risk.

Also, the majority of studies included were conducted in non-African countries in high-income settings; while most cases occur in low-income settings where access to health care is limited (83, 84). The incidence of IPD in these countries may in fact be much higher, which is supported by the reported incidences in the pre-ART era, but which we could not establish for the advanced-ART era.

Finally, only few studies reported information on the case fatality rate, and almost no study reported information on hospitalization due to IPD. For this reason, we were unable to assess consequences of IPD concerning these aspects properly.

Conclusions

This SR and meta-analysis provides a comprehensive analysis of the incidence of IPD, including an analysis of the case-fatality rate and risk factors for IPD. The findings of this study show high IPD incidences, particularly in patients with HIV, SOT and SCT. IPD incidence was lower in patients with CID, which is probably an underestimation. These data support the relevance of pneumococcal vaccination in these patient groups.

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APPENDIX (AVAILABLE ONLINE)

Supplementary File 1: Prisma checklist

Supplementary File 2: Search terms and strategy

Supplementary File 3A: Summary sheet of included studies on IPD

Supplementary File 3B: Summary sheet of IPD in healthy control cohorts/surveillance data

Supplementary File 3C: Summary sheet of included studies on pneumococcal meningitis

Supplementary File 3D: Summary sheet of pneumococcal meningitis in healthy control cohorts/surveillance data

Supplementary File 3E: Summary sheet of included studies on pneumococcal bacteremia (PB) or septicemia (HIV)

Supplementary File 3F: Summary sheet of PB in healthy control cohorts/surveillance data

Supplementary File 4: Critical appraisal assessment

Chapter 3

The effect of immunosuppressive agents on immunogenicity of pneumococcal vaccination: a systematic review and meta-analysis

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Abstract

INTRODUCTION: Patients with a weakened immune system due to immunosuppressive treatment are at increased risk of infection with *Streptococcus pneumoniae*. Although pneumococcal vaccination is highly recommended for those patients, the effectiveness of pneumococcal vaccination in this population remains largely unknown. Therefore, the objective of this PROSPERO-registered systematic review and meta-analysis was to evaluate the effect of the most commonly prescribed immunosuppressive agents such as azathioprine, methotrexate, anti-Tumor Necrosis Factor α (TNFα), or rituximab, on the initial serologic response to pneumococcal vaccination in patients with auto-immune disease.

METHODS: We included 22 articles comprising 2,077 patients, of whom 1,623 were treated with immunosuppressive agents, and 454 were controls.

RESULTS AND DISCUSSION: The findings of our systematic review indicate that, in patients treated with immunosuppressive medication and compared to controls, the initial serologic response to pneumococcal conjugate vaccine (PCV) and pneumococcal polysaccharide vaccine (PPSV) are impaired. Moreover, this impaired response was more profound after PCV than after PPSV. We hypothesize that the immunosuppressive medication mainly compromises the cellular immunity, explaining the more severely reduced response rate to PCV (which induces a T-cell dependent immune response), compared to PPSV. Treatment with TNFα blocking agents was associated with a more favorable response, compared to patients treated with other immunosuppressive medication. Targeted research applying uniform correlates of protection is needed to bridge the knowledge gap in vaccination immunology in this patient group.

PROSPERO REGISTRATION: CRD42017058364

Introduction

Streptococcus pneumoniae is the most important cause of pneumonia, meningitis and bacterial sepsis worldwide (1). In case of invasive disease, mortality rates vary from 5 to 35% (2). Patient groups at increased risk for invasive pneumococcal disease (IPD) are those with an impaired immune response (1, 3) (see Table 1).

To prevent IPD in these patients, international guidelines recommend pneumococcal vaccination with a sequential vaccination schedule of 7- or 13-valent pneumococcal conjugated vaccine (PCV), followed by the 23-valent pneumococcal polysaccharide vaccine (PPSV) two months later (4). The rationale behind this vaccination schedule is that PCV is more immunogenic than PPSV, because of the conjugation to the diphtheria toxoid CRM197. Through this conjugation, a robust T cell-dependent immune response is evoked, through which T helper cells provide help to memory B cells in the generation of a humoral immune response (5, 6). PCV covers 13 (or 7) most prevalent of 96 known pneumococcal serotypes; PPSV provides both coverage of a broader spectrum than PCV, as well as a booster stimulus to serotypes present in both vaccines (7). However, PPSV provokes a T cell-independent immune response; with minimal T cell-mediated B cell stimulation. Therefore, at least theoretically, long-lasting memory against PPSV serotypes not covered by PCV may be limited (5, 6).

In immunocompetent individuals, pneumococcal vaccination reduces the IPD risk (8). However, clinical efficacy data of the sequential vaccination schedule of PCV followed by PPSV in immunocompromised patients (ICPs) are scarce. Research on this topic is hampered by the fact that vaccine efficacy studies require complex study designs, large cohorts, and long follow-up periods. Instead, vaccine immunogenicity is often used as a proxy to evaluate efficacy. Although research suggests beneficial effects of PPSV in ICPs in terms of post-vaccination immunogenicity, the response in these patients is weaker than in healthy individuals (9). Thus, precisely those who most need protection because of their increased infection risk, least benefit from vaccination (9).

Immunocompromising conditions consist of different subgroups, depending on underlying immunologic deficits. A major subgroup comprises patients treated with immunosuppressive agents, which are most frequently used to treat autoimmune diseases (AD), and to prevent rejection in solid-organ transplant recipients, or graft-versus-host disease in stem cell transplantation recipients.

In this systematic review, we evaluated the impact of different types of immunosuppressive agents on the initial serologic response to vaccination with PCV and/or PPSV (10). To reach sufficient homogeneity of the studied group, we focused on the post-vaccination immune response in patients with AD treated with immunosuppressive agents, and did not include transplantation recipients.

In a meta-analysis, we analyzed how different immunosuppressive agents affected seroconversion rates and pre/post-vaccination antibody concentrations.

The aim of this systematic review and meta-analysis was to provide an inclusive insight in the immunogenicity of pneumococcal vaccination in patients with AD treated with immunosuppressive agents, and to provide guidance for health care providers advising on pneumococcal vaccinations in these patients.

Table 1: Summary sheet of included studies on the short-term immunogenicity of pneumococcal vaccination

Study	Year	Auto-immune disease	Immuno-suppressive therapy	Steroid use	Subjects	Age	Vaccine type	Correlate of protection	Geometric mean concentration*									Seroconversion rate (%)			
									6B			23F			Total						
Ref				N / (%)	N	Mean		Fold increase	Pre	Post	Ratio	Pre	Post	Ratio	Pre	Post	Ratio	6B	23F	6B+23F	Total
Studies on PPSV																					
[15]	2010	RA	MTX Rituximab + MTX	8 (25) 28 (41.2)	32 68	NR	PPSV23	≥ 2 or an increase of >1 µg/ml from pre-vaccination	NR	NR	NR	NR	NR	NR	NR	NR	NR	61 38	34 25	NR	NR
[24]	2004	RA, anky-losing spondy-litis	DMARDS Anti-TNF	9 (55.3) 3 (19)	17 16	41.0 48.3	PPSV23	≥ 2	NR	1.98 2.45	NR	NR	NR	5.4 1.6	NR	NR	NR	NR	53 13	NR	NR
[25]	2012	IBD IBD	AZA Anti-TNF Combination Controls (5-ASA)	NR	19 26 16 35	NR	PPSV23	≥ 2	NR	NR	NR	NR	NR	NR	NR	NR	3.25 2.69 2.84 5.71	NR	NR	NR	79 58 63 89
[26]	2007	RA	DMARDS Anti-TNF	50 (45.9) 45 (45.5)	109 99	51.1 52.2	PPSV23	≥ 2	NR	2.26 1.84	NR	NR	4.22 4.01	NR	NR	NR	NR	NR	38 44	NR	NR
[27]	2006	RA Healthy	MTX Anti-TNF Combination Controls	19 (51) 31 (50) 26 (52) 0	37 62 50 47	61.3 53.7 52.8 30.3	PPSV23	≥ 2	1.1 0.9 1.0 2.1	2.1 3.8 3.9 4.6	NR	0.8 0.7 0.8 1.2	1.6 2.4 1.7 2.8	NR	NR	NR	NR	35 68 46 51	24 68 54 55	14 50 32 38	NR
[28]	2014	CD	AZA, MTX Anti-TNF	NR	70 40	26.5 32.0	PPSV23	≥ 2	NR	NR	NR	NR	NR	NR	4.49 4.64	5.93 5.69	NR	NR	NR	NR	79 50

			Combination		50	30.5									4.65	5.84					58
		CD	Controls (5-ASA)		47	36.0									4.89	6.57					78
[16]	2010	IBD	Combination	NR	20	36.5**	PPSV23	≥ 2 or GMT ≥ 1 µg/mL	NR	NR	NR	NR	NR	NR	NR	NR	NR	49	43	NR	NR
		IBD	Controls (5-ASA)		24	40**												78	80		
		Healthy	Controls		19	37**												84	58		
[30]	2015	RA	MTX	30 (54.5)	55	63.8	PPSV23	≥ 2	1.42	4.36	NR	1.79	7.41	NR	NR	NR	NR	55	65	50	NR
			Combination	3 (12)	24	62.7			1.12	2.13		1.28	3.04					25	48	20	
		RA	Controls	21 (60)	35	70.5			0.84	4.05		1.17	11.61					72	84	66	
[29]	2015	RA	MTX	30 (54.5)	55	63.8	PPSV23	≥ 2	1.42	4.36	NR	1.79	7.41	NR	NR	NR	NR	55	65	50	NR
			Combination	NR	15	NR			1.12	2.29		1.22	4.61					43	67	43	
		RA	Controls	21 (60)	35	70.5			0.84	4.05		1.17	11.61					72	84	66	
[31]	2015	RD	MTX	13 (25)	52	50	PPSV23	≥ 2	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	70.5
			Combination	4 (33)	13	49.5															75
		Healthy	Controls	0	31	NR															69
[32]	2013	ITP	Rituximab	1 (6)	17	40**	PPSV23	≥ 4	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	21
		ITP	Controls	0	7	40**															67
[17]	1996	RA	MTX	6 (60)	10	< 50	PPSV23	≥ 2 or antibody level ≥ 300 NG/mL	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	73
			MTX	5 (50)	10	> 60															60
		RA	Controls	7 (70)	10	< 50															58
		RA	Controls	6 (60)	10	> 60															75
[33]	2010	RA	Rituximab + MTX	5 (45)	11	60.4	PPSV23	≥ 1,1	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	36.3
			MTX	1 (10)	10	63.6															70
[34]	2007	RA	MTX	6 (42.9)	14	50**	PPSV23	≥ 2*	2.05	NR	NR	3.85	NR	NR	NR	NR	NR	12	44	NR	NR

			MTX + anti-TNF 3 mg/kg	10 (50.0)	20	52			1.40			1.45						28	20		
			MTX + anti-TNF 6 mg/kg	16 (44.4)	36	50			1.65			3.60						8	26		
Study	**Year**	**Auto-immune disease**	**Immuno-suppressive therapy**	**Steroid use**	**Subjects**	**Age**	**Vaccine type**	**Correlate of protection**	**Geometric mean concentration***									**Seroconversion rate (%)**			
									6B			**23F**			**Total**							
Ref				**N / (%)**	**N**	**Mean**		**Fold increase**	**Pre**	**Post**	**Ratio**	**Pre**	**Post**	**Ratio**	**Pre**	**Post**	**Ratio**	**6B**	**23F**	**6B+23F**	**Total**
Studies on PCV																					
[37]	2011	RA	MTX	27 (31.3)	85	61.5	PCV7	≥ 2	2.0	3.5	NR	0.7	1.9	NR	NR	NR	NR	26	48	21	NR
			Anti-TNF	34 (43.1)	79	60.1			1.4	3.6		0.6	1.9					48	56	37	
			Combination	14 25 (28.0)	89	59.8			1.5	2.3		0.7	1.4					20	42	16	
		SpA	Anti-TNF	11 (13.6)	83	50.4			1.5	4.8		0.7	3.1					58	75	51	
			Combination	16 (18.9)	83	49.2			1.7	3.0		0.8	2.5					30	56	27	
		SpA	Controls	5 (6.2)	86	51.6			2.9	9.5		0.97	6.4					52	80	48	
[18]	2012	RA	MTX	27 (31.3)	85	63.5	PCV7	≥1 mg/L	2.0	3.5	NR	0.7	1.9	NR	NR	NR	NR	NR	NR	67	NR
			Anti,TNF	34 (43.1)	79	59.9			1.4	3.6		0.6	1.9							58	
			Combination	25 (28.0)	89	60.5			1.5	2.3		0.7	1.4							52	
		SpA	Anti-TNF	11 (13.6)	83	50.3			1.5	4.8		0.7	3.1							78	
			Combination	16 (18.9)	83	51.6			1.7	3.0		0.8	2.5							65	
		SpA	Controls	5 (6.2)	86	52.8			2.9	9.5		0.97	6.4							84	
[35]	2013	RA	MTX	27 (31.3)	85	61.5	PCV7	≥ 2	2.0	3.5	NR	0.7	1.9	NR	NR	NR	NR	26	48	21	NR

			Anti-TNF	12 (70.0)	17	56.6			0.6	1.1		0.4	1.1					40	35	18	
			Rituximab	16 (55.2)	29	68.9			0.3	0.4		0.2	0.3					10	20	10	
			Rituximab + MTX	17 (65.4)	26	59.9			0.4	0.4		0.3	0.4					3	15	0	
		RA	Controls	5 (6.2)	86	51.6			2.9	9.5		0.97	6.4					52	80	48	
[36]	2017	RA	MTX	0	10	67.4**	PCV13	≥ 2	1.3	2.1	NR	1.0	1.7	NR	NR	NR	NR	20	20	10	NR
		RA	Controls	0	10	67.3			2.5	5.7		2.4	10.1					40	80	40	
[38]	2016	RA	Anti-TNF	1(14.3)	7	NR	PCV13	≥ 2	NR	NR	NR	NR	NR	NR	NR	NR	1.76	NR	NR	NR	NR
			Combination	4 (26.7)	15												2.22				
		Osteo-arthritis	Controls	0	24												5.2				
[39]	2007	RA	MTX	27 (31.3)	85	NR	PCV7	≥ 2	NR	NR	1.8	NR	NR	2.5	NR	NR	NR	NR	NR	32.9	NR
			Anti-TNF	34 (43.1)	79						2.7			3.4						21.2	
			Combination	25 (28.0)	89						1.6			2.2						36.7	
		SpA	Anti-TNF	11 (13.6)	83						3.1			4.8						50.6	
			Combination	16 (18.9)	83						1.6			3.0						20.5	
		SpA	Controls	5 (6.2)	86						3.3			6.6						47.7	
Study	**Year**	**Auto-immune disease**	**Immuno-suppressive therapy**	**Steroid use**	**Subjects**	**Age**	**Vaccine type**	**Correlate of protection**	**Geometric mean concentration***									**Seroconversion rate (%)**			
									6B			**23F**			**Total**						
Ref				**N / (%)**	**N**	**Mean**		**Fold increase**	**Pre**	**Post**	**Ratio**	**Pre**	**Post**	**Ratio**	**Pre**	**Post**	**Ratio**	**6B**	**23F**	**6B+23F**	**Total**
Studies comparing PCV to PPSV																					
[40]	2015	CD	AZA	NR	29	NR	PCV13	GMC	0.15	1.03	NR	0.28	2.66	NR	NR	NR	NR	NR	NR	NR	NR
			Combination		13				0.23	1.15		0.56	4.97								

		CD	Controls		35				0.17	2.34		0.62	10.91							
		CD	AZA		27		PPSV23		0.24	1.14		0.36	1.37							
			Combination		13				0.15	0.52		0.47	1.45							
		CD	Controls		34				0.18	1.27		0.42	2.90							
[41]	2011	RA	MTX	27 (31)	85	61.5	PCV7	≥ 2	NR	NR	1.4	NR	NR	1.9	NR	NR	NR	26	48	21	NR
			Anti-TNF	34 (43)	79	59.8					1.8			2.5				48	56	37	
			Combination	25 (28)	89	60.1					1.3			1.5				20	42	16	
			MTX	19 (51)	37	61.3	PPSV23				1.6			1.4				35	23	14	
			Anti-TNF	31 (50)	62	53.7					3.4			2.8				68	68	50	
			Combination	26 (52)	50	52.8					1.8			2.0				46	54	32	
		Healthy	Controls	0	47	30.3					2.2			2.3				51	55	38	

Methods

We registered the protocol of this systematic review and meta-analysis with the PROSPERO systematic protocol registry (www.crd.york.ac.uk/prospero/; ID: CRD42017058364).

Search strategy

We conducted a literature search in PubMed and Embase (ovid) on February 5th 2018 (search terms and strategy are listed in Supplementary File 1). The search strategy was not limited to study design, year of publication, or language. We focused our search on studies evaluating the immune response to pneumococcal vaccination in adult patients treated with immunosuppressive agents because of AD.

Intervention(s), exposure(s)

Pneumococcal vaccination.

Comparator(s)/controls

We focused on the effect of immunosuppressive agents on the immune response to pneumococcal vaccination. We compared this response in patients with AD using immunosuppressive agents, to the response in both healthy controls and in patients with AD not using immunosuppressive agents.

Study selection

Eligibility criteria for inclusion in the systematic review were:

- Evaluation of the immunogenicity of pneumococcal vaccination, divided in cohorts according to the different used immunosuppressive agents;
- Adult (age ≥ 18 years) patients with AD;
- Treatment with the following immunosuppressive agents: corticosteroids, disease modifying anti-rheumatic drugs (DMARDs), e.g. methotrexate (MTX), azathioprine or mercaptopurine; Tumor Necrosis Factor-α inhibitors (anti-TNFα); rituximab; and immunosuppressive combination therapy (DMARD plus anti-TNFα).

Additional eligibility criteria for inclusion in the meta-analysis were:

- Reported seroconversion rates (SCRs) to serotypes 6B, 23F, or both. These two types are both covered by PCV and PPSV;
- Inclusion of a control group of healthy participants, or AD patients not receiving immunosuppressive therapy.

We used Rayyan (11) to manage and screen the references for eligibility. Duplicates were first digitally removed from the search by the Rayyan software, followed by a manual check for remaining duplicates, which were subsequently removed by MvA and ACL. Endnote X7.2 (Thomson Reuters, New York, United States of America) was used to upload included articles (12). The study selection process is summarized in Fig. 1.

We excluded pediatric studies, animal studies, case reports, review articles, abstracts, and studies of which the full text was not available.
Two authors (MvA and ACL) independently screened titles, abstracts, and keywords to select articles meeting the inclusion criteria. Discrepancies were resolved by discussion. Subsequently, MvA and ACL reviewed and analyzed the selected studies for eligibility. Citations and reference lists from review articles found in the initial search were analyzed to identify any other eligible studies. Excluded studies, determined during the second selection, are reported separately with explanation of the reasons for exclusion.

Data extraction
MvA and ACL developed a data extraction sheet, in which the following date were extracted and reviewed: first author, publication year, study country, study design, immunocompromising condition, medication use, and factors associated with a higher or lower antibody response.

Outcomes
The primary outcome was the short-term SCR to serotypes 6B, 23F, or both, <2 months post-vaccination, since the antibody response is normally induced 2–4 weeks post-vaccination (13, 14). Although considerable variation existed in the assessed serotypes to study the immune response, serotypes 6B and 23F were assessed most frequently in the included studies, enabling us to perform a meta-analysis.

The secondary outcome was the geometric mean concentration (GMC) of antibody to serotypes 6B and 23F before and after vaccination.

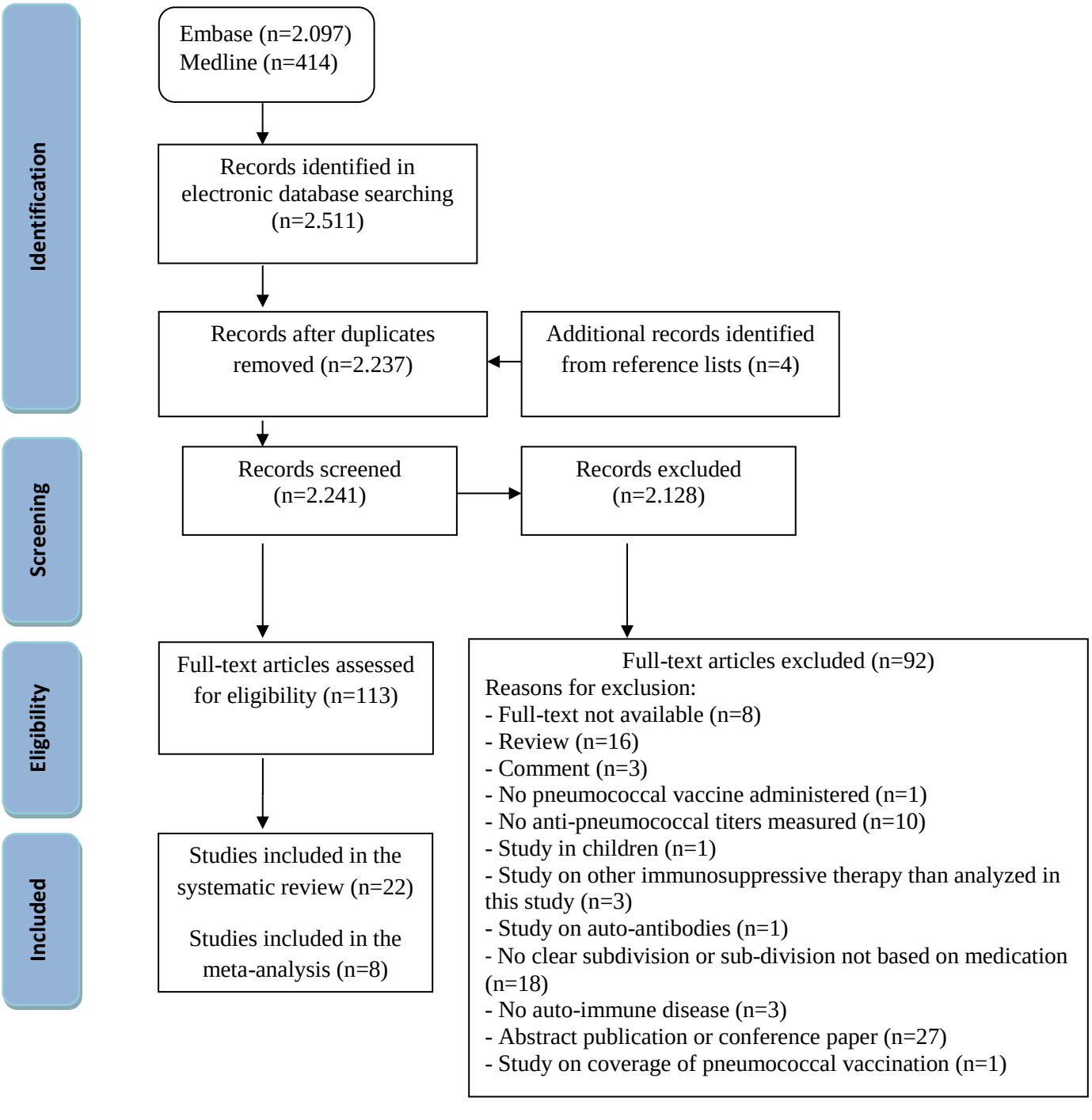
Definition of seroconversion
SCRs to serotypes 6B and 23F were most often defined as the rate of participants with a two-fold increase in antibody concentrations pre- and post-vaccination. One study defined SCR as the rate of participants with a two-fold increase in antibody concentration and/or an increase of ≥1 µg/ml compared to pre-vaccination levels (15); one study as a two-fold increase and/or a GMC of antibody of ≥1 µg/ml (16); one study as a two-fold increase and/or a GMC of antibody of ≥300 NG/ml (17); and one study as a GMC of antibody of ≥1 µg/ml (18).

Quality assessment
We used a modified version of the Newcastle-Ottawa assessment tool, which provides a checklist for observational studies to evaluate the methodological quality of the included studies (19). We used the Cochrane Risk of Bias Scale to assess the quality of randomized studies (20).

Data synthesis and analysis

All included studies reported data on pre- and post-vaccination immunogenicity, with a post- vaccination titer assessment after 3–8 weeks, corresponding to the IgG antibody peak following vaccination (13, 14). Odds ratios (OR) and their 95% confidence intervals (CI) per vaccine type (PCV7/13 and PPSV23) and per pneumococcal serotype (6B and 23F) were analyzed. Standard deviations were calculated from the 95% CIs. Pooled mean differences (MDs) were calculated from GMCs of antibody to serotypes 6B and 23F before and after vaccination. MDs with 95% CIs per vaccine type and per pneumococcal serotype were evaluated. The I2 statistic was used to assess heterogeneity, with higher values indicating higher heterogeneity. In case of high heterogeneity among included studies, random-effects models were applied. Review Manager version 5.3 (London, United Kingdom) was used for statistical analysis (20). P-values less than 0.05 were considered statistically significant.

Figure 1: Flow diagram of the selection process



Results

Literature search and results

We identified 2515 articles through database searching and through screening of reference lists of review articles. After removal of duplicates, we screened 2237 remaining studies on title and abstract, of which we selected 113 studies for full-text review. From these, we included 22 articles that met the eligibility criteria for this systematic review, and eight articles that met the eligibility criteria for the meta-analysis (Fig. 1). We excluded one study that evaluated the response to PCV followed by PPSV in AD patients because participants treated with different immunosuppressive agents were analyzed together (21). We did not find other studies on PCV followed by PPSV. Two studies that solely evaluated corticosteroids in patients with AD were excluded because these did not fulfill our eligibility criteria (22, 23): one study (22) did not clearly make a subdivision based on the immunosuppressive medications. In the other study (23), no pneumococcal vaccine was administered.

Double reported patients

The same cohorts of either cases or controls were used in different analyses in several studies. We included each cohort only once (Supplementary File 3).

Study characteristics

Systematic review

The response to PPSV was evaluated in fourteen studies (15-17, 24-34) and to PCV in six studies (18, 35-39). Two studies compared the response to PPSV with the response to PCV (40, 41).

Control groups were healthy individuals in four studies (16, 27, 31, 41) and patients with AD not receiving immunosuppressive therapy in twelve studies (17, 18, 25, 28-30, 32, 35, 37-40).

ADs included inflammatory bowel disease (IBD) including Crohn's disease (CD) and ulcerative colitis (UC) (four studies) (16, 25, 28, 40); immune thrombocytopenic purpura (ITP) (one study) (32); and rheumatoid diseases (RD), comprising rheumatoid arthritis (RA) (eighteen studies) (15, 17, 18, 24, 26, 27, 29-31, 33-38, 41); spondylo-arthritis (SpA) (including ankylosing spondylitis) (four studies) (18, 24, 37, 39); systemic sclerosis (one study) (31); and dermato/polymyositis (one study) (31).

Meta-analysis

Of the eight studies included in the meta-analysis, three evaluated the response to PCV (35- 37), four to PPSV (16, 27, 29, 30), and one study compared the response to PCV with the response to PPSV (41). Five studies had a control group of healthy individuals (29, 30, 35-37), and two studies of patients with AD not receiving immunosuppressive therapy (27, 41). One study had control groups of both types (16). Studies analyzed patients with RA (27, 29, 30, 35, 36, 41), SpA (37) and IBD (16).

Study participants

Systematic review

The 22 included studies comprised 2077 participants in total. Of these, 586 (28%) were treated with MTX or azathioprine; 429 (21%) with anti-TNFα; 151 (7%) with rituximab with or without additional MTX; and 457 (22%) with a combination of anti-TNFα and a DMARD. The control group consisted of 454 participants, of which 97 (21%) were healthy individuals, and 357 (79%) were patients with ADs not receiving immunosuppressive therapy. Of these 357 control patients with ADs, 39 (11%) received low-dose systemic corticosteroids. Among all participants, 1283 (62%) were treated for RD. Of these 454 (35%) patients concomitantly received low-dose systemic corticosteroids, of which 99% (448/454) received < 10 mg prednisolone/day) (15, 17, 18, 24, 26, 27, 29-31, 33-35, 37-39, 41). Of all participants, 323 (15%) were treated for IBD; systemic corticosteroid use was not reported for these participants (16, 25, 28, 40). Seventeen participants were treated for ITP of which one (6%) concomitantly received systemic corticosteroids (dose unknown) (32).

Meta-analysis

The eight included studies in the meta-analysis comprised 764 ICPs and 221 controls. Of control participants, 66 (30%) were healthy individuals and 155 (70%) were patients with AD not receiving immunosuppressive therapy. PCV was administered to 501/764 (66%) patients and 96/221 (43%) controls; and PPSV to 263/764 (34%) patients and 125/221 (57%) controls. Of the patients in the DMARD-treatment group, 187/764 (24%), received MTX; 241/764 (32%) received TNFα blocking agents; 55/764 (7%) received rituximab or a combination of rituximab and MTX; and 281/764 (37%) received combination therapy (excluding any combination of immunosuppressive medications with rituximab).

Quality assessment

Supplementary File 2 presents the quality assessment. All included studies were of moderate-to-good quality (score 3–7). Since we only included studies in which the immune response to pneumococcal vaccination in patients with AD was evaluated by measuring GMCs of antibody, all studies scored high on representativeness of the exposed cohort, ascertainment of exposure, and assessment of outcome. Studies with a control cohort were regarded as of superior quality. Study characteristics between cohorts, such as age or sex, differed in sixteen studies (15, 16, 18, 24, 25, 27-33, 35, 37-39), compromising comparability of cohorts on the basis of design and the conducted analysis, thereby potentially increasing their risk of bias. Follow-up was considered adequate if GMCs of antibody were assessed before, and 3–8 weeks after vaccination, which seventeen studies did (15-18, 24, 26-30, 32, 34, 35, 37, 38, 40, 41).

Seroconversion

Pooled ORs of seroconverted subjects following pneumococcal vaccination with PCV or PPSV were calculated. Pooled ORs and number of seroconverted participants to serotypes 6B, 23F, and 6B + 23F are shown in Fig. 2a, Fig. 2b, Fig. 3a, Fig. 3b, Fig. 3c, Fig. 4a, Fig. 4b, Fig. 4c.

Figure 2a: Number of seroconverted participants after PCV vaccination

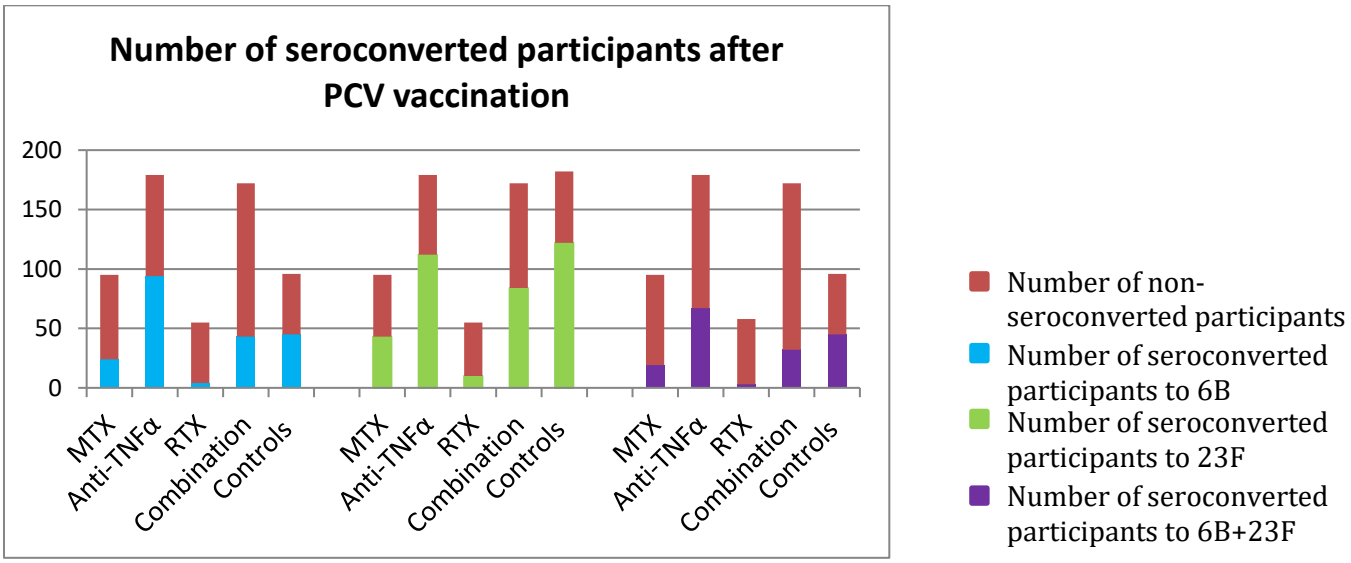


Figure 2b: Number of seroconverted participants after PPSV vaccination

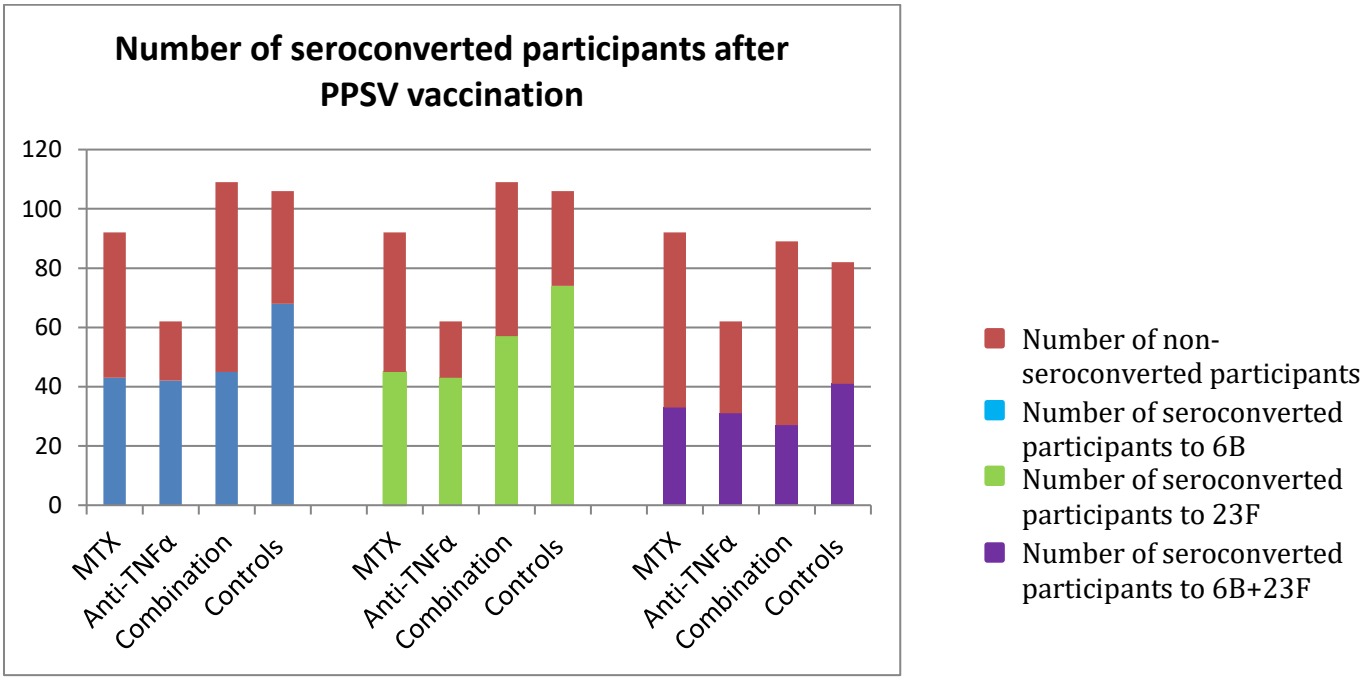
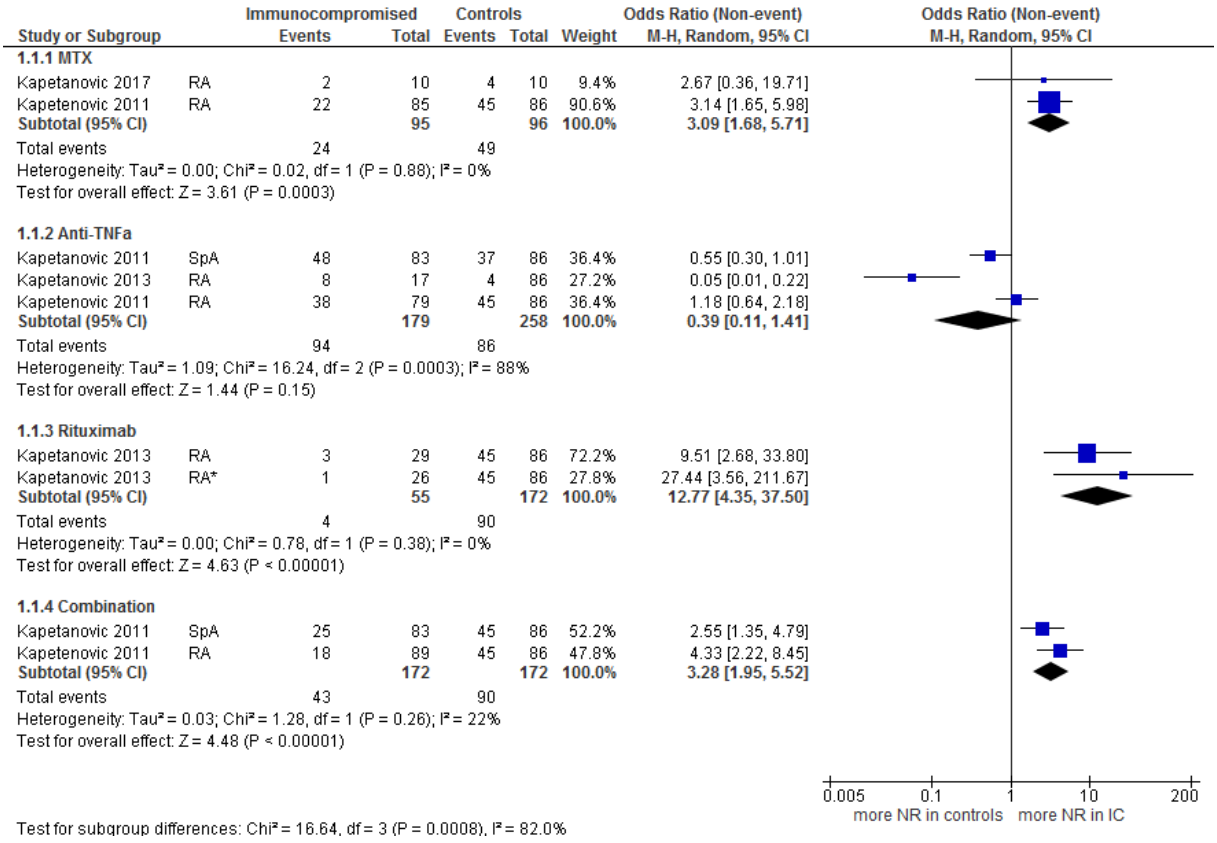


Figure 3a: Forest plot of odds ratio for seroconversion of serotype 6B following immunization with PCV



Abbreviations:

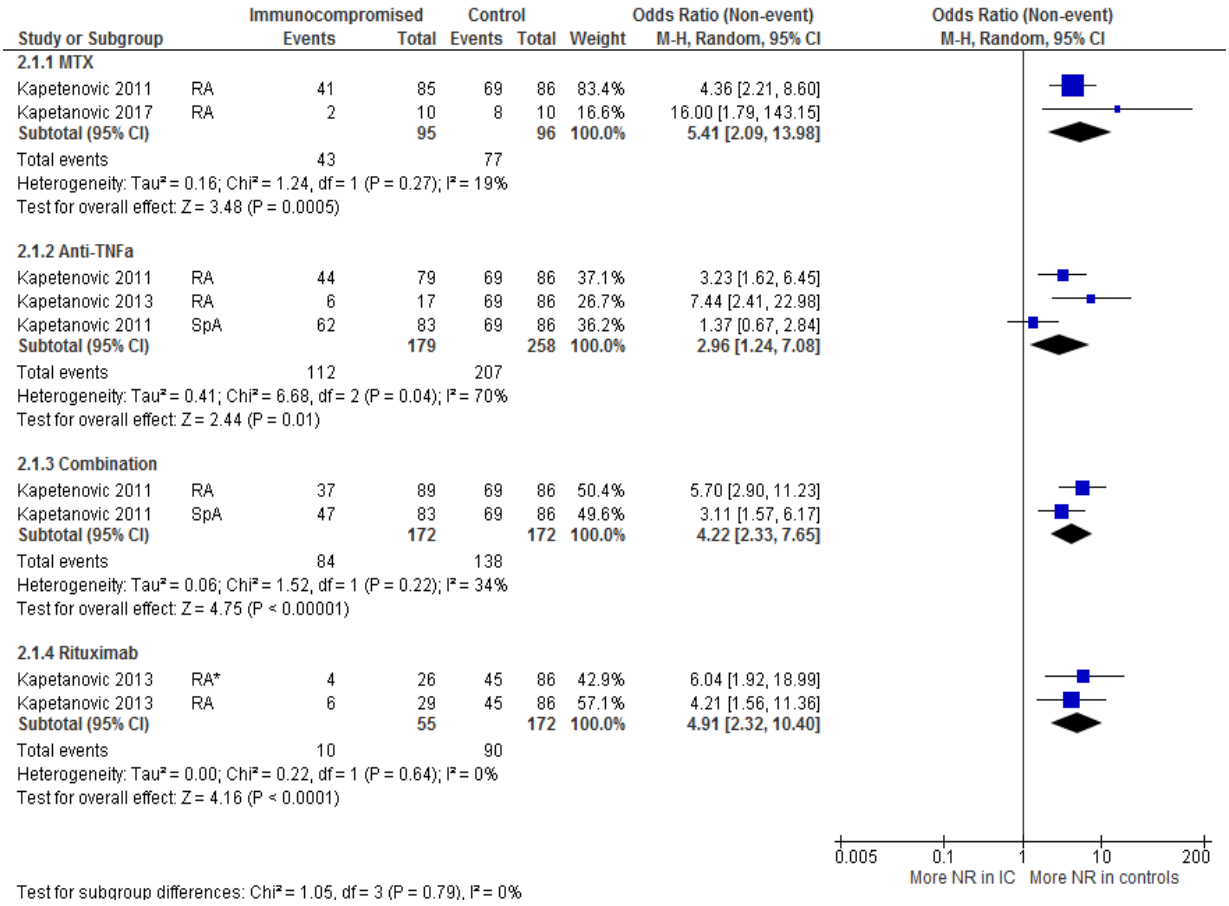
Events = seroconverted participants

NR = Non-response

IC = immunocompromised

RA* = patients were treated with rituximab and methotrexate

Figure 3b: Forest plot of odds ratio for seroconversion of serotype 23F following immunization with PCV



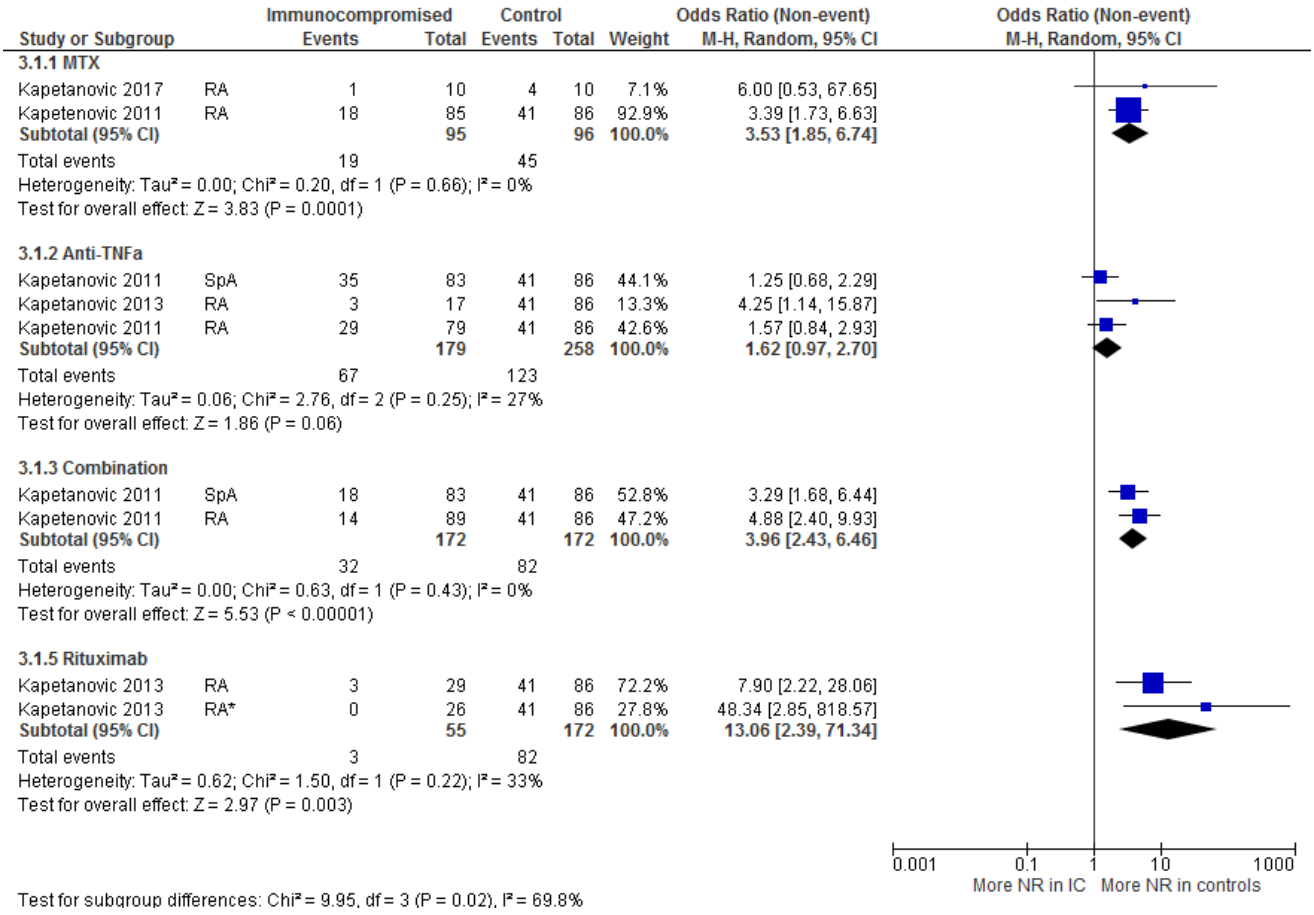
Abbreviations:

Events = seroconverted participants

NR = Non-response

IC = immunocompromised

Figure 3c: Forest plot of odds ratio for seroconversion of serotype 6B + 23F following immunization with PCV



Abbreviations:

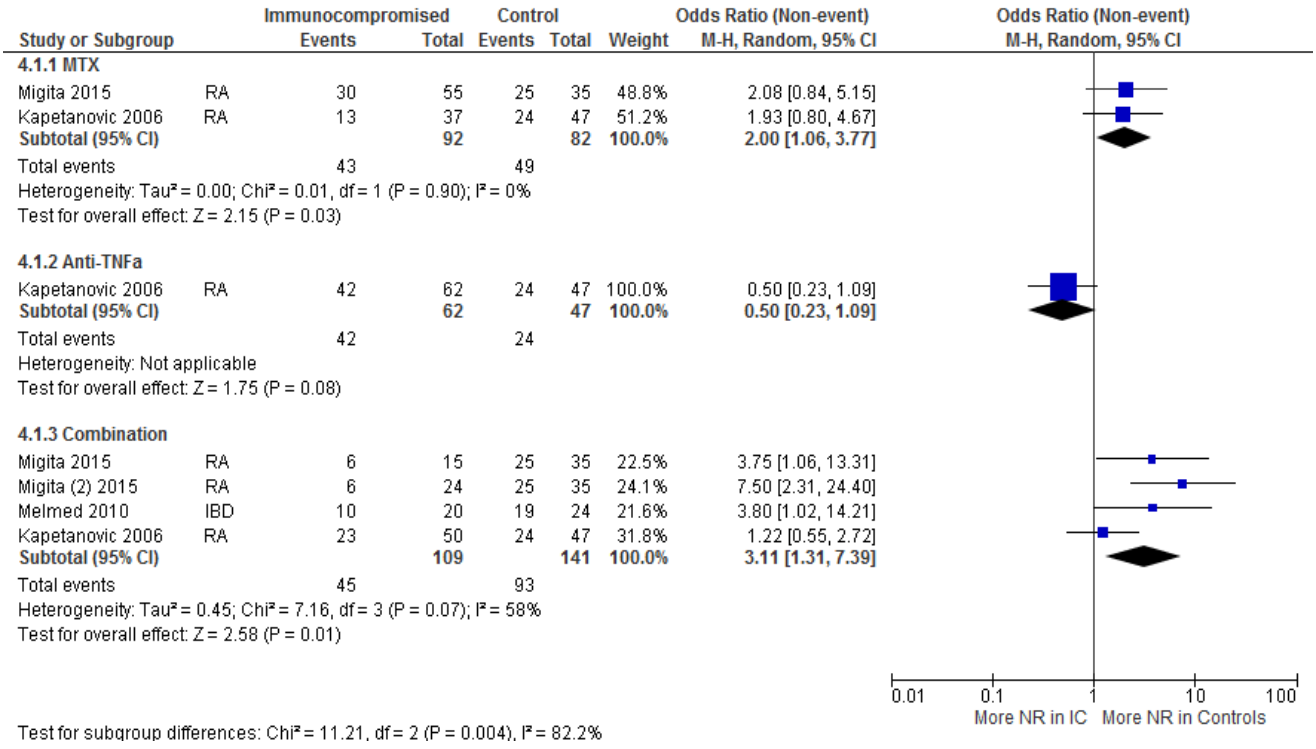
Events = seroconverted participants

NR = Non-response

IC = immunocompromised

RA* = patients were treated with rituximab and methotrexate

Figure 4a: Forest plot of odds ratio for seroconversion of serotype 6B following immunization with PPSV



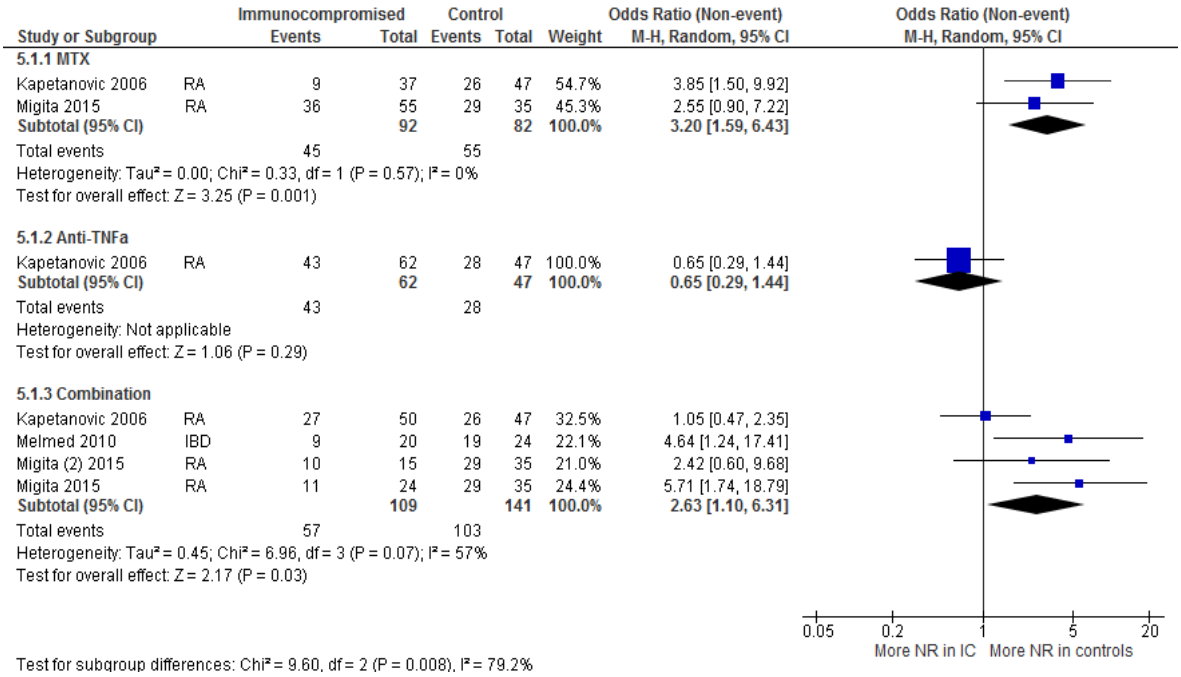
Abbreviations:

Events = seroconverted participants

NR = Non-response

IC = immunocompromised

Figure 4b: Forest plot of odds ratio for seroconversion of serotype 23F following immunization with PPSV



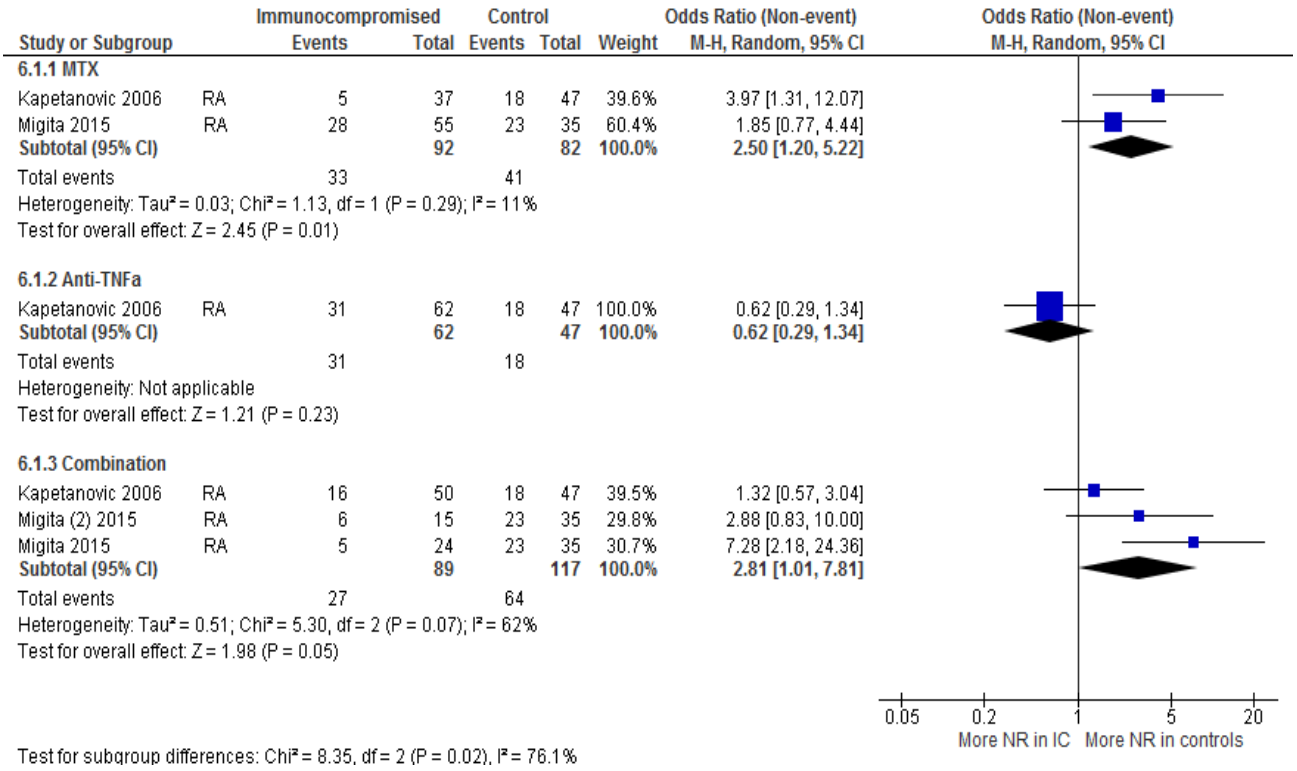
Abbreviations:

Events = seroconverted participants

NR = Non-response

IC = immunocompromised

Figure 4c: Forest plot of odds ratio for seroconversion of serotype 6B + 23F following immunization with PPSV



Abbreviations:
Events = seroconverted participants
NR = Non-response
IC = immunocompromised

After PCV vaccination, 118/446 (26%), of ICPs seroconverted to serotypes 6B + 23F compared to 45/96 (47%) of controls. After PPSV, SCRs were 91/243 (37%) and 41/82 (50%), respectively (Fig. 2a, Fig. 2b). SCRs were significantly higher after PPSV than after PCV vaccination in ICPs, but not in controls, OR 0.6 (95% CI 0.4–0.8) and 0.9 (95% CI 0.5–1.6), respectively. The study of Melmed et al. [16] was excluded in this analysis because seroconversion to serotypes 6B + 23F was not reported. Furthermore, the 55 patients on rituximab were excluded in this analysis because SCRs were only assessed after PCV and not after PPSV vaccination in these patients. Overall, meta-analysis demonstrated an impaired humoral immune response to pneumococcal vaccination in AD patients on immunosuppressive therapy compared to control cohorts.

SCRs to serotypes 6B, 23F and 6B + 23F after vaccination with PCV or PPSV were significantly lower in patients using MTX, combination therapy, or rituximab. In the anti-TNFα cohorts, an impaired immune response to serotype 23F, but similar responses to serotypes 6B and 6B + 23F, were observed after PCV vaccination. Similar immune responses compared to control cohorts in anti-TNFα cohorts were also observed after PPSV, to serotypes 6B, 23F, and 6B + 23F.

Our meta-analysis included one study with patients using rituximab (35). This study reported an impaired response to PCV (35). Three studies included in the systematic

review, but not in the meta-analysis, reported lower SCRs in rituximab cohorts compared to cohorts treated with MTX or cohorts not treated with immunosuppressive therapy (15, 32, 33).

Geometric mean concentrations pre- and post-vaccination

Seven studies reported pre- and post-vaccination GMCs of antibody to serotypes 6B and 23F (18, 27, 29, 30, 35, 37, 40). Pre-GMCs of antibody varied widely: 0.2–2.0 and 0.2–2.9 mg/liter to serotype 6B in the immunosuppressive treatment and control groups respectively, and 0.2–3.9 and 0.4–2.4 mg/liter to serotype 23F in immunosuppressive treatment and control groups, respectively. Two studies of Migita and colleagues (29, 30) found lower pre-vaccination GMCs of antibody to serotypes 6B and 23F in the control cohort compared to the immunosuppressive treatment cohorts, while Kapetanovic and colleagues found the opposite for these serotypes: lower pre-vaccination GMCs of antibody in the immunosuppressive treatment cohorts (35-37).

Pooled post-vaccination GMCs of antibody to serotypes 6B and 23F following PCV in cohorts treated with MTX, anti-TNFα or combination therapy (DMARD plus anti-TNFα) were compared to GMCs of antibody to serotypes 6B and 23F in control cohorts. Post-vaccination GMCs were significantly lower in all immunosuppressive treatment cohorts.

Pooled post-vaccination GMCs of antibody to serotypes 6B and 23F following PPSV in cohorts treated with MTX or with combination therapy were significantly lower in the combination therapy cohort compared to control cohorts. Higher GMCs of antibody were observed for a single cohort treated with MTX. These findings were irrespective of pre-vaccination GMC antibody levels.

Risk factors

Responders and non-responders to pneumococcal vaccination were compared in univariable - with or without multivariable (logistic) - analyses in eleven studies (Table 2) (15, 17, 18, 25, 26, 28, 30, 34, 35, 37, 41).

Treatments with DMARDS (five studies) (17, 18, 35, 37, 41), with anti-TNFα (two studies) (25, 28), with rituximab (one study) (35) and with combination therapy (four studies) (18, 25, 26, 30) were associated with non-response. In a study of Lee et al. (28) female sex, and in three studies of Kapetanovic et al. (18, 37, 41) higher age, were associated with non-response.

Disease-related or immunological factors that were associated with non-response were longer disease duration (one study) (35), higher disease activity (one study) (35) and higher baseline antibody concentrations (26).

Factors associated with response were low dose corticosteroid use (one study) (34), high IgG-2 levels at the time of vaccination (one study) (15), and an elevated baseline CRP (one study) (26). High baseline antibody concentrations were associated with both response (26) and non-response (18) to pneumococcal vaccination.

Table 2: Factors associated with response and non-response to pneumococcal vaccination in IBD patients treated with immunosuppressive drugs

Author	Type of auto-immune disease	Factors associated with non-response
Sociodemographic factors		
Lee [28]	CD	Female gender
Kapetanovic [18], Kapetanovic [41], Kapetanovic [37]	RA, SpA	Higher age
Visvanathan [34]	RA	Smoking
Drug-associated factors		
Kapetanovic [35], Kapetanovic [18], Kapetanovic [41], Kapetanovic [37], O'Dell [17]	RA	MTX or DMARD use
Lee [28], Fiorino [25]	CD	Anti-TNF
Migita [30], Fiorino [25], Kapetanovic [18], Kaine [26]	RA, SpA, IBD	Combination therapy
Kapetanovic [35]	RA	Rituximab
Disease related/immunological factors		
Kapetanovic [35]	RA	Longer disease duration
Kapetanovic [35]	RA	Higher disease activity
Kaine [26]	RA	Protective antibody titers at baseline
Factors associated with response		
Bingham [15]	RA	High IgG2 level at time of immunization
Visvanathan [34]	RA	Corticosteroid use
Kapetanovic [18]	RA, SpA	High baseline antibody titers
Kaine [26]	RA	Elevated baseline CRP

Discussion

The findings of our systematic review indicate that in patients treated with immunosuppressive agents; immune responses to PCV and PPSV are impaired, compared to controls. Moreover, this impaired response was more profound after PCV than after PPSV. A more favorable response was observed in patients treated with TNFα blocking agents, compared to treatment with other immunosuppressive agents.

PCV versus PPSV

Although PCV is thought to provoke a more robust immune response than PPSV, because of its conjugation to the diphtheria toxoid; we found that in ICPs, short-term immune responses to PCV vaccination were inferior to immune responses to PPSV vaccination. By contrast, responses to PPSV and PCV in controls were similar. We hypothesize that the response to PCV, which is T cell-dependent, is reduced because of impaired T cell-mediated immunity evoked by immunosuppressive medications, and

that the response to PPSV is less compromised because this response is T cell-independent. PCV is thought to be the more important vaccine for the development of long-term immunity. However, in a review on PCV versus PPSV in adults, no clear advantage of PCV was found (42). In a study in older adults, anti-pneumococcal antibody levels one year post-vaccination did not differ between recipients of PCV and recipients of PPSV vaccination (43). However, when a second vaccination (PCV or PPSV) was administered, 4 years after the first vaccination, the PCV group had better immune responses compared to participants who received PPSV as a first vaccination (44). Three published studies, that evaluated long-term immunogenicity (1.5–10 years post-vaccination) of pneumococcal vaccination in patients with AD, showed that antibody concentrations decreased over time and to lower levels than in vaccinated healthy controls (45-47). A logical extrapolation would be that intervals of protection as defined in the healthy population do not apply to patients receiving immunosuppressive therapy. Therefore, these findings emphasize the need to perform titer measurements to assess the need for booster vaccinations because ICPs will probably need revaccinations on a shorter time interval.

Possibly, different vaccination regimens in ICPs are needed, consisting of two or more PCV vaccinations, followed by PPSV vaccination, similar to pneumococcal vaccination guidelines in hematological stem cell recipients (48, 49). However, to date, strong evidence for a sequential schedule is lacking (42). Furthermore, hyporesponsiveness to subsequent doses of, at least, PPSV has been described in the literature (50). Therefore, further research on pneumococcal vaccination regimens in ICPs is highly necessary.

Immunosuppressive agents

Among the different immunosuppressive treatments, TNFα-blocking agents least affected the anti-pneumococcal immune response. This finding is supported by Hua and colleagues (51), who reviewed immune responses to influenza and pneumococcal vaccination in RA patients, and by Garcia Garrido and colleagues (52), who studied the immune response to hepatitis A vaccination in ICPs. Conversely, Nguyen and colleagues (53) who reviewed the immune response to different vaccinations analyzed together in IBD patients found that TNFα blocking agents mitigated the immune response more severely than DMARDs. However, because this study analyzed different vaccinations together, comparison was not possible.

DMARDs have a negative impact on the immune response by blocking of clonal expansion of effector T- and B-cells after stimulation by vaccination. By contrast, anti-TNFα interferes with the immune system more specifically, by reducing migration of dendritic cells, inhibition of T cell activation and reducing memory cell survival (54). This may explain the less pronounced negative effect on the immune response with anti-TNFα than with DMARDs.

Geometric mean concentrations

After vaccination with PCV or PPSV, post-vaccination GMCs of antibody were significantly lower in all evaluated cohorts compared to controls, except for one single cohort of patients using MTX. However, in this cohort the mean age was lower and fewer patients used corticosteroids, compared to the control cohort (29, 30) (same cohort in Refs. (24, 25)). Therefore, the question is whether this finding was due to confounding.

The relation between baseline GMCs of antibody and the immune response is controversial. One study in our systematic review associated high baseline GMCs of antibody with response and another study with non-response to pneumococcal vaccination (18, 26). A meta-analysis in healthy subjects showed that the immune response was independent of baseline GMCs of antibody (23). This could be different in ICPs, but we lack power to draw conclusions, because the association between high baseline GMCs of antibody and non-response was found in univariable analysis and not confirmed in multivariable analysis (26).

Concomitant use of corticosteroids

One study in our systematic review described a positive association between low dose corticosteroid use and the immune response (34). The authors hypothesized that corticosteroids reduce inflammatory processes, thereby enabling the immune system to provoke a robust immune response (34). However, in two studies not included in our review (55, 22), corticosteroid use negatively affected the immune response; and in three studies (27, 37, 56), it did not have any effect. However, the broad range of corticosteroid doses (between 4 and 21 mg/day) precluded us to draw additional conclusions. Theoretically, we expect that high-dose (>10 mg prednisone/day) corticosteroids negatively affect immune responses (57). In many studies included in our systematic review, the study design allowed for concomitant corticosteroid use; however, doses were <10 mg/day in 99% of reported cases. Therefore, we do not expect a large bias in this respect.

Strengths and limitations

Our systematic review has several strengths and limitations. The most important strength is that PCV and PPSV were analyzed separately, in order to study vaccine immunogenicity of each vaccine. A second strength is that all ADs were analyzed together, with relevance for a broad range of patients and physicians.

First, a limitation in the studied literature is the fact that almost all published studies investigated short-term immunogenicity, as opposed to long-term immunogenicity. The main limitation of our systematic review is that consensus on correlates of protection is lacking (58-60). Consequently, different definitions of seroconversion were used, and studies differed in the number of serotypes for which the SCR was assessed: four studies (15, 24, 26, 34) assessed SCRs to a range of serotypes, nine studies (18, 27, 29, 30, 35-37, 39, 41) measured concentrations of antibody to serotypes 6B and 23F,

six studies (17, 25, 28, 31- 33) assessed SCRs to all serotypes pooled together, one study (16) assessed SCRs to all serotypes together and a range of serotypes separately, and two studies (38, 40) did not report SCRs, but reported GMCs of antibody. These mixed methods resulted in heterogeneous outcomes, reducing the number of studies that could be included in the meta-analysis. Therefore, internationally accepted correlates of protection would impact positively on the identification of patients failing to mount an immune response to vaccination, and, therefore, at risk of infection. In children, a GMC of antibody of ~ 0.35 mg/L appears to be protective for serotypes in PCV (protection of 97%) (61). However, in adults a higher GMC of antibody is needed to some of these serotypes to reach protection (>1.00 mg/L) (58). For serotypes in PPSV not covered by PCV, correlates of protection are not defined at all. Furthermore, measurement of an opsonic titer with use of the opsonophagocytic assay (OPA) may even be more relevant, since this is a functional (killing) assay which can reflect both IgG and IgM. However, it may be difficult to define correlates of protections based on OPA, since data with OPA are scarce. A second limitation is that our control group consisted of both healthy controls and patients with AD not receiving immunosuppressive therapy. To measure effects of immunosuppressive agents, the ideal control group exists of patients with AD not receiving immunosuppressive therapy because immunosuppressive effects of AD itself are largely unknown, which would be filtered out in that scenario. However, since this would narrow our scope too much, we chose to allow studies with a healthy control cohort. Another limitation is the fact that we could only include studies that evaluated the response to either PCV or PPSV, while in fact the current recommendation is to vaccinate patients receiving immunosuppressive therapy first with PCV, and sequentially with PPSV two months later (4). Further research is therefore needed to determine the value of this currently recommended schedule.

Conclusion

The findings of this systematic review and meta-analysis indicate a reduced immune response to both PCV and PPSV in patients receiving immunosuppressive therapy with a more modest effect of TNFα blocking agents. Furthermore, our study indicates that the short-term immune response to PCV is more severely reduced than the response to PPSV in ICPs. However, the shortcomings in our knowledge of the immunogenicity of pneumococcal vaccinations are also emphasized. This knowledge gap needs to be closed. Furthermore, internationally accepted cut-off values and correlates of protection need to be defined. Until then, post-vaccination titer assessments remain of paramount importance.

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APPENDIX (AVAILABLE ONLINE)

Supplementary File 1: Search strategy, performed February 5, 2018

Supplementary File 2: Quality assessment

Supplementary File 3: Double reported patients

Supplementary File 4: PRISMA checklist

Chapter 4

Immunogenicity of the currently recommended pneumococcal vaccination schedule in patients with inflammatory bowel disease

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Abstract

BACKGROUND: Patients with inflammatory bowel disease (IBD) are at increased risk of invasive pneumococcal infections. Therefore, vaccination with the 13-valent pneumococcal conjugated vaccine (PCV13) followed by 23-valent pneumococcal polysaccharide vaccine (PPSV23) two months later - is recommended. However, the level of immunogenicity induced by this vaccination schedule in IBD patients with and without immunosuppressive medication remains unclear.

METHODS: We prospectively assessed the immunogenicity of PCV13 followed by PPSV23 in IBD patients by measuring serotype specific pneumococcal IgG antibody concentrations at baseline and 4-8 weeks post-vaccination. Response to vaccination was defined as a post-vaccination antibody concentration >1.3mcg/mL for 70% of the measured serotypes. We analyzed the immunogenic effect of four different medication regimens: 1) conventional immunomodulators (i.e. oral prednisolone >10mg/d, thiopurines, methotrexate); 2) anti-Tumor Necrosis Factor agents; 3) combination therapy and 4) no treatment with immunosuppressive agents (control group).

RESULTS: 141 IBD patients were included, of whom 37 were controls. Adequate response to vaccination was 59% (61/104) in patients using immunosuppressive agents (group 1, 2, 3) versus 81% (30/37) in controls (OR 0.33 95% CI 0.13-0.82). A combination of different immunosuppressive drugs most severely impaired the immune response to pneumococcal vaccination (response 52%, 15/29).

CONCLUSIONS: Although the sequential vaccination schedule of PCV13 followed by PPSV23 is safe, immunogenic and hence beneficial in the majority of IBD patients, those receiving immunosuppressive agents and especially those receiving combination therapy, have an impaired immune response compared to controls. Therefore, preferably, vaccinations should be administered before starting immunosuppressive therapy.

Introduction

Invasive pneumococcal disease (IPD) is a severe infection with a high mortality rate (1). Patients with inflammatory bowel disease (IBD), who are often treated with immunosuppressive agents, have an increased risk of IPD (1). Therefore, international guidelines recommend pneumococcal vaccination in IBD patients (2). Since 2012, a sequential vaccination schedule is advised, consisting of a 13-valent pneumococcal conjugated vaccine (PCV13), followed by a 23-valent pneumococcal polysaccharide vaccine (PPSV23) two months later (2). The rationale of this prime-boost schedule is that PCV13 causes a T-cell dependent immune response, leading to the formation of immunological memory; and that subsequent PPSV23 administration boosts the response to the serotypes that are present in both vaccines, while simultaneously broadening the serotype spectrum (3).

However, data on immunogenicity of the currently recommended sequential vaccination schedule of PCV13 followed by PPSV23 in patients using immunosuppressive treatment are scarce. Most studies investigated single vaccine regimens, which showed a weaker immune response to vaccination in patients receiving immunosuppressive agents compared to controls (4, 5). In the few studies that have been conducted using PCV13 followed by PPSV23, limited numbers of vaccine serotypes were investigated, and reported seroconversion rates varied widely (6, 7). This knowledge gap may explain why vaccine uptake is low in IBD patients and other immunocompromised patients (8). The main reason for the low pneumococcal vaccination rate seems to be hesitancy of health care providers to recommend vaccination (8-10).

The objective of this prospective cohort study was to assess vaccine immunogenicity of the sequential pneumococcal vaccination schedule in IBD patients treated with immunosuppressive agents compared to IBD patients without immunosuppressive agents. The ultimate goal is to contribute to a more solid scientific base for the pneumococcal vaccination recommendations in IBD patients which may result in an increased vaccine uptake.

Methods

This study was approved by the Amsterdam UMC ethics committee, and registered in the Dutch trials register (No. 6315).

Study population

All consenting IBD patients (age ≥18 years) were eligible for inclusion in this study. Patients with other primary or acquired immunocompromising conditions were excluded from study participation. Participants were recruited between February 2017 and February 2018 at the Amsterdam UMC, The Netherlands, either from the Gastroenterology Department, or from the Centre of Tropical Medicine and Travel Medicine. Participants were included in the treatment group if they received treatment with either systemic corticosteroids of ≥ 10 mg prednisolone/day or equivalent, conventional immunomodulators (cIMs) including thioguanines and methotrexate

(MTX), biological immunomodulators (including anti-Tumor Necrosis Factor (TNF) agents or a combination of 2 or more immunosuppressive agents. Patients were included in the control group if they did not receive treatment with immunosuppressive agents except for low-dose prednisolone (<10mg/day), topical corticosteroids or topical 5-aminosalicylates. Within the treatment group, 3 subgroups were made based on the medication regimen:

- Use of prednisolone >10mg/day or cIM monotherapy defined as MTX, Azathioprine (AZA), 6-mercaptopurine or thioguanine;
- Anti-TNF monotherapy;
- Patients treated with any combination of 2 or more cIMs or bIMs and/or ≥ 10 mg prednisolone/day or equivalent.

Low-dose prednisolone (<10mg/day, orally administered) does not significantly affect the systemic immune response, nor do topical corticosteroids and 5-aminosalicylates (5-ASA), referred to as 'locally acting agents', whose anti-inflammatory effects are mostly limited to the gut.

Study procedures and laboratory assessments

Participants received PCV13 followed by PPSV23 two months later as part of the regular care. PCV13 includes 13 conjugated antigens (serotypes 1, 3, 4, 5, 6A, 6B 7F, 9V, 14, 18C, 19A, 19F and 23F), and PPSV23 includes 23 polysaccharide antigens (serotypes 1, 2, 3, 4, 5, 6B, 7F, 8, 9N, 9V, 10A, 11A, 12F, 14, 15B, 17F, 18C, 19A, 19F, 20, 22F, 23F, and 33F), of Streptococcus pneumoniae. Blood samples were collected at baseline and 4-8 weeks post-vaccination.

Serotype-specific pneumococcal IgG concentrations were measured using an in-house 23-plex multiplex immunoassay (Luminex technology), as described previously (11, 12). This assay includes all serotypes of the PCV13 and PPSV23 vaccines, except serotype 17F, which is included in the PPSV23 vaccine only. Briefly, samples were diluted in 5% antibody depleted human serum (ADHS, Valley Biomedical Inc, Winchester, VA) and 15 µg/mL pneumococcal cell wall polysaccharide (CWPS multi, SSI) (13). Samples were measured on a Magpix (Merck Millipore). Specific antibody concentrations were calculated using a standard calibrated with reference serum 007sp (14, 15).

Definitions

Defining seroconversion in response to pneumococcal vaccination is complex, because consensus on the correlates of protection is lacking. The cut-off value of 0.35 µg/mL recommended by WHO is based on three clinical studies in children, who received PCV7 (16-18). However, this cut-off is not serotype-specific, and a recent study showed that this concentration may be an underestimation of the real protective concentration for several serotypes (19), even more so in adults. Therefore, we chose a more conservative correlate of protection, based on the definition of the American Academy of Allergy, Asthma & Immunology (AAAAI), who defined seroconversion as a post-immunization antibody concentration of ≥1.3 µg/mL for ≥70% of all measured

serotypes (20, 21). Furthermore, and applying the same seroconversion definition, we separately analyzed seroconversion for the 13 PCV13 serotypes (of which all but 6A are also present in PPSV23) and the 10 serotypes that are exclusive to PPSV23. For each individual serotype, we calculated the -fold increases in antibody concentrations post-vaccination, and the proportion of patients with post-immunization antibody concentrations ≥1.3 µg/mL.

Outcomes

The primary outcome was the seroconversion rate (SCR) 4-8 weeks after pneumococcal vaccination with PCV13 and PPSV23. Secondary outcomes were the difference in SCR, and differences in pre- and post-vaccination median concentrations (MC) between treatment groups and controls. We assessed the effect of age, sex and intoxications on the primary outcome.

Statistical analysis

For data analysis we used SPSS version 23.0. We applied a 0.05α significance level. Means and standard deviations (SD) were presented for normally distributed data, and medians and interquartile ranges (IQR) for not-normally distributed data. The chi-square test was used for dichotomous variables and the student's T-test or Mann-Whitney U test for normally or non-normally distributed continuous variables respectively. The Wilcoxon Signed Rank test was used to compare median pre- and post-vaccination antibody concentrations. Simple and multivariable logistic regression were used to analyze associations with the primary outcome. We ignored missing data.

Results

Baseline characteristics

We included 141 IBD patients of whom 104 were included in the treatment group and 37 in the control group. Baseline characteristics (Table 1) were equal in treatment and control groups, with three exceptions: the proportion of patients with Crohn's Disease (CD) (76% vs. 49%), the proportion of patients using low-dose prednisolone (6% vs. 19%), and the percentage of patients receiving locally acting agents (18% vs. 43%).
Out of 35 patients receiving treatment with cIMs, 33 (94%) were treated with AZA, mercaptopurine or tioguanine, and 2 (6%) with MTX. Out of 40 patients receiving treatment with anti-TNF-monotherapy, 25 (63%) were treated with infliximab; 13 (33%) with adalimumab, 1 (2%) with golimumab, and 1 (2%) with etanercept. Of the 29 patients in the combination therapy group, 24 (83%) were treated with a cIM combined with an anti-TNF agent, 2 (7%) patients were treated with a cIM, anti-TNF agent and prednisolone >10mg/day, 2 (7%) patients were treated with a cIM and oral prednisolone >10mg/d, and 1 (3%) patient received treatment with two bIMs.

Table 1: Baseline characteristics of study participants.

Total number *N* (%)	**Total**	**Immunosuppressive treatment**				**Controls**	**P-value**
	141	DMARDs n=35	TNFi monotherapy n=40	Combination therapy n=29	Groups Combined n=104	n=37	Groups combined vs controls
Sex *N* (%) male	55 (39)	13 (37)	18 (45)	11 (38)	42 (40)	13 (35)	0.57
Age, median [IQR]	45 [29-56]	49 [30-60]	41 [25-56]	38 [30-51]	44 [27-56]	46 [31-56]	0.44
Body Mass Index, median [IQR]	24 [22-27]	24 [21-27]	25 [22-27]	23 [22-27]	24 [22-27]	24 [20-27]	0.41
Smoking *N* (%)	14 (10)	5 (14)	4 (10)	2 (7)	11 (11)	3 (8)	0.27
Alcohol use *N* (%)	75 (53)	20 (57)	25 (62)	13 (45)	58 (56)	17 (46)	0.30
Disease type *n* (%)							<0.01*
- Crohn's disease	97 (69)	25 (71)	30 (75)	24 (83)	79 (76)	18 (49)	
- Ulcerative colitis	44 (31)	10 (29)	10 (25)	5 (17)	25 (24)	19 (51)	
Interval PCV13-PPSV23 in weeks, median [IQR]	9 [8-10]	9 [8-9]	8 [8-10]	8 [8-8]	9 [8-10]	9 [8-10]	0.91
Interval PPSV23-antibody concentration measurement in weeks, median [IQR]	6 [4-7]	6 [4-7]	6 [4-7]	6 [5-8]	6 [4-7]	5 [4-8]	0.15
Immunosuppressive treatment *n* (%)						NA	NA
- Prednisolone (>10mg/day)	5 (3)			5 (17)	5 (5)		
AZA / Mercaptopurine / Tioguanine	56 (40)	33 (94)		23 (79)	56 (54)		
- MTX	6 (4)	2 (6)		5 (17.2)	6 (6)		
- anti-TNFα	66 (47)		40 (100)	26 (90)	66 (63)		
§ *IFX*	40		25 (63)	15 (52)	40		
§ *Adalimumab*	22		13 (33)	9 (31)	22		
§ *Golimumab*	3		1 (3)	2 (7)	3		
§ *Etanercept*	1		1 (3)	0	1		
Dose of immunosuppressive drugs, median [IQR]						NA	NA
- Prednisolone (>10mg/day)	15 [10-23]			15 [10-23]	15 [10-23]		
AZA / Mercaptopurine / Tioguanine (mg/day)	75 [50-144]	75 [50-113]		75 [50-150]	75 [50-144]		
- MTX (mg/week)	15 [14-18]	15 [NA]		15 [11-23]	15 [14-18]		
- TNFi(mg/week)							
§ *IFX*	50 [44-71]		50 [44-67]	50 [38-75]	50 [44-71]		
§ *Adalimumab*	20 [20-40]		20 [20-35]	40 [20-40]	20 [20-40]		
§ *Golimumab*	17 [NA]		25 [NA]	15 [NA]	17 [NA]		
§ *Etanercept*	50 [NA]		50 [NA]		50 [NA]		
Concomitant prednisolone use *n* (%)	13 (9)	2 (6)	3 (8)	1 (3)	6 (6)	7 (19)	0.04*
Dose of concomitant prednisolone use (mg/day), median [IQR]	8 [5-9]	5 [NA]	5 [NA]	8 [NA]	5 [5-6]	9 [9-9]	0.03*
Concimitant use of locally acting agents *n* (%)	35 (25)	6 (17)	9 (23)	4 (14)	19 (18)	16 (43)	<0.01*

Seroconversion rates

Table 2 and Figure 1 depict seroconversion rates (SCRs) after vaccination in the different treatment groups. The SCR for all 23 serotypes among patients using immunosuppressive drugs was 59% (61/104), which was significantly lower than among controls: 81% (30/37). This difference was also significant for serotypes common to both vaccines (50% (52/104) vs. 84% (31/37)), but not for the serotypes present in PPSV23 only (70% (73/104) vs. 81%; (30/37)). In the cIM and the anti-TNF subgroups, this difference was only statistically significant for PCV13 serotypes (49% (17/35) and 58% (23/40) in the IM and anti-TNF groups, versus 84% (31/37) in the control group). The lowest SCRs were observed in the group using combination therapy: 41% (12/29) for serotypes present in both PCV13 and PPSV23, 52% (15/29) for all serotypes together, and 55% (16/29) for serotypes present only in PPSV23.

Table 2: Seroconversion rates and odds ratios for seroconversion in the different treatment groups and controls for all PCV1313 and PPSV23 serotypes only rates. Univariable logistic regression analysis.

	Immunosuppressive treatment								Controls	
	Group 1 (n=35)		Group 2 (n=40)		Group 3 (n=29)		Groups 1,2,3 combined (n=104)			
	DMARDs		TNFi		Combination therapy					
	n (%)	OR (95% CI)	n (%)	OR (95% CI)	n (%)	OR (95%CI)	n (%)	OR (95% CI)	n (%)	OR (95% CI)
All 23 serotypes	21 (60)	0.35 (0.12-1.02)	25 (63)	0.39 (0.14-1.10)	**15 (52)**	**0.25 (0.08-0.75)***	**61 (59)**	**0.33 (0.13-0.82)***	30 (81)	Reference
PCV1313 serotypes	**17 (49)**	**0.18 (0.06-0.55)***	**23 (58)**	**0.26 (0.09-0.77)***	**12 (41)**	**0.14 (0.04-0.43)***	**52 (50)**	**0.19 (0.07-0.50)***	31 (84)	Reference
PPSV2323 only serotypes	26 (74)	0.67 (0.22-2.06)	31 (78)	0.80 (0.27-2.43)	**16 (55)**	**0.29 (0.10-0.86)***	73 (70)	0.55 (0.22-1.38)	30 (81)	Reference

* Statistically significant lower seroconversion rate compared to reference group (controls).

Serotype-specific antibody concentrations before and after vaccination.

Table 3 and Figure 2A+B show median pre- and post-vaccination antibody concentrations per serotype for all groups.

Median post-vaccination antibody concentrations were higher than pre-vaccination antibody concentrations for all measured serotypes in both treatment and control groups ($p<0.001$).

Median pre-vaccination antibody concentrations were similar in the treatment and control groups; except for serotypes 1, 14, 19A, 19F and 8, which were significantly higher in the treatment group (Table 3; Figure 2A+B). In the treatment groups, post-vaccination antibody concentrations were significantly lower for eight of the 12 serotypes shared across both vaccines (3, 4, 5, 6B, 7F, 9V, 18C, 23F) and 2 of the 10 PPSV23-only serotypes (22F, 33F) compared to the control group (Table 3; Figure 2A+B). Response to serotype 3 was poor across all groups including the controls, with only 16% and 30% of IBD patients reaching a concentration above 1.3 mcg/ml, respectively. Serotype 2 was the most immunogenic, with high median concentrations and 95-97% of patients reaching concentrations above 1.3mcg/ml. A lower proportion of patients in the treatment group had adequate antibody concentrations for PCV13 serotypes 9V (64% vs 89%) and 23F (61% vs 84%) compared to controls. Fold

changes ranged from 3 (serotype 12F) to 35 (serotype 4) in the control group and from 1.6 (serotype 12F) to 19 (serotype 19) in the treatment group.

Multivariable logistic regression

We assessed the effect of sex, age, disease type, treatment subgroup, smoking, alcohol use, body mass Index, concomitant use of prednisolone and topical steroids on the primary outcome SCR (Table 4). Only treatment group and disease type (UC or CD) were significantly associated with SCR in univariable analysis, but the latter lost statistical significance after adjusting for the treatment group. Patients using immunosuppressive drugs were less likely to seroconvert after vaccination compared to controls. After adjusting for disease type, this association was only statistically significant for the group using combination therapy (OR 0.32, CI 0.10-0.98).

Efficacy, safety and tolerability

None of the vaccinated patients developed pneumococcal disease during the follow-up period. Vaccination was generally safe and well tolerated. There were 13 adverse events (AE) in total; 10 in the treatment group and 3 in the control group (p=1.00). Swelling, erythema and pain in the vaccination arm were reported most frequently (n=9). Two patients reported intestinal complaints following vaccination which were assessed as most likely not vaccination-related. There were two serious AEs that were not study-related (hospital admissions for cholecystitis and diverticulitis).

Figure 1: Seroconversion rates of all 23 serotypes, the 13 serotypes covered by PCV13 and PPSV23 and the 10 serotypes covered by PPSV23 only.

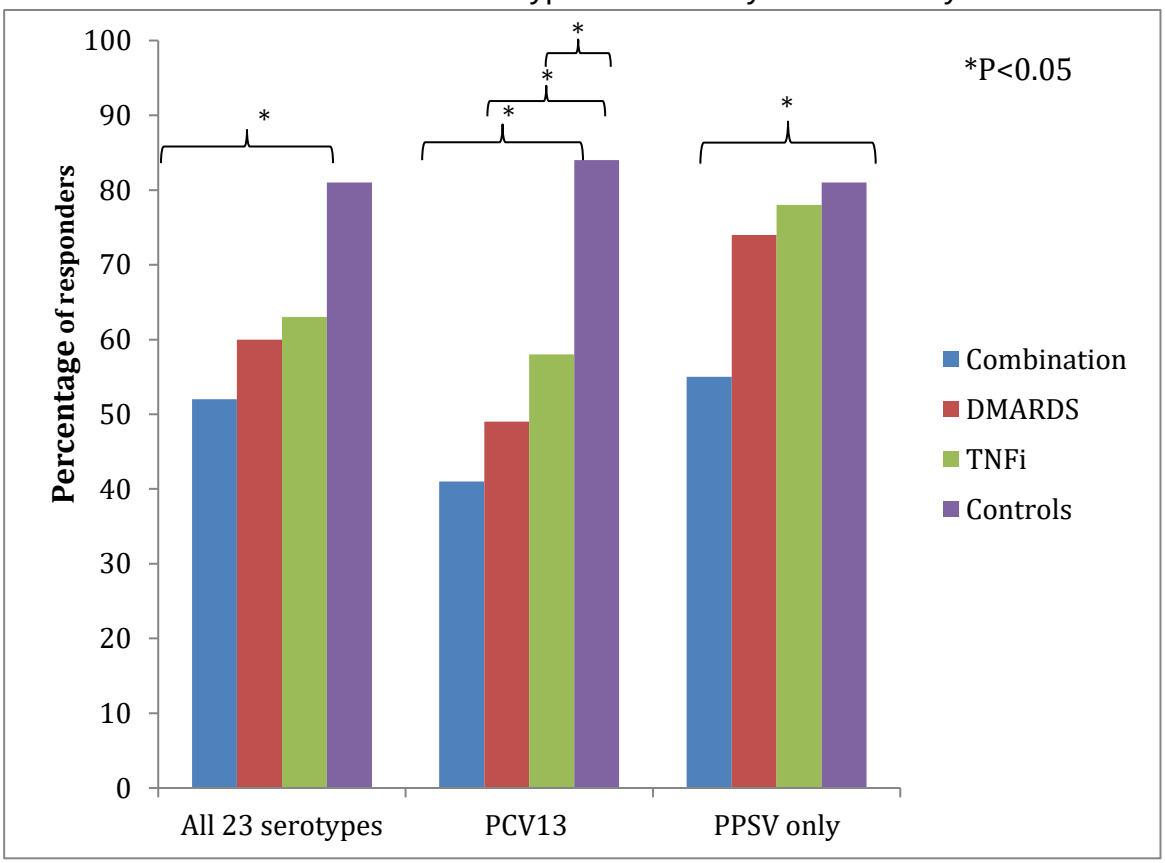

Table 3: Pre- and post-vaccination serotype specific antibody concentrations, fold changes and the proportion of patients with a >3 fold increase and an antibody concentration >1.3 mcg/ml.

Serotype		Using immunosuppressive drugs (*N* 110)				Controls (*N* 37)			
		MC, median [IQR]				MC, median [IQR]			
		Pre MC	Post MC	Fold-change	> 1.3 mcg/mL	Pre MC	Post MC	Fold-change	> 1.3 mcg/mL
PCV/PPSV	1	**0.39 [0.08-1.69]***	4.33 [1.17-10.7]	6.59 [2.62-20.2]	73	0.16 [0.04-0.72]	8.04 [2.69-10.6]	21.6 [7.03-77.0]	84
	3	0.09 [0.03-0.21]	**0.31 [0.10-0.71]#**	3.31 [1.57-7.21]	16	0.06 [0.02-0.30]	0.86 [0.39-1.47]	9.34 [2.29-34.1]	30
	4	0.09 [0.02-0.49]	**2.24 [0.37-4.64]#**	9.68 [3.41-41.5]	61	0.07 [0.02-0.23]	4.41 [1.39-4.64]	35.4 [13.1-87.4]	78
	5	0.46 [0.20-1.55]	**4.06 [1.24-11.3] #**	4.42 [2.19-13.3]	74	0.95 [0.42-1.85]	11.3 [4.64-11.2]	7.78 [2.84-12.5]	87
	6A	0.06 [0.01-0.36]	1.20 [0.32-4.21]	11.0 [3.89-29.1]	49	0.13 [0.01-0.55]	3.97 [0.40-4.84]	19.6 [6.31-57.2]	62
	6B	0.18 [0.04-0.95]	**3.04 [0.58-5.53]#**	6.58 [2.44-15.9]	66	0.26 [0.02-1.85]	5.53 [2.14-5.53]	18.1 [2.70-50.4]	81
	7F	0.65 [0.13-2.71]	**3.62 [1.19-11.0]#**	4.00 [1.78-10.8]	74	0.53 [0.17-1.58]	10.0 [2.93-11.0]	13.6 [3.93-37.3]	87
	9V	0.21 [0.07-0.74]	**2.10 [0.65-5.63]#**	7.16 [3.14-18.0]	**64** ±	0.24 [0.11-1.38]	7.85 [2.24-7.85]	14.1 [5.03-38.0]	89
	14	**0.84 [0.19-3.28]***	11.8 [2.03-24.8]	8.12 [2.32-22.9]	80	0.21 [0.05-1.79]	11.2 [2.55-24.8]	14.0 [3.95-74.9]	78
	18C	0.52 [0.15-1.86]	**5.14 [2.12-7.05]#**	5.77 [2.15-16.2]	79	0.41 [0.10-1.99]	7.05 [3.92-7.05]	12.9 [3.18-36.5]	84
	19A	**0.94 [0.25-2.75]***	4.98 [1.96-9.06]	3.68 [1.58-10.6]	84	0.26 [0.07-1.15]	7.46 [3.22-9.06]	14.7 [4.54-52.6]	87
	19F	**0.56 [0.20-2.03]***	4.02 [1.21-9.95]	4.87 [1.86-11.6]	74	0.21 [0.05-0.80]	5.92 [2.74-17.0]	21.1 [10.2-63.7]	87
	23F	0.20 [0.04-0.71]	**2.46 [0.57-4.25]#**	8.13 [2.47-25.3]	**61** ±	0.18 [0.03-0.82]	4.25 [2.07-4.25]	10.8 [3.56-84.5]	84
PPSV only	2	3.59 [1.11-12.1]	17.4 [10.8-17.4]	2.96 [1.31-7.14]	95	2.86 [0.65-11.5]	17.4 [9.96-17.4]	4.08 [1.30-16.7]	97
	8	**2.18 [0.81-8.48]***	14.2 [3.57-14.2]	2.15 [1.19-8.05]	88	1.04 [0.45-2.80]	14.5 [3.36-17.7]	6.63 [2.65-14.5]	89
	9N	0.38 [0.16-1.50]	5.56 [1.04-9.56]	5.56 [2.41-19.4]	70	0.18 [0.09-0.89]	6.56 [2.51-9.56]	12.7 [3.53-49.0]	81
	10A	0.68 [0.11-2.54]	4.56 [0.96-17.9]	4.02 [1.80-9.17]	73	0.52 [0.07-1.71]	7.92 [1.84-17.9]	10.9 [3.57-27.1]	81
	11A	0.28 [0.06-1.14]	1.29 [0.29-3.34]	2.29 [1.27-7.70]	50	0.38 [0.06-1.05]	2.96 [0.73-3.34]	4.00 [1.87-11.4]	68
	12F	0.45 [0.16-0.95]	0.93 [0.38-3.28]	1.55 [1.04-4.12]	44	0.30 [0.16-0.99]	1.65 [0.55-3.28]	3.01 [1.32-5.27]	54
	15B	0.56 [0.16-1.84]	6.58 [1.47-11.6]	6.48 [2.02-21.9]	78	0.27 [0.10-1.35]	8.46 [1.42-11.6]	18.2 [3.49-50.8]	78
	20	1.01 [0.23-3.11]	3.51 [1.20-14.4]	3.04 [1.51-7.37]	73	1.14 [0.26-4.05]	11.8 [1.41-14.4]	4.31 [2.05-9.72]	76
	22F	0.19 [0.04-0.51]	**5.54 [1.40-13.3]#**	19.0 [4.48-53.5]	76	0.18 [0.03-0.99]	12.9 [1.92-13.3]	25.6 [7.69-123]	87
	33F	0.38 [0.08-1.08]	**3.57 [1.05-9.77]#**	8.06 [2.36-24.6]	68	0.68 [0.12-1.73]	7.99 [1.51-15.1]	10.1 [4.54-21.3]	78

* Higher median pre-vaccination antibody concentration compared to control group (p<0.05)

Lower median post-vaccination antibody concentration for this serotype compared to controls (p<0.05)

§ Lower proportion of patients with a >3 fold increase for this serotype compared to controls (p<0.05)

± Lower proportion of patients with a post-vaccination concentration >1.3 mcg/ml for this serotype compared to controls (p<0.05).

N.B.: all serotype-specific postvaccination concentrations were higher than pre-vaccination concentrations (significance level p<0.001)

Figure 2A: Pre- and post-vaccination median concentration for PCV13 serotypes.

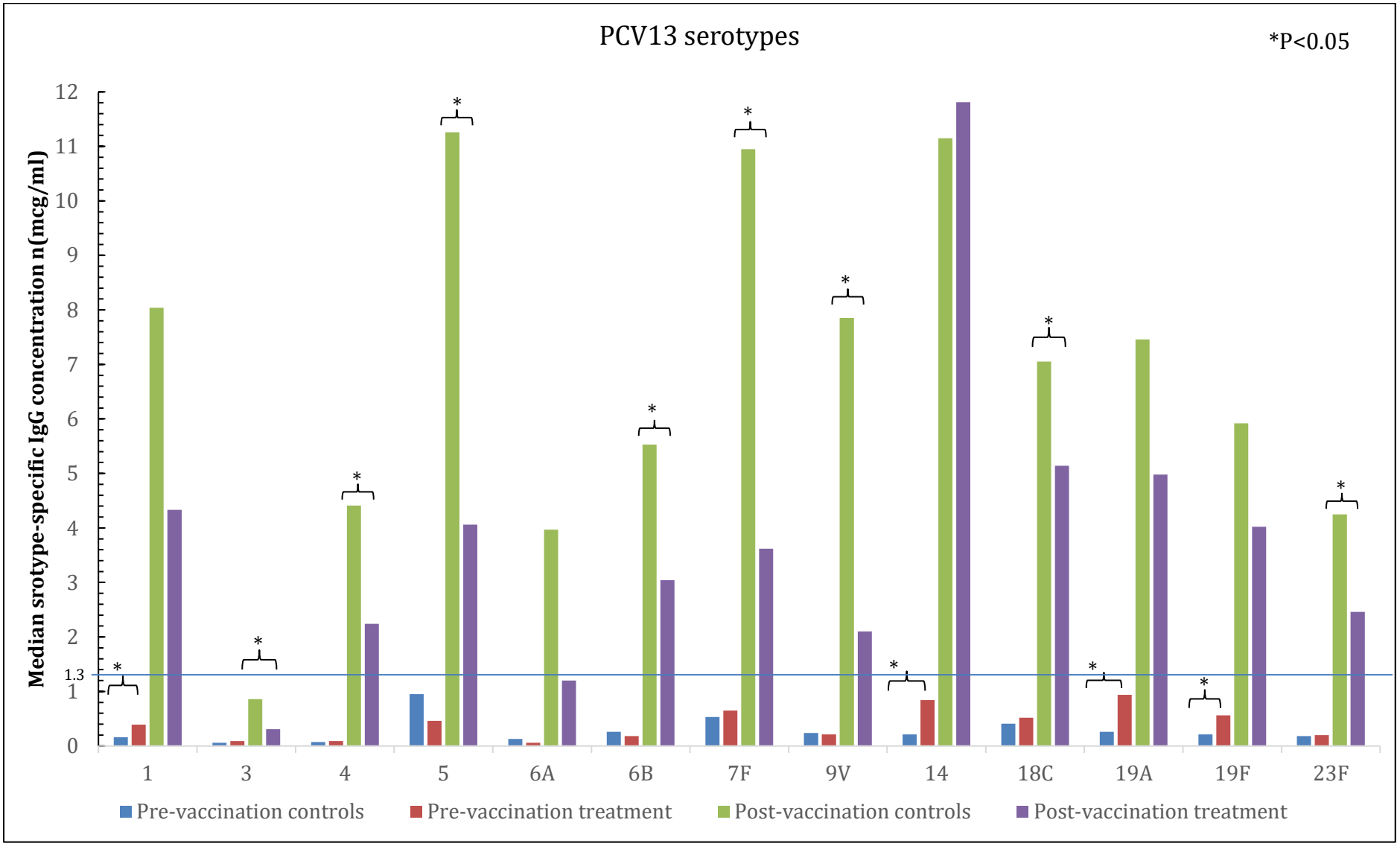

Figure 2B: Pre- and post-vaccination median concentration for serotypes unique to PPSV23.

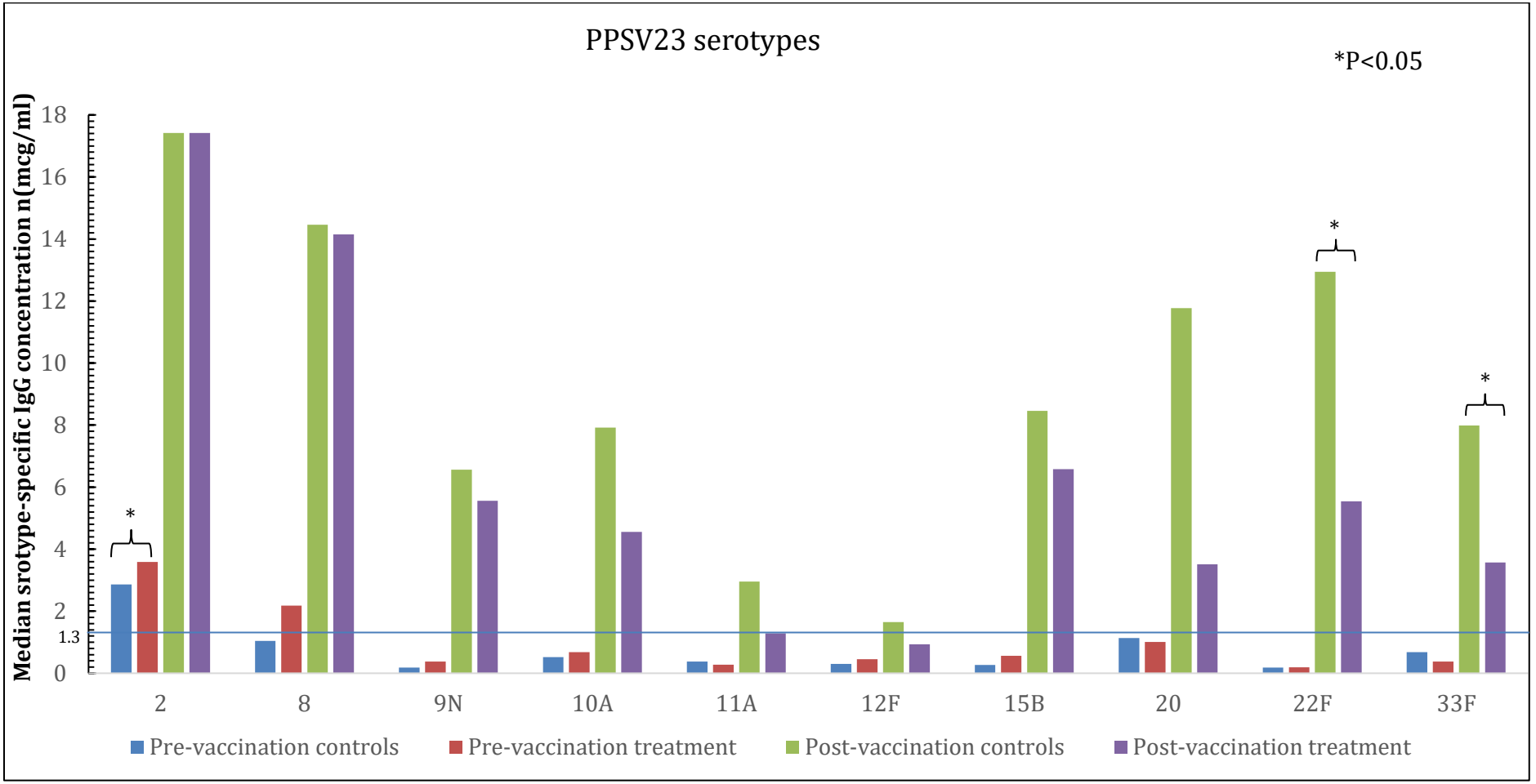

Table 4: Multivariable analysis

Independent variable	SCR %	Raw OR (95% CI)	Adjusted OR (95% CI)
Sex			NA
Male (n=55)	71	Ref	
Female (n=86)	61	0.62 (0.30-1.30)	
Treatment group			
No drugs (n=37)	81	Ref	Ref
Any immunosuppressive drug (n=104)	59	0.33 (0.13-0.82)	NA
DMARDS (n=35)	60	0.35 (0.12-1.02)	0.41 (0.14-1.21)
Use of TNFi (n=40)	63	0.39 (0.14-1.10)	0.47 (0.16-1.37)
Combination therapy (n=29)	52	0.25 (0.08-0.75)	0.32 (0.10-0.98)
Age			NA
18-40 years	69	Ref	
41-60 years	64	0.82 (0.38-1.75)	
> 61 years	52	0.50 (0.18-1.37)	
BMI			NA
0-25.0	67	Ref	
25.1-30.0	57	0.63 (0.29-1.39)	
> 30.1	67	0.97 (0.33-2.84)	
Smoking			NA
No	69	Ref	
Yes	50	0.46 (0.15-1.41)	
Previous	58	0.63 (0.27-1.45)	
Alcohol			NA
No	67	Ref	
Yes	63	0.84 (0.42-1.68)	
Disease type			
Crohn’s disease	58	Ref	Ref
Ulcerative colitis	80	2.85 (1.23-6.57)	2.33 (0.99-5.54)
Concomitant prednison use			NA
No	64	Ref	
Yes	69	1.26 (0.37-4.33)	
Concomitant use of locally acting agents			NA
No	60	Ref	
Yes	77	2.22 (0.92-5.34)	

Discussion

The present study was designed to investigate the immunogenicity of the currently recommended vaccination schedule combining PCV13 and PPSV23 in IBD patients.
Our study shows that sequential administration of PCV13 and PPSV23 is safe and elicits protective immunity against pneumococcal serotypes in the majority of IBD patients. Patients using immunosuppressive drugs had an impaired antibody response compared to controls, resulting in a lower SCR (59% vs 81%) for all 23 serotypes together, and lower antibody concentrations for 10 out of 23 serotypes analyzed separately. These findings emphasize the benefit of starting with vaccinations before the introduction of immunosuppressive therapy in IBD patients.
Two previous studies assessed the immunogenicity of the sequential vaccination schedule of PCV13 following PPSV23 in patients using immunosuppressive drugs (6, 7). The most recent study comprised 24 patients with rheumatoid arthritis (RA) using combination therapy of cIMs and bIMs , reported similar percentages of protection after vaccination (55-63%, cut off >1.3 mcg/ml) (7). Another study among RA patients using cIMs or biologicals, reported higher seroconversion rates compared to this study (87-94%) (6). However, the definition of seroconversion used in that study (IgG concentration >0.35 mcg/ml for 6/12 serotypes) was much less conservative. A recent study showed that this cut-off value leads to overestimation of the actual protection against some serotypes (19).
Although the sequential vaccination regimen was less immunogenic in patients using immunosuppressive drugs than in controls, it still was more immunogenic than single vaccination regimens using PCV713 or PPSV23 only. A meta-analysis of 764 patients using immunosuppressive drugs receiving either PCV13 or PPSV23 reported SCRs of 26% after PCV13 administration and 37% after PPSV23 administration. In 221 controls, SCRs were also lower compared to our study (47% and 50% versus 81%, respectively) (5).

Antibody concentrations of all vaccine serotypes significantly increased following vaccination. However, serotype 3 was poorly immunogenic, which is consistent with previous studies in healthy children, stem cell transplant recipients and HIV patients (22-24). Furthermore, a specific characteristic of serotype 3 is capsular polysaccharide release to which the antibodies attach in case of an infection. Together with the poor immunogenicity, this explains the lack of vaccine efficacy against IPD, pneumonia and otitis media caused by serotype 3 after vaccination (19, 25-27). This is problematic, since serotype 3 has been identified as one of the emerging serotypes after the introduction of conjugate vaccines (28).

Surprisingly, our study shows that patients using immunosuppressive medication had a lower SCR (50%) to serotypes present in both PCV13 and PPSV23 compared to the SCR (70%) to the serotypes exclusive to PPSV23. This was also reflected by a lower median concentration for 8/13 PCV13 serotypes in patients versus controls, as opposed to only 2/10 PPSV23 serotypes. The absence of a PPSV23 booster effect for PCV13 serotypes in immunocompromised patients has previously been described

(22). Possibly, the time interval between PCV13 and PPSV23 is too short for immunocompromised patients to generate a booster response. Another explanation could be that the immunological advantage of priming with a T-cell dependent vaccine might be limited in the scope of immunosuppressive treatment regimens that impair T-cell immunity. This is supported by a recent meta-analysis studying patients using immunosuppressive medication, in which lower SCRs after PCV13 were observed compared to PPSV23 (5). Multiple priming doses of PCV13 may be necessary, similar to vaccination regimens in newborns or in patients having undergone hematopoietic stem cell transplantation. Another possibility is that an initial dose of PCV13 limits the number of responding B-cells in immunocompromised patients after revaccination with PPV23, as has been described recently in HIV positive patients (29). However, this phenomenon, called hypo-responsiveness, would likely affect controls too, and is mostly seen after administration of PCV13 after PPSV23, or when multiple doses of PPSV23 are administered within short periods of time (30, 31).

Our study demonstrates that an increased number of different immunosuppressive drugs aggravates the immune response impairment to pneumococcal vaccination resulting in a lower SCR. This is consistent with previous pneumococcal and hepatitis A vaccination studies in patients using immunosuppressive medication (32-34), and can be explained by the fact that different steps in the immune response are simultaneously inhibited (35). In our study, both patients using anti-TNF and cIM monotherapy had lower SCRs for all serotypes compared to controls. However, this difference was not statistically significant when adjusting for disease type. The SCRs for PCV13 serotypes was less impaired in patients using anti-TNF compared to cIM or combination therapy, but still significantly lower than in controls. In theory, anti-TNF should target the immune system more specifically than cIMs and steroids, resulting in less interference with the response to vaccination (36) This theory is supported by three systematic reviews on pneumococcal vaccine immunogenicity and a study on hepatitis A vaccine immunogenicity (4, 5, 37, 38). In contrast, two pneumococcal vaccination studies in IBD patients using PPSV23 or PCV13 only, report that anti-TNF therapy impairs response to vaccination more profoundly than other drugs (33, 39). However, the studies showing a less harmful effect of anti-TNF mainly concerned rheumatologic patients, who generally use MTX instead of AZA, and lower doses of anti-TNF (e.g. 3 mg/kg versus 5 mg/kg infliximab). This could also explain why IBD patients had a lower immunologic response to vaccination compared to patients with rheumatic diseases after hepatitis A vaccination (38).

The major strength of this study is that we evaluated serotype-specific antibody responses of 23 different serotypes separately. Only serotype 17F was not included in our assay. Most studies only use 2 serotypes as a surrogate for the assessment of immunogenicity (4, 5). Therefore, our study provides a more comprehensive picture of the immune response to pneumococcal vaccines.
An important limitation of this study is that we did not assess the antibody response after the administration of PCV13, before PPSV23. This would have provided

information on the topic of hypo-responsiveness. In addition, our control group consisted of IBD patients without immunosuppressive therapy, instead of healthy controls. However, a recent study showed that IBD patients without anti-TNF and DMARDS had similar immune responses as healthy controls (40).
Importantly, the present study evaluated the short-term immune response to pneumococcal vaccination only. The lower post-vaccination peak antibody concentrations for several serotypes in patients using immunosuppressive medication indicate a shorter duration of serologic protection. This has been described previously, and has implications for the timing of a booster vaccination (7). Last, our study was not powered to investigate clinical endpoints. To the best of our knowledge, there are no published pneumococcal vaccine efficacy studies in patients using immunosuppressive medication. This highlights the need for clinical studies establishing standardized correlates of protection against pneumococcal disease in adults.

In conclusion, IBD patients using immunosuppressive drugs, especially those using combination therapy, show an impaired response to pneumococcal vaccination compared to the response in untreated IBD patients. Therefore, we recommend pneumococcal vaccination before starting immunosuppressive therapy. However, vaccination is still beneficial in the majority of patients using immunosuppressive medication. Further studies are needed to assess the response to pneumococcal vaccination at additional time points, to explore the possibility of hypo-responsiveness, to investigate alternative vaccination strategies and to provide more information on the duration of protection after vaccination.

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Chapter 5

Long-term pneumococcal vaccine immunogenicity following allogeneic hematopoietic stem cell transplantation

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Abstract

Infection with *Streptococcus pneumoniae* is a life-threatening, but vaccine preventable complication in patients with allogeneic hematopoietic stem cell transplantation (allo-HSCT). The international consensus on post allo-HSCT immunization schedules, starting 3–6 months after HSCT, focuses on short-term immunogenicity while long-term immunogenicity is not well characterized. The current Dutch immunization schedule, which starts at 12 months post allo-HSCT, was developed as a result of concerns on the coverage of long-term immunogenicity in international guidelines. We recently encountered two cases of allo-HSCT recipients who developed invasive pneumococcal disease (IPD) despite adequate revaccinations, which led us to question the immunogenicity of pneumococcal vaccinations in this patient group, and whether the currently existing vaccination schedules are appropriate. We included allo-HSCT recipients, vaccinated from one year after transplantation, and tested antibody responses to pneumococcal vaccination. We also performed a systematic review. Antibody concentrations were measured in 42 of 103 (41%) patients, with a response rate of 85% to PCV13 and 62% to PPSV23-unique serotypes. In six relevant studies, protection rates varied between 64 and 98%. Antibody responses in early and late vaccination schedules were similar, but adequate antibody responses were maintained better after late vaccination. Therefore, we propose a vaccination schedule that combines the advantages of early and late vaccination. This new schedule has been introduced since March 2018 in the two academic hospitals in Amsterdam, The Netherlands.

KEYWORDS: Hematopoietic stem cell transplantation, Allogeneic, Invasive pneumococcal disease, Pneumococcal vaccination, PCV13, PPSV23

Introduction

Streptococcus pneumoniae is the most important cause of community acquired bacteraemia, pneumonia and meningitis in the general population (1). Due to being immunocompromised, particularly when graft-versus-host-disease (GvHD) is present, a condition that is both associated with hyposplenia and prolonged immunosuppressive treatment, allogeneic hematopoietic stem cell transplant (allo-HSCT) recipients are at risk to develop invasive pneumococcal disease (IPD) (2-6). Compared to the general population, studies have shown a 50-fold increased risk of contracting IPD in allo-HSCT recipients (7). IPD is a serious cause of morbidity and mortality in these patients, affecting 4–20% during the first 100 days after transplantation, with a mortality rate of 25–30% (2, 4, 5, 7, 8).

An essential strategy to prevent IPD after allo-HSCT is vaccination. Vaccination is recommended for all allo-HSCT recipients by international guidelines, such as those of the Centers for Disease Control and Prevention (CDC) and the European Group for Blood and Marrow Transplantation (EBMT) (Table 1) (9). The Academic Medical Center (AMC) mostly applies the consensus post allo-HSCT immunization schedule as proposed by the society of adult hematology-oncology in the Netherlands (HOVON). The consensus is largely based on international guidelines, but also on expert opinion (Table 1). To date, an international consensus exists on post allo-HSCT immunization schedules. However, this consensus primarily focuses on short-term and not on long-term immunogenicity. Immune reconstitution following allo-HSCT, in particular T-cell construction, is generally slow, and patients receive immunosuppressants to prevent GvHD over considerable time periods. Therefore, and in contrast to the CDC and EBMT guidelines, which recommend to start vaccinations 3–6 months post allo-HSCT, the Dutch immunization schedule advises not to start until 1 year after allo-HSCT (Table 1).

Table 1: Pneumococcal immunization schedules.

	Time after allo-HSCT					
	First PCV13	*Second PCV13*	*Third PCV13*	*Fourth PCV13*	*PPSV23*	*Repeated PPSV23*
CDC and EBMT guideline	3-6 mo	4-7 mo	5-8 mo	n/a	≥12 mo */**	n/a
AMC/VUmc guideline	12 mo	13 mo	14 mo	n/a	18 mo	Every 5 years
Recommended international guideline	4-6 mo ***	5-7 mo	6-8 mo	12-14 mo	14-16 mo	n/a

Abbreviations: mo, months; n/a, not applicable.

* If there is no GvHD; if there is GvHD substitute PCV13 for PPSV23.

** If the patient is immunocompromised after five years, give an additional dose of PPSV23.

*** If there is no use of immunosuppression for more than 1 month or a prednisolone doses <10 mg per day.

Existing data on the immunogenicity and efficacy of pneumococcal vaccines in this patient group, especially on longer term, are very limited. The currently available vaccines against IPD are the conjugate vaccines (PCV7, 10 and 13) and the 23-valent pneumococcal polysaccharide vaccine (PPSV23). PCV13 covers the 13 most prevalent serotypes that cause IPD and elicits a strong T-cell dependent immune response resulting in long-lasting memory (10-13). By contrast, PPSV23, covering 23 serotypes, induces a T-cell independent immune response without the development of long-lasting memory (14, 15). Sequential vaccination of PCV13, followed by PPSV23, increases the response rate to PCV13 serotypes and broadens the narrow spectrum of PCV13 (14). In the current Dutch immunization schedule total of three doses of PCV13 followed by a single vaccination with PPSV23 is recommended (Table 1).

We recently encountered two cases of IPD after allo-HSCT, despite adequate revaccinations; one of whom nearly died as a result of severe pneumococcal meningitis (Supplementary File 1). These cases prompted us to re-evaluate the level of long-term immunogenicity of pneumococcal vaccinations in this patient group. In addition, we investigated whether better guidance is needed regarding the measurement of post-vaccination antibody responses and which scientific data underlie various immunization schedules. The main aims of our study were to define the optimal timing of post allo-HSCT pneumococcal revaccinations, and to assess the need for post-vaccination antibody measurements, based on analysis of our own data and on existing literature.

Methods

Study setting and definition of IPD

All patients who received post allo-HSCT immunizations at the AMC between January 2009–2017 were included in this study. Under the existing immunization schedule (Table 1), it is advised to start vaccinations in allo-HSCT recipients 1 year after transplantation, on the condition that patients are not treated with immunosuppressive medication other than prednisolone in a dose lower than 10 mg/day at the moment of vaccination. During the first year after transplantation and until the completion of vaccinations, patients routinely receive trimethoprim/sulfamethoxazole as antimicrobial prophylaxis against IPD. The reason for choosing this prophylaxis is that resistance against trimethoprim/sulfamethoxazole is very low in the Netherlands. Therefore, trimethoprim/sulfamethoxazole is used as prophylaxis for both pneumococcal infection and pneumocystis pneumonia. IPD was defined as an infection confirmed by isolation of S. pneumoniae from a normally sterile site. Early IPD was defined as any episode <1 year and late IPD as ≥1 year post allo-HSCT.

Data collection

An electronic hospital database was used to obtain demographic and clinical information. Data were collected on underlying medical conditions, transplant type,

post-transplant care, occurrence of GvHD, pneumococcal vaccinations, and post-vaccination antibody concentration measurements.

Immunogenicity assessment

Post-vaccination concentrations were measured 4–6 weeks after the final (PPSV23) vaccination. Serotype-specific antibody concentrations were determined using Luminex 23-plex technology (Luminex Corporation, USA), in which responses to all serotypes of PCV13 and PPSV23 were evaluated separately (16). The used standard was calibrated against the 007sp reference serum (NIBSC). An insufficient post immunization antibody response was defined as a concentration of <0.35 µg/mL; a sufficient response was defined as concentration between 0.35 and 1.3 µg/mL. A good response was defined as a concentration of ≥1.35 µg/mL. The 0.35 µg/mL cut-off was based on the internationally accepted minimal threshold for vaccination response, (17) and the 1.3 µg/mL cut-off was based on a commonly applied threshold defining an immune response as adequate (18).

Literature review

We performed a literature search in PubMed and Cochrane database on December 1, 2017 (Supplementary File 2). ACL and MvA independently screened articles retrieved from the above databases. Studies were included if they met the following inclusion criteria: (1) The study included adult subjects after allo-HSCT; (2) Patients received pneumococcal vaccines; (3) Immunogenicity was measured as outcome of interest. No language restrictions were applied. We excluded paediatric studies and studies on autologous HSCT.

Results

Study subjects

A total of 103 patients were included in the study (52 males and 51 females) with a median age at the time of allo-HSCT of 49 (16–68) years. Patient characteristics are given in Table 2. In 74 patients (72%), acute leukemia (AML/ALL) had been the primary diagnosis. GvHD had been diagnosed in 70 (68%) patients. All these patients suffered from chronic GvHD. The median time period between allo-HSCT and pneumococcal vaccination was 609 days (range 365–4932 days); 9/75 (12%) patients were vaccinated exactly 1 year after allo-HSCT. Ninety-two of 103 (89%) allo-HSCT recipients were fully vaccinated according to the MATCH protocol. Of the other eleven patients, seven had an unknown vaccination schedule, one had received an abbreviated schedule, and three had not yet received their vaccinations. Data on time intervals to revaccination were lacking for 28/103 (27%) patients. Among the remaining 75 (73%) patients, the median time period to pneumococcal vaccination for patients suffering from GvHD (n = 54; 72%) was 731 days, as compared to 426 days for patients without GvHD (n = 21; 28%). Post HSCT pneumococcal concentration was not correlated with the presence of GvHD before vaccination ($r = -0.034$, $p = 0.83$). In addition, 15 (15%) patients were using prednisone and 38 (37%) patients were using

antibiotics at the time of vaccination, but none of them developed a pneumococcal infection.

Serotype-specific antibody assessment

Blood samples for measurement of antibody concentrations were collected in 39/103 (38%) patients. PCV13 serotype specific antibody responses were measured in 39 (38%) patients, while PPSV23 serotype specific antibody responses, measured one year after the PCV13 responses, were available for 30 (29%) patients. Good antibody responses against PCV13 serotypes varied from a minimum of 30/39 (77%) for serotype 5 to a maximum of 37/39 (95%) for serotype 19F (Fig. 1). Across all PCV13 serotypes, sufficient seroprotection as defined earlier was demonstrated in 33/39 (85%) patients.

Fig. 2 shows the results obtained for the 10 additional PPSV23 serotypes that are not covered by PCV13. The response to several of these PPSV23 serotypes was found to be lower compared to serotypes included in PCV13. The lowest responses were observed for serotypes 11 (12/30, 60%) and 12F (7/30, 23%), respectively.

Table 2: Allo-HSCT patient characteristics.

Variables	**Cases (*n = 103)***
Age at transplantation (range)	50 (16-68)
Mean age in years	
Sex (%)	
Male	52/103 (50)
Female	51/103 (50)
Underlying condition (%)	
Acute leukemia	74/103 (72)
Other	29/103 (28)
HSCT donor[1] (%)	
MUD	49/103 (48)
SIB	44/103 (43)
CB	8/103 (8)
Comorbidities (%)	
GvHD	70/103 (68)
Post-transplant care (%)	
Prednison[2]	15/103 (15)
Antibiotics	38/103 (37)
Antibody concentration measurements (%)	
No	61/103 (59)
Yes	42/103 (41)

Abbreviations: MUD, matched unrelated donor; SIB, sibling; CB, cord blood.

[a] Both myeloablative (MA) and non-myeloablative (RIST). In one patient, the transplant type was not described in the dossier.

[b] More than 10 mg a day or more than 700 mg in 2 weeks.

Figure 1: Protection against PCV13 serotypes (n = 39) following the MATCH protocol. Post-vaccination antibody concentrations were measured 4–6 weeks after the final (PPSV23) vaccination.

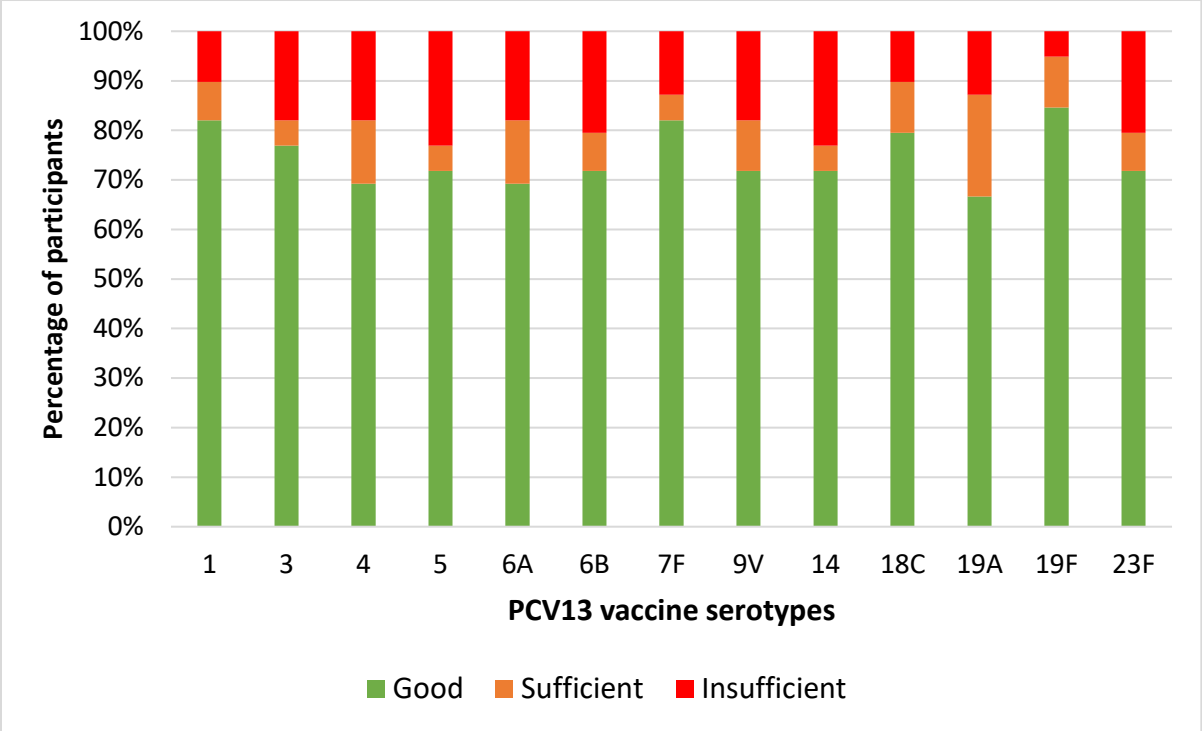

Figure 2: Protection against PPSV23 serotypes not included in PCV13 (n = 30) following the MATCH protocol. Post-vaccination antibody concentrations were measured 4–6 weeks after the final (PPSV23) vaccination.

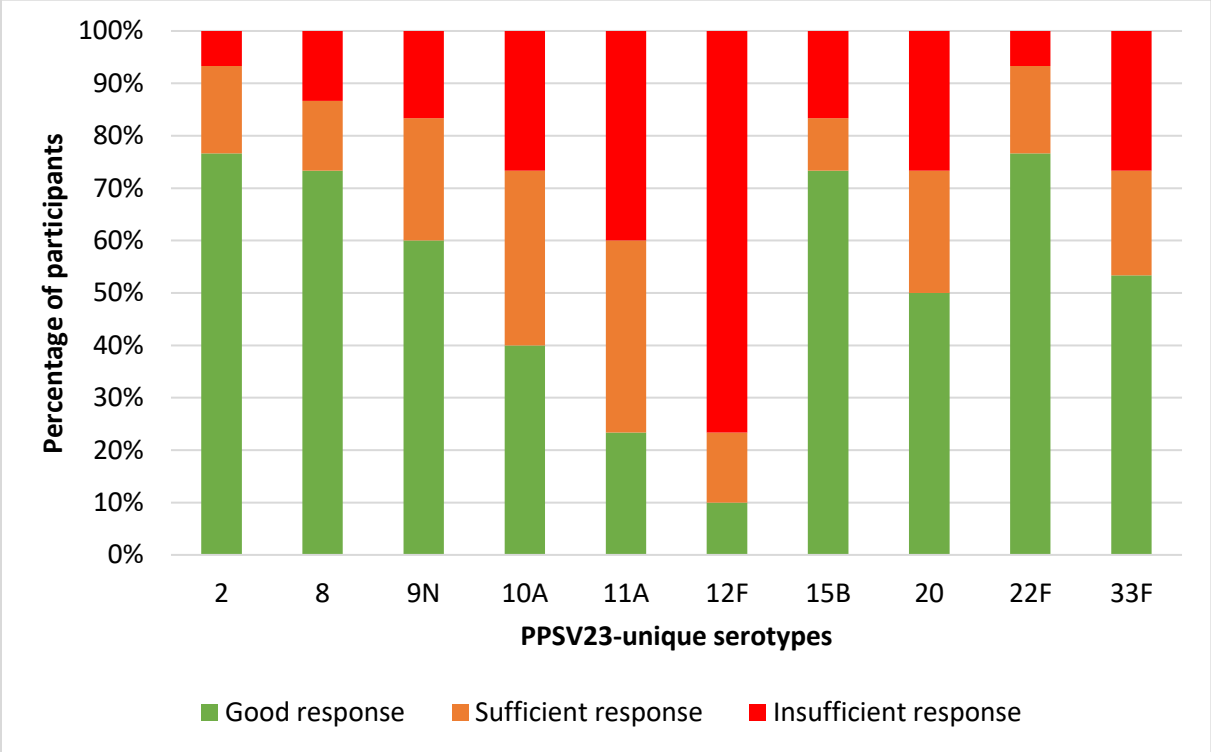

Table 3: Literature overview on immunogenicity in allo-HSCT recipients.

Study	Year	Design	Study Participants, No. Patients	Controls	Vaccine Regimen	Immunization schedule after HSCT	Vaccine-Antibody Measurement Interval	Primary Outcome	Protection Rate, %	Cut-off Values, µg/mL
Molrine et al [13]	2003	Randomized controlled trial	30	35	PCV7	3x PCV7 at 3, 6 and 12 mo	4 wk	Seroprotection	64	PVL ≥0.50
Meerveld-Eggink et al [21]	2009	Clinical trial	26	n/a	PCV7 PPSV23	2x PCV13 (1 yr +2 wk and +8 wk) 1x PPSV23 (+26 wk)	NR	Seroprotection	85	Protection against ≥3 serotypes
Cordonnier et al [22]	2009	Randomized clinical trial (multicentre)	158	n/a	PCV7 PPSV23	3x PCV7 (3 or 6 mo) 1x PPSV23 (12 or 18 mo)	1 mo	Early vs. late post allo-HSCT immunization	*1.* 79 (PCV7) *2.* 82 (PCV7)	PVL ≥0.15
Cordonnier et al[a] [15]	2010	Randomized clinical trial (multicentre)	101	n/a	PCV7 PPSV23	3x PCV7 (3 or 6 mo) 1x PPSV23 (12 or 18 mo)	1 mo	Early vs. late post allo-HSCT immunization	*1.* 88 (PPSV23) 2. 69 (PPSV23)	PVL ≥0.15
Cordonnier et al[a] [23]	2015	Randomized prospective trial (multicentre)	30	n/a	PCV7 PPSV23	3x PCV7 (3 or 6 mo) 1x PPSV23 (12 or 18 mo)	1 mo	Seroprotection	66	PVL ≥0.15
Cordonnier et al [6]	2015	Open-label clinical trial (multicentre)	251	n/a	PCV13 PPSV23	3x PCV13 (3 or 6 mo) 1x PPSV23 (12 or 18 mo)	1 mo	Seroprotection	After dose 3: 89-98 After dose 4: 83-99	PVL ≥0.35

Abbreviations: NR, not reported; PVL, post-vaccination level; mo, months, wk, weeks; yr, years; n/a, not applicable.

[a] Surviving patients of the cohort of Cordonnier et al (2009).

IPD episodes

Of 103 included patients, seven (7%) developed microbiologically confirmed IPD, of whom three (43%) had early IPD and four (57%) had late IPD. The median time to the occurrence of early IPD was 6 (range 4–8) months and of late IPD 56 (range 12–91) months post allo-HSCT. All pneumococcal infections within the first year occurred despite antimicrobial prophylaxis during this period. In addition to these 7 patients with confirmed IPD, 14/103 (14%) patients were diagnosed with pneumonia without microbial testing results, some of which probably also caused by S. pneumoniae as this is the most common cause of community-acquired pneumonia. Taken together, an estimated 7–21/103 (7–20%) of patients developed IPD.

Literature review

We performed a literature search, initially yielding 100 articles, narrowed down to six relevant studies after exclusion criteria were applied (Table 3). Among the included studies, four described the serologic response to pneumococcal vaccinations in allo-HSCT recipients, and two studies investigated the immunogenicity of early versus late vaccination after allo-HSCT.

Among the four studies on post allo-HSCT serologic response rates, protection varied from 64 to 99%, depending on the vaccine types, time intervals between allo-HSCT and revaccination, and the used definition of the correlate of protection (12, 15, 19). Two studies assessed the effect of early versus late post allo-HSCT vaccination. Both found similar antibody responses after early (3 months) and late (9 months) vaccination. These responses were however not maintained: two years after allo-HSCT, 26/44 (59%) early vaccinated patients still had adequate antibody concentrations compared to 35/42 (84%) later vaccinated patients ($p = 0.013$) (14, 20). Two studies by Cordonnier (14, 20), derived from the same patient cohort, assessed the effect of early versus late post allo-HSCT vaccination. Both found similar results.

Discussion

Summary of main findings

Allo-HSCT recipients mounted sufficient immune responses to PCV13 vaccination, with an overall protection rate of 85%; provided that these patients were vaccinated >1 year after allo-HSCT and were not treated with immunosuppressive medication at the time of vaccination. These results were comparable to the results obtained from our literature search. The finding that 15% of allo-HSCT recipients did not develop adequate antibody responses underscores the importance of routine post-vaccination antibody measurements, to identify patients without protection by vaccination. In addition, regular follow-up concentration measurements are important, because immunity can disappear more quickly than in the healthy population. It should be noted that vaccination confers protection against the 23 most prevalent serotypes of around 90 distinct pneumococcal serotypes that have been identified to date. As a consequence, even in the presence of adequate post-vaccination immunity, patients could still develop IPD caused by a non-vaccine serotype. Furthermore, since the

measurement of antibodies is a derivative of protection; theoretically, IPD by a vaccine strain could still occur. The clinical vignette illustrates that both unrecognised antibody decline and vulnerability to non-vaccine strain pneumococcal serotypes pose a real and possibly mortal risk to this group of patients. Based on the literature, antibody decline seems to occur at a faster pace when patients are vaccinated relatively early (3 months) after allo-HSCT. Because the initial antibody response to vaccination was similar in early vs. late vaccinated patients, early vaccination followed by a booster vaccination strategy from 1 year post allo-HSCT may therefore be an attractive option. The efficacy and safety of such an approach does however require confirmation through prospective studies.

Early vs. late vaccination

The optimal time-interval between allo-HSCT and the start of routine vaccinations with PCV13 is controversial. Early immunization offers an earlier protection and may avoid life-threatening IPD shortly after allo-HSCT, but is also associated with a lower antibody response and faster decline of antibody concentrations during the second year after transplantation. By contrast, late immunization offers better chances of achieving adequate antibody concentrations and a better long-lasting immunity, but the price is inadequate protection in the vulnerable time period early after transplantation (14). The high clinical impact of IPD is emphasized by our finding of a 7% rate of confirmed IPD, possibly increasing to 20% when unconfirmed cases were included, reflecting a considerable underestimation in clinical practice.

The estimated incidence of IPD in allo-HSCT recipients is 347 infections per 100,000, compared to an incidence of 7 per 100,000 persons in the general population (21). Almost half of the IPD cases occurred during the first year after transplantation, despite the fact that patients still used antimicrobial prophylaxis, which underscores the importance of optimal protection in this time period (4, 22, 23). The clinical impact of early IPD is high: one study reported a mortality of 2/7 (29%) in patients with early IPD, versus 8/44 (18%) in patients with late IPD (2). These findings suggest that the best vaccination strategy would be to start earlier rather than later after allo-HSCT. Therefore, we propose a vaccination schedule that combines the advantages of early and late vaccination, in which the first PCV13 is administered 4–6 months post allo-HSCT, followed by two PCV13 booster vaccinations with a 1-month interval, then a fourth PCV13 vaccination 6 months after the previous PCV13 dose, and subsequently one PPSV23 vaccination 2 months later (Table 1). The theoretical groundwork for this schedule is supported by the recent study of Cordonnier et al. that provides evidence of a higher antibody response after the administration of an additional fourth PCV13 vaccination (15). Based on the results of our serological data in combination with the findings from the literature review, we hypothesize that this fourth vaccination would be most effective when administered ≥6 months after the previous PCV13 vaccination. The postponed timing of this last PCV13 vaccination will elicit a late booster response, when immune reconstitution has evolved further, leading to a stronger and longer-

lasting immune response. However, this regimen needs to be evaluated in clinical practice.

Late IPD was often associated with GvHD (2, 24). It is important to note that vaccinations are often delayed when allo-HSCT recipients develop GvHD, firstly because this complication is treated with immunosuppressive medication and secondly because of fear that vaccinations may trigger or aggravate GvHD. The immunosuppressed state associated with GvHD renders patients exceptionally vulnerable to IPD, which makes adequate protection all the more important. In our study, 70 (68%) patients were diagnosed with GvHD, with a median time of around 2 years between transplantation and pneumococcal vaccination. Another study reported a median time of 1.3 years, in which only 35% of patients had started the vaccination schedule at 1 year after allo-HSCT, for similar reasons as in our study (19). In this context, we advise to vaccinate patients with GvHD. Furthermore, it has been suggested that hyporesponsiveness to PPSV23 can occur after repeated vaccinations at short time intervals (25). Therefore, more research is required to determine dynamics and protective levels of anti-serotype antibodies at regular time-intervals in this patient population.

PCV13 vs. PPSV23

We found lower protection rates against PPSV23 serotypes compared to PCV13 serotypes, with very low protection against PPSV23 serotype 12F. Although this finding may be an intrinsic flaw in the diagnostic panel, a more logical explanation is that PPSV23 is indeed less immunogenic compared to PCV13, which is supported by previous studies (12-15, 26). We hypothesize that in a setting of nascent immunity after allo-HSCT, T-cell independent vaccines such as PPSV23 do not work that well in this patient population, similar to the situation in small children (11). The main advantages of PPSV23 vaccination are that more serotypes are included than in PCV13, and that this vaccination is thought to act as a booster of the immune response to the PCV13 serotypes (27).

Antibody measurements

In our study, antibody concentration measurements were only performed in 39/103 (38%) patients. Reasons for this rate of attrition are unknown. Assuming that this is rule rather than exception in clinical practice, increased awareness among health care providers about the risks of insufficient or fading protection is needed, which was also emphasized in recent work of Cordonnier et al., who stressed the importance of routine individual assessments of vaccine serotype antibodies to identify and possibly revaccinate non-responders (28). We have therefore included specific time intervals for antibody measurements in our new guideline.

Correlates of protection

In the international literature, there is no consensus on the exact correlates of protection, nor on the required number of reactive serotypes in response to

vaccination. For allo-HSCT recipients, reported cut-off concentrations differ between an absolute increase to ≥0.15–1.3 µg/mL or a ≥2–4-fold increase in antibody concentrations (12, 14, 15, 19, 20, 29-31). The definition of the required number of reactive serotypes varies between five and eight (32). Internationally accepted reference intervals would therefore be very useful to identify and compare patients with inadequate post-vaccination pneumococcal antibody responses.

Conclusion

In conclusion, although few studies have been performed in which the optimal time intervals of pneumococcal immunizations are determined, we propose a uniform immunization schedule for allo-HSCT recipients, which combines the advantages of early and late vaccination (Table 1). We recommend starting the immunization schedule 4–6 months following allo-HSCT with three early PCV13 vaccinations, followed by a late PCV13 booster vaccination and a vaccination with PPSV23. The evidence base of our vaccination recommendation is weak at best. However, this also applies to the currently accepted guidelines (33). Clearly, more research on this topic is needed. That none withstanding, we feel that this recommendation is a more logical extrapolation from the limited evidence to date. We have introduced this vaccination schedule in two academic hospitals in Amsterdam, The Netherlands, and we will evaluate the immunogenicity of this schedule prospectively.

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APPENDIX (AVAILABLE ONLINE)

Supplementary File 1: Clinical vignettes

Supplementary File 2: Search strategy

Section 2

Immunocompromised Travellers

Chapter 6

Pre-travel care for immunocompromised and chronically ill travellers: A retrospective study

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Abstract

BACKGROUND: Immunocompromised and chronically ill travellers (ICCITs) are susceptible to travel related diseases. In ICCITs, pre-travel care regarding vaccinations and prophylactics is complex. We evaluated the protection level by preventive measures in ICCITs by analysing rates of vaccination protection, antibody titres, and the prescription of standby antibiotics.

METHODS: We analysed, and reported according to STROBE guidelines, pre-travel care data for ICCITs visiting the medical pre-travel clinic at the Academic Medical Centre, The Netherlands from 2011 to 2016. Results: We analysed 2104 visits of 1826 ICCITs. Mean age was 46.6 years and mean travel duration 34.5 days. ICCITs on immunosuppressive treatment (29.7%), HIV (17.2%) or diabetes mellitus (10.2%) comprised the largest groups. Most frequently visited countries were Suriname, Indonesia, and Ghana. Most vaccination rates were >90%. Of travellers in high need of hepatitis A and B protection, 56.6 and 75.7%, underwent titre assessments, respectively. Of ICCITs with a respective indication, 50.6% received a prescription for standby antibiotics.

CONCLUSION: Vaccination rates in our study population were overall comparable to those of healthy travellers studied previously in our centre. However, regarding antibody titre assessments and prescription of standby antibiotics, this study demonstrates that uniform pre-travel guidelines for ICCITs are highly needed.

Introduction

The number of immunocompromised and chronically ill travellers (ICCITs) has increased over the past decades (1, 2). Novel therapies improve patients' capacity to lead active, 'normal' lives, including travelling. In turn, those may put ICCITs at increased risk of travel related disease and a complicated disease course (3, 4). Travellers' diarrhoea (TD), which among healthy travellers already has an estimated incidence between 20-50%, may, rather than in healthy travellers, more easily lead to severe complications such as dehydration (5, 6). Furthermore, ICCITs are at increased risk of acquiring general (severe) health problems whilst travelling (5, 7). For those reasons, pre-travel guidelines recommend to prescribe standby antibiotics for certain patient groups and for patients to start treatment when experiencing first symptoms of intestinal infection (8, 9). However, evidence for this recommendation has not been established (7, 10).

Adequate pre-travel care possibly reduces travel related disease risks. Guidelines recommend to vaccinate against vaccine preventable diseases and to assess hepatitis A (hepA) and B (hepB) antibody titres regularly in immunocompromised travellers (ICTs), as studies showed that approximately 25% of ICTs did not develop protective antibodies after hepA vaccination and that the durability of protection was impaired(8, 11-13). Regarding rabies, immunoglobulins are routinely required as post-exposure treatment, despite adequate pre-exposure vaccinations (14, 15). Life-attenuated vaccines (e.g. yellow fever (YF)) are contra-indicated in ICTs, because of the risk of vaccine-associated neurotropic and viscerotropic disease (16).

To date, little research has been carried out concerning pre-travel care for ICCITs; consequently, few (supra)national pre-travel guidelines for ICCITs exist. As a first step forward, we describe characteristics of ICCITs regarding travel destination and duration, and analyse the frequency of prescription of standby antibiotics and the measurement of post-vaccination protection rates by antibody titre assessment.

Methods

We analysed data on pre-travel advice for ICCITs regarding vaccination and prescription of standby antibiotics. We report according to STROBE (Strengthening the Reporting of Observational studies in Epidemiology) guidelines (17).

We analysed data of ICCITS from 0-90 years of age who visited the medical travel clinic of the Centre of Tropical Medicine and Travel Medicine (TC) of the Academic Medical Centre (AMC), Amsterdam, the Netherlands, from May 2011 to May 2016. A patient's record could not be taken up in the analysis if information was lacking, or if a patient visited the travel clinic for other reasons than pre-travel counselling.

Visits for a different travel episode were handled as separate inclusions because travel destination, travel duration, vaccination indication, and medication use may differ at different time points; whereas repeated visits in preparation for a single travel episode counted as single inclusion.

Outcomes

The primary outcome was protection to exposure ratio (P/E) for each vaccination (see definitions). Secondary outcomes were P/E for malaria chemoprophylaxis; ratio of antibody titre assessments and total number of patients with an indication for this assessment (A/I); ratio of prescription of standby antibiotics and total number of patients with an indication for this prescription (P/I).

Definitions

To analyse P/E we used the definition applied by Wieten et al. (2014), defining P/E as the number of protected travellers (P) divided by the total number of travellers to disease endemic countries where vaccination is recommended according to the LCR guideline (E) (8).

Protection was defined as (1) having pre-existing antibodies either through vaccination or through a medical history of the vaccine-preventable disease, or (2) having received vaccination at a time that a protective immune response should still be present according to manufacturers' Summary of Product Characteristics or prescribed chemoprophylaxis on date of departure.

We defined P/I as the number of patients who received a prescription for a standby antibiotic during travelling, divided by the total number of patients with an indication for this prescription; and A/I as the number of patients in whom an antibody titre was assessed, divided by the total number of patients with such an indication, both according to the LCR (National Coordination Centre for Traveller's Health) and supported by other travel health guidelines (Table 1 for an overview of recommendations) (8, 18, 19). Antibody titre assessment was recorded as 'yes' if the antibody titre was assessed at any time before travelling.

Data collection

We collected data on a patient's medical history, medications, travel itineraries and duration, and vaccination status regarding the diphtheria/tetanus/polio combination vaccine (DTP), hepA, hepB, YF, typhoid fever – inactivated injectable - (TF), and rabies vaccines, from Epic® (1979 Milky Way, Verona, United States of America), an electronic patient dossier for clinical care. If a patient's medical record included information on antibody titre(s), laboratory results were checked. If a medical record yielded insufficient information, we checked for additional information in Orion® (WKM Business Software BV, Assen, the Netherlands), a client database for registration of vaccinations, and for malaria chemoprophylaxis.

Indication for vaccination and malaria chemoprophylaxis

We divided indications for vaccination in two categories; (1) vaccines against diseases endemic in certain countries (DTP, hepA, YF, and TF vaccines), recommended when travelling to these countries; and (2) vaccines against low incidence/high impact diseases (rabies and hepB), recommended for travellers with specific high-risk itineraries or high risk activities (8, 9).

Table 1: Overview of patient categories and recommendations concerning vaccines, standby antibiotics and titre assessment (8, 9).

Underlying disease/ medication use	Special recommendation	Contra-indication live attenuated vaccines	Standby-antibiotics indicated	Titre assessment indicated
1. HIV (CD4 count < 200)	Double doses of hepB vaccine	Yes	Yes	Yes
2. HIV (CD4 count 200-500)		t.b.c.	t.b.c.	No
3. HIV (CD4 count > 500)		No	No	No
4. (Functional) asplenia		No	Yes	No
5. HSCT		Yes	Yes	Yes
6. Primary immune disease	Vaccination in specific cases not useful	Yes	Yes	Yes
7. Autoimmune disease (immunosuppressive treatment)		Yes	Yes	Yes
8. SOT (immunosuppressive treatment)		Yes	Yes	Yes
9. Use of vitamin K antagonists/NOACs/coagulation disorder	Subcutaneous administration of vaccine	No	No	Yes
10. Allergy for any substance in the vaccine		No	No	No
11. IDDM		No	t.b.c.	No
12. Severe renal impairment/haemodialysis	Double doses of hepB vaccine	No	t.b.c.	t.b.c.
13. Severe liver disease	hepA and/or hepB	No	No	No
14. "Remaining"				

Legend

Yes: contra-indication for live attenuated vaccines; standby-antibiotics and titer assessment indicated

No: live attenuated vaccines can be administered safely; standby-antibiotics and titer assessment not indicated

Contra-indication for live attenuated vaccines; standby-antibiotics and titer assessment indicated to be considered (t.b.c.)

Regarding TF as well as YF vaccination and malaria prophylaxis, a distinction was made between high-risk (1) versus low-risk (2) countries (8). For T1 areas, TF vaccination is recommended for all travellers with a travel duration ≥ two weeks, and for T2 areas, when travel duration is ≥ three months or when a certain risk factor for TF is present in an individual patient (for example the use of a proton pump inhibitor) (8). For M1 areas, malaria chemoprophylaxis is routinely recommended; whereas for

M2 areas, this depends on itineraries to endemic regions within these countries and on seasonal transmission risk (8). In both YF1 (high transmission risk) and YF2 (low transmission risk) areas, YF vaccination is recommended, for which in YF2 areas this holds unless there is a relative contra-indication (8).

Geographical destination

We grouped travel destinations into geographical regions as defined by the United Nations Geoscheme (20).

Categories of underlying disease

Because the indication for vaccination, titre assessment and prescription of standby antibiotics may differ per underlying disease or medication use, we categorised our study population in 14 different groups (Table 1) (Box 1).

Box 1: Description of underlying diseases/medication use

	Description of underlying diseases/ medication use
(Functional) asplenia	Splenectomy, congenital asplenia, asplenia due to trauma, sickle cell disease, thalassemia
HSCT	Autologous or allogenic hematopoietic HSCT
Primary immune disease	Common variable immune disease, IgG subclass deficiencies, a/hypogammaglobulinemia
Autoimmune disease (immunosuppressive treatment)	Rheumatoid arthritis, inflammatory bowel disease, psoriasis, sarcoidosis, autoimmune hepatitis, multiple sclerosis etc.
SOT (immunosuppressive treatment)	Transplantation of kidney, liver or lung
Use of vitamin K antagonists/ NOACs/ coagulation disorder	Treatment with vitamin K antagonists or NOACs, Von Willebrand disease, haemophilia, thrombocytopenia etc.
(Suspected) allergy for any substance in the vaccine	Egg yolk allergy, formaldehyde, Neomycin, Thiomersal history of allergic reaction to vaccination
IDDM	Diabetes mellitus type I or II
Severe renal impairment/haemodialysis	Chronic renal insufficiency, nephrotic syndrome, minimal change nephropathy, IgA nephropathy, multiple myeloma etc.
Severe liver disease	Liver cirrhosis, Chronic hepatitis B or C
Remaining	Hypertension, Parkinson's disease, asthma, COPD, autoimmune disease not treated with immunosuppressive drugs, multiple sclerosis, history of carcinoma, cardiovascular disease, pregnancy, glaucoma, epilepsy etc.

Data analysis

We performed statistical analyses using SPSS version 23.0 for Windows®. We used a 0.05 alpha level for significance. We reported mean and standard deviations (SD) for continuous data with normally distributed variables. We compared patient categories

with all other participants; male to female, and younger and older adults to other participants. We used the Chi-square test for categorical, and the T-test for continuous normally distributed variables to compare baseline characteristics. We used the Mann-Whitney U test for not normally distributed continuous variables and the Chi-square test for significant differences in P/E; P/I; A/I. Fisher's exact test was used if the value in any of the cells of the contingency table was below five. We assessed odds ratios with a 95% confidence interval for P/E, A/I, and P/I.

Ethical approval

This data analysis did not require approval of the AMC ethics committee (written confirmation of the ethics committee with the authors).

Results

Baseline characteristics

In total, 2,383 patients visited the AMC medical pre-travel clinic. We excluded 557 patients, of which 401 visited for other reasons than pre-travel care. For 156 patients, documentation was insufficient.

We analysed 2,104 visits of 1826 ICCITs (Box 1; Table 2). We categorised patients according the immunocompromised or chronic condition leading to specific pre-travel recommendations (Table 1). Baseline characteristics are depicted in Table 2. Young adults, ICCITs on immunosuppressive treatment (autoimmune disease), those with post-vaccination allergic reactions, and ICCITs in the 'remaining' group (Table 2) were significantly more often female. Older adults, ICCITs with HIV and with a coagulation dysfunction (due to anticoagulant treatment or a coagulation disorder) were more often male.

Mean age was 46.6 years. ICCITs with insulin dependent diabetes mellitus (IDDM); severe renal impairment or haemodialysis, those with a coagulation dysfunction, and ICCITS in the "remaining" group were significantly older. ICCITs with HIV (CD4>500), with (functional) asplenia, vaccine allergy, and ICCITs on immunosuppressive treatment (autoimmune disease) were significantly younger (Table 2).

Table 2: Baseline characteristics of study population

General groups	N (%)	Age (SD)	p[a]	Male (%)	Female (%)	p[b]	Travel duration (SD)	p[a]	Travel destination (n; %)
All ICCITs (%)	2,104	46.6 (17.5)		968 (46.0)	1136 (54.0)	N a	34.5 (62.6)		Suriname (239; 11.4), Indonesia (220; 10.5), Ghana (187; 8.9)
Male (%)*	968 (46.0)	**47.4 (18.0)**	**.014**	N a	N a	N a	36.8 (75.4)	.053	Indonesia (108; 11.2), Suriname (103; 10.6), Ghana (90; 9.3)
Female (%)**	1136 (54.0)	45.8 (17.1)		N a	N a		32.5 (48.9)		Suriname (136, 12.0), Indonesia

									(112, 9.9), Ghana (97, 8.5)
Young adults (%) 18-29 years old	252 (12.0)	24.3 (3.1)	N a	**100 (39.7)**	**152 (60.3)**	**.032**	47,4 (74.9)	.081	Indonesia (24; 9.5), Suriname (23; 9.1), Turkey (18; 7.1)
Older adults (%) >60 Years old	537 (25.5)	66.8 (5.5)	N a	**267 (49.7)**	**537 (50.3)**	**.045**	35.8 (87.4)	.663	Indonesia (73; 13.6), Suriname (65; 12.1), India (37; 6.9)
Patient categories									
1. HIV (CD4 count < 200)	11 (0.5)	47.8 (9.7)	.594	**10 (90.9)**	**1 (9.1)**	**.003**	**44.3 (24.1)**	**.011**	All different countries
2. HIV (CD4 count 200-500)	106 (5.0)	45.9 (10.4)	.126	**68 (64.2)**	**38 (35.8)**	**.000**	**41.2 (54.0)**	**.001**	Ghana (23; 21.7), Nigeria (7; 6.6), Suriname (5; 4.7)
3. HIV (CD4 count > 500)	246 (11.7)	**42.7 (13.2)**	**.000**	**147 (59.8)**	**99 (40.2)**	**.000**	**38.9 (62.9)**	**.000**	Ghana (36; 14.6), Nigeria (18; 7.3), Suriname (17; 6.9)
4. (Functional) asplenia	141 (6.7)	**31.4 (22.2)**	**.000**	71 (50.4)	70 (49.6)	.284	38.1 (57.9)	.075	Ghana (27; 19.1), Suriname (26; 18.4), Indonesia (12; 8.5)
5. HSCT	37 (1.7)	51.5 (14.2)	.073	15 (40.5)	22 (59.5)	.501	**19.2 (16.6)**	**.000**	Indonesia (6; 16.2), Turkey (5; 13.5%), Egypt/Morocco (3; 8.1%)
6. Primary immune disease	24 (1.1)	40.1 (17.7)	.065	7 (29.2)	17 (70.8)	.096	29.2 (35.0)	.274	Indonesia (5; 20.8), Thailand (5; 20.8), all different countries
7. Autoimmune disease (immunosuppressive treatment)	466 (22.1)	**44.9 (16.1)**	**.008**	**161 (34.5)**	**305 (65.5)**	**.000**	34.9 (59.6)	.080	Indonesia (52; 11.2), Suriname (45; 9.7), Thailand (34; 7.3)
8. SOT (immunosuppressive treatment)	160 (7.6)	46.5 (14.7)	.638	76 (47.5)	84 (52.5)	.710	40.8 (SD 145.0)	.525	Turkey (25; 15.6), Suriname (24; 15.0) Indonesia/Morocco (13; 8.1)
9. Use of vitamin K antagonists/NOACs or coagulation dysfunction	117 (5.6)	**56.1 (17.2)**	**.000**	**77 (63.6)**	**44 (36.4)**	**.000**	32.4 (SD 40.2)	.097	Indonesia (14; 11.6), India (11; 9.1), Thailand/Turkey (7; 5.8)
10. Allergy for any substance in the vaccine	101 (4.8)	**32.7 (20.1)**	**.000**	**31 (30.7)**	**70 (69.3)**	**.002**	27.1 (24.7)	.222	Suriname (16; 15.8), Tanzania (6; 5.9), Thailand/Brazil (5; 5.0)
11. IDDM	215 (10.2)	**54.7 (13.8)**	**.000**	97 (45.1)	118 (54.9)	.782	**33.7 (37.7)**	**.014**	Suriname (49; 22.8), Ghana (35; 16.3), Indonesia (28; 13.0)

12. Severe renal impairment/haemodialysis	44 (2.1)	**52.2 (15.4)**	**.021**	23 (52.3)	21 (47.7)	.399	24.6 (15.1)	.883	Suriname (13; 29.5), Ghana (9; 20.5), Turkey (5; 11.4)
13. Severe liver disease	23 (1.1)	**52.1 (14.2)**	**.161**	15 (65.2)	8 (34.8)	.063	**41.0 (37.7)**	**.011**	Ghana (6; 26.1), Brazil (4; 17.4), Cambodia/Indonesia (3; 13.0)
14. Remaining	397 (18.9)	**51.5 (17.8)**	**.000**	**162 (40.6)**	**237 (59.4)**	**.016**	**30.7 (44.0)**	**.007**	Indonesia (59; 14.8), Suriname (35; 8.8), Thailand (27; 6.8)

* P-value compared to female. **P-value compared to male. a Mann Whitney U test used. b Chi-square test used.

Travel duration and destination

Mean travel duration among all participants was 34.5 days, but varied widely (SD 62.6 days).

Travel duration of HIV patients was significantly longer (mean travel duration 38.9, 41.2, and 44.3 days in the different HIV groups, respectively), and of patients with a hematopoietic HSCT (HSCT) history significantly shorter (19.2 days, p=0.000) (Table 2). Most frequently visited countries were Suriname, Indonesia, and Ghana. Most visited regions were Southeast Asia, South America, and West Africa.

For ICCITs with stem cell or solid organ transplant (SOT) recipients, Egypt, Morocco, Turkey, and Indonesia were particularly popular destinations. ICCITs with HIV travelled less often to Indonesia and more often to Nigeria, corresponding with around 50% of them visiting Eastern and Western Africa (Table 2, Figure 1).

Figure 1: Distribution of visits per region per patient category

Figure 1A: All participants

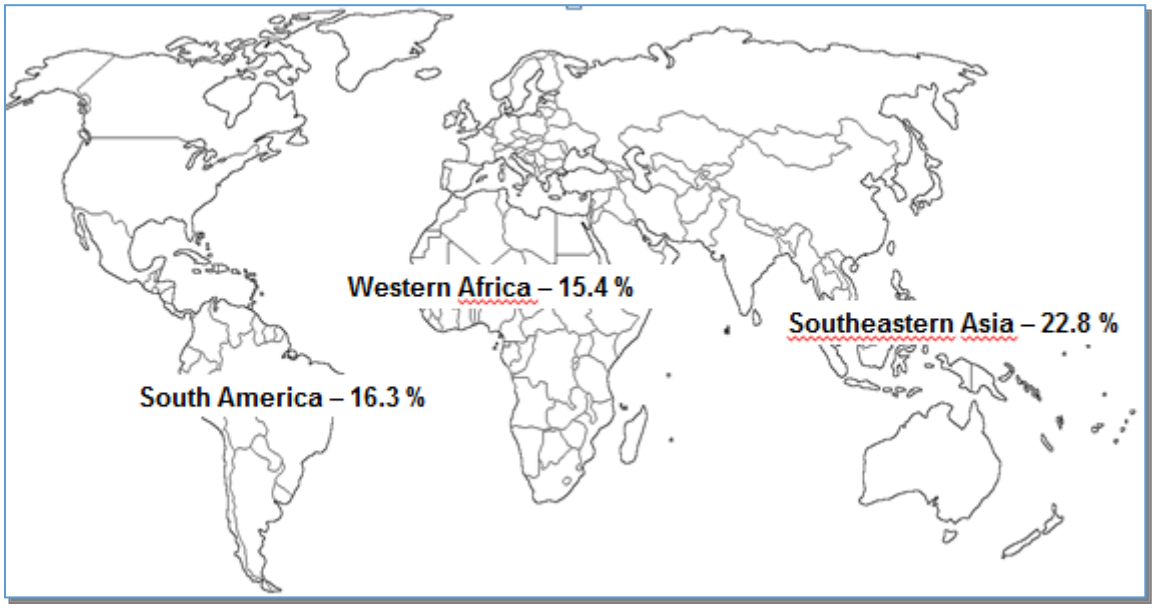

Figure 1B: HIV CD4 < 200 (n=11)

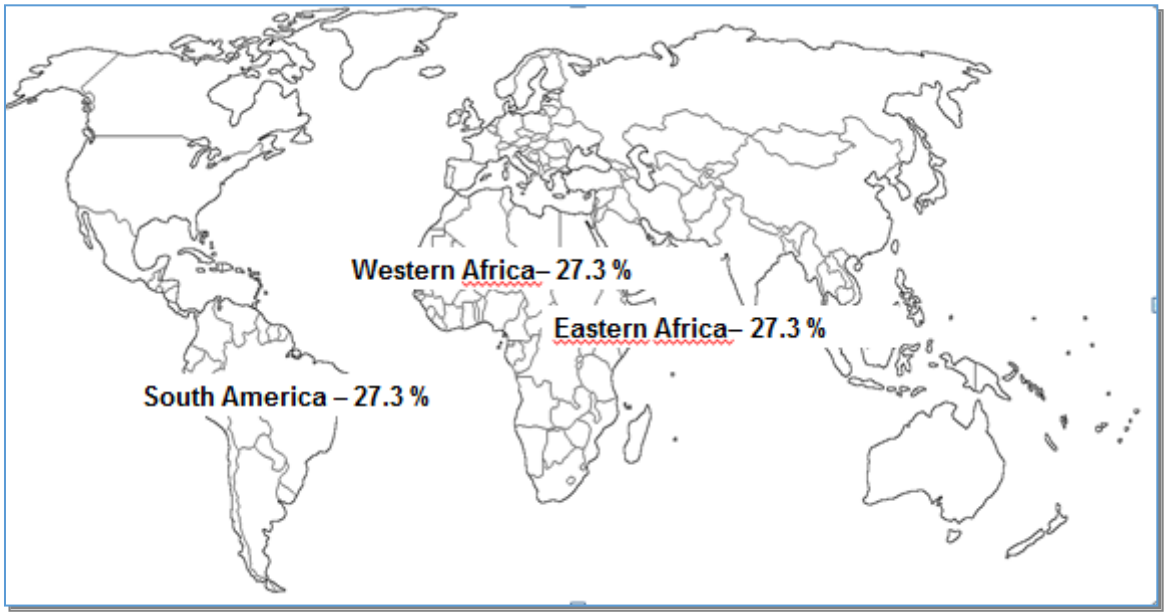

Figure 1C: HIV CD4 200-500 (n=106)

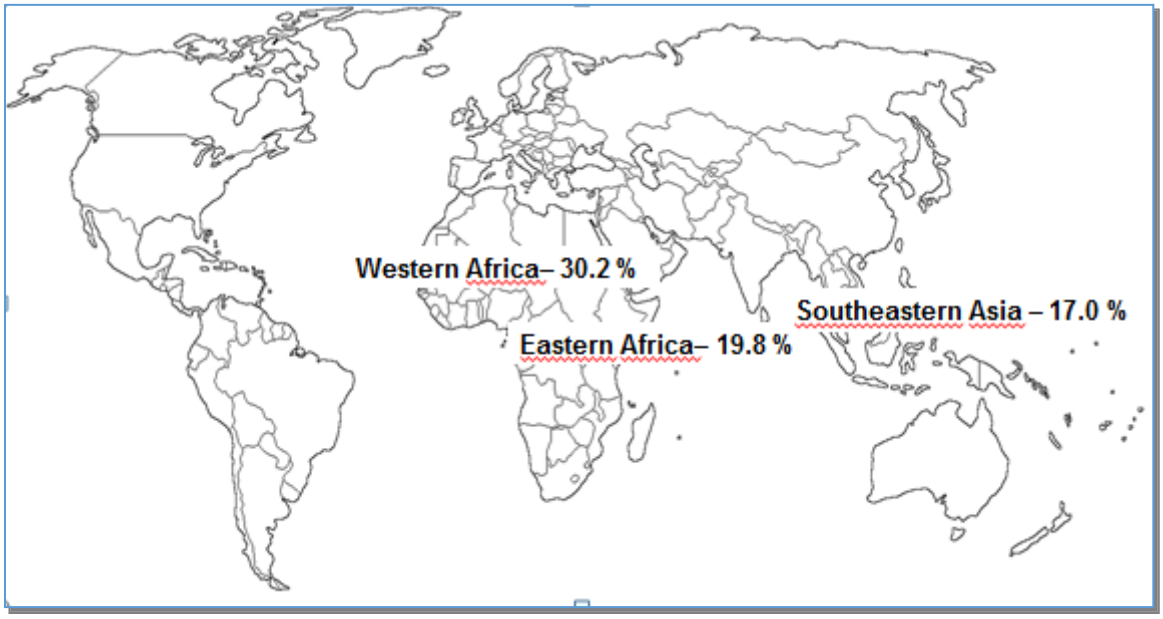

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Figure 1D: HIV CD4 > 500 (n=246)

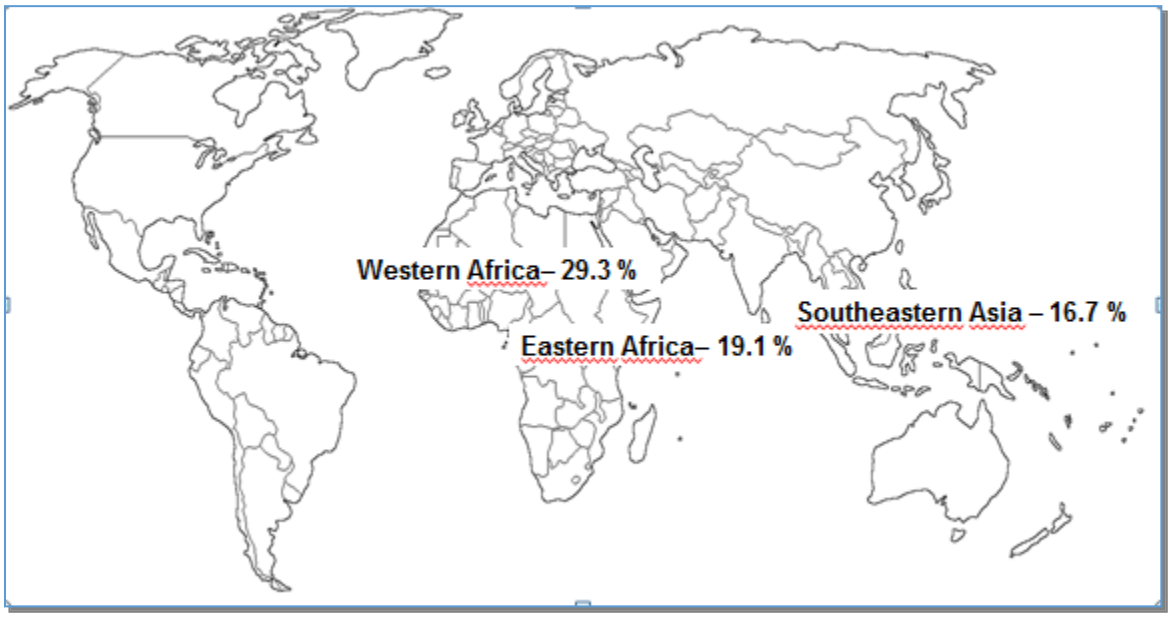


Figure 1E: (Functional) asplenia (n=141)

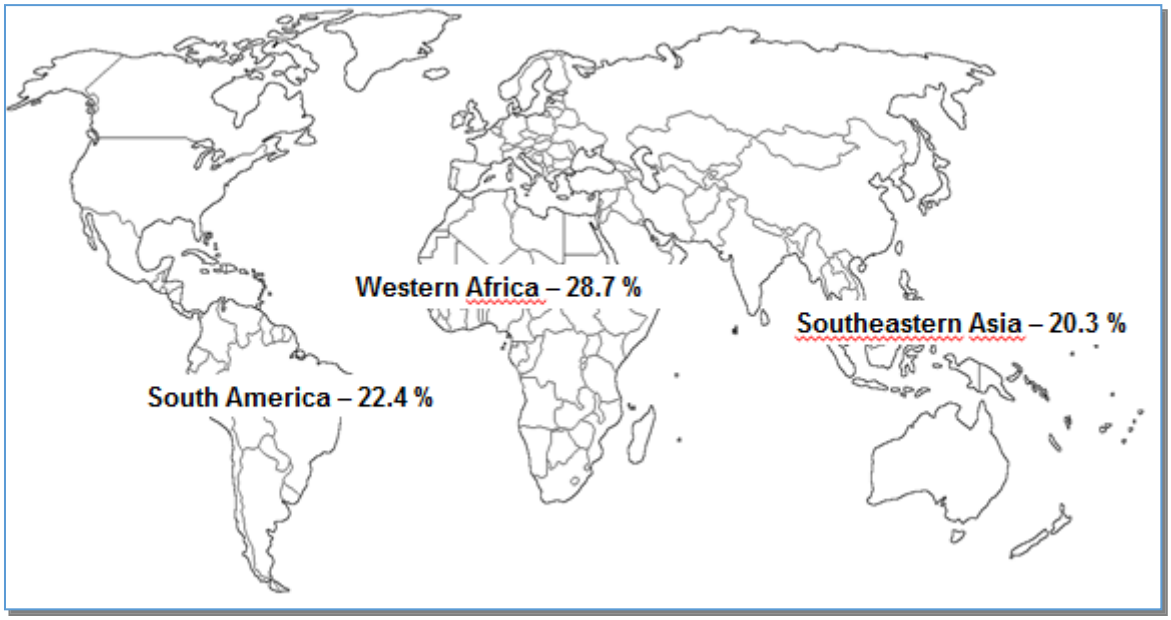


Figure 1F: HSCT (n=37)

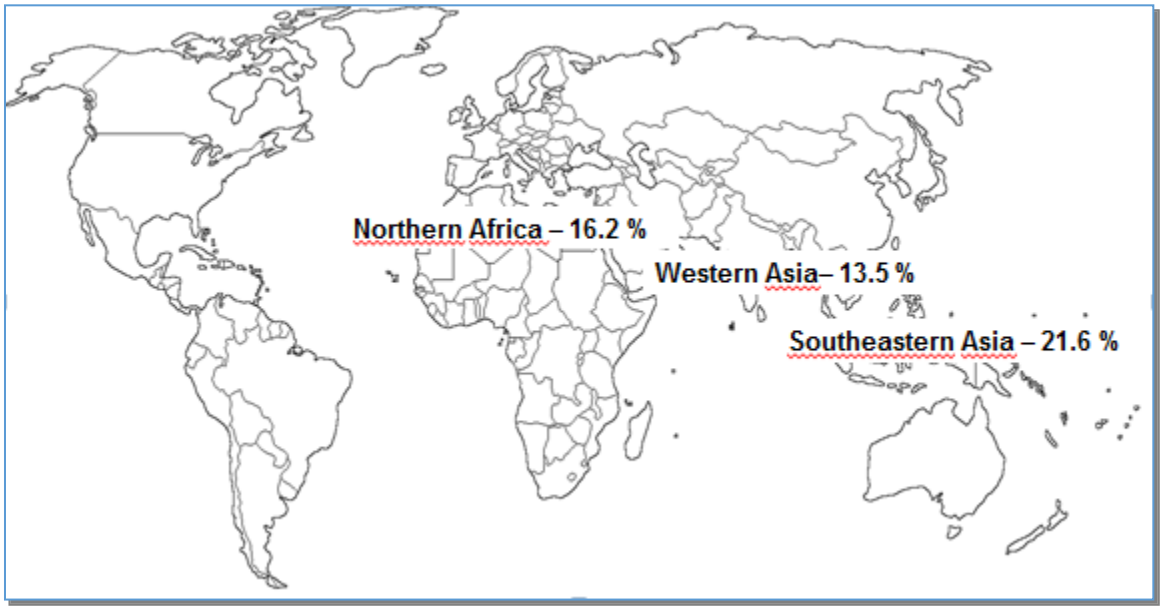


Figure 1G: IDDM (n=215)

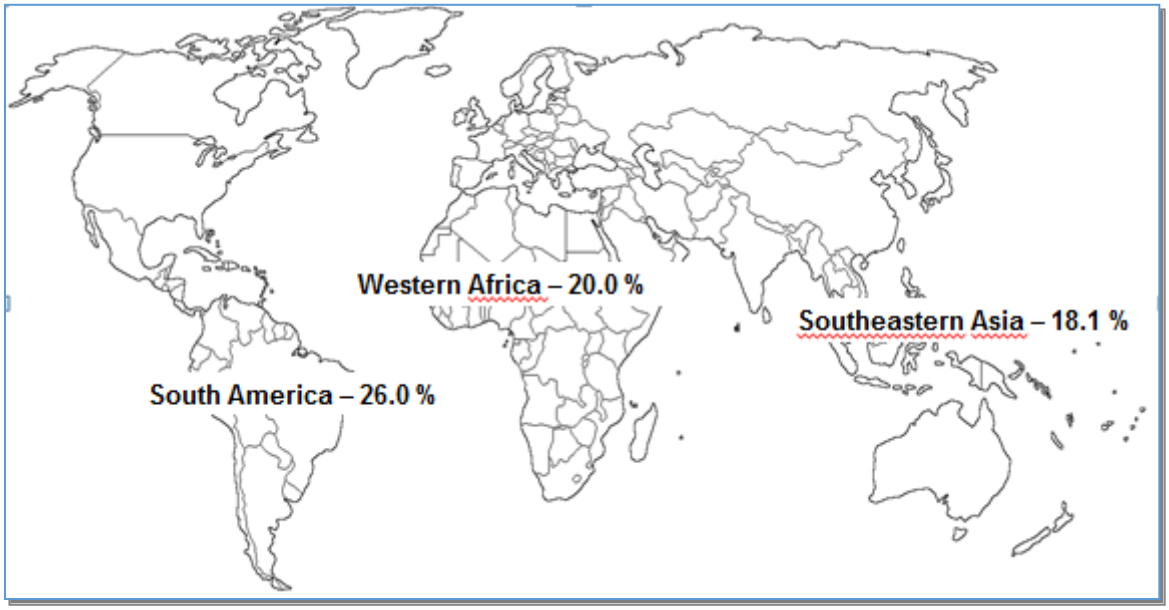


Figure 1H: Coagulation disorder (n=117)

Figure 1I: Primary immune disease (n=23)

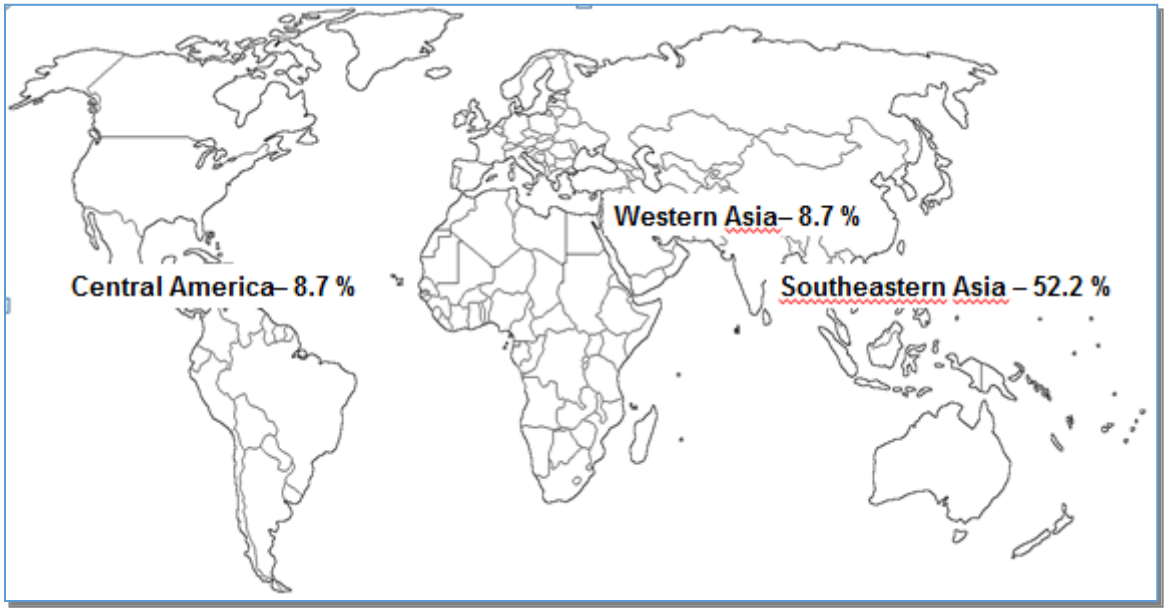


Figure 1J: SOT (n=156)

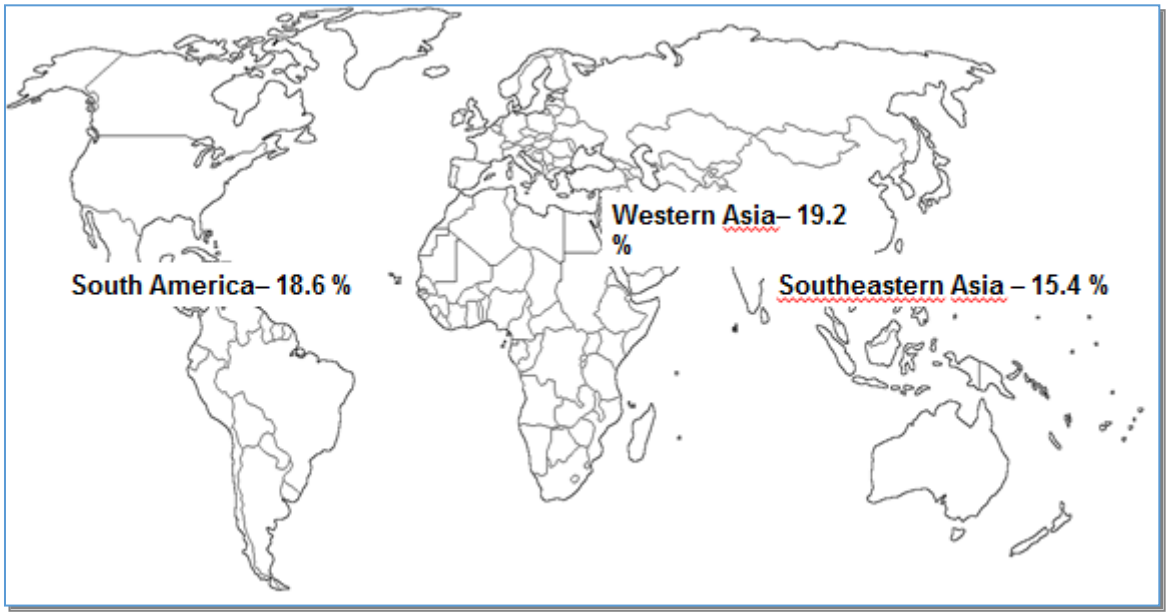


Figure 1K: Allergy (n=96)

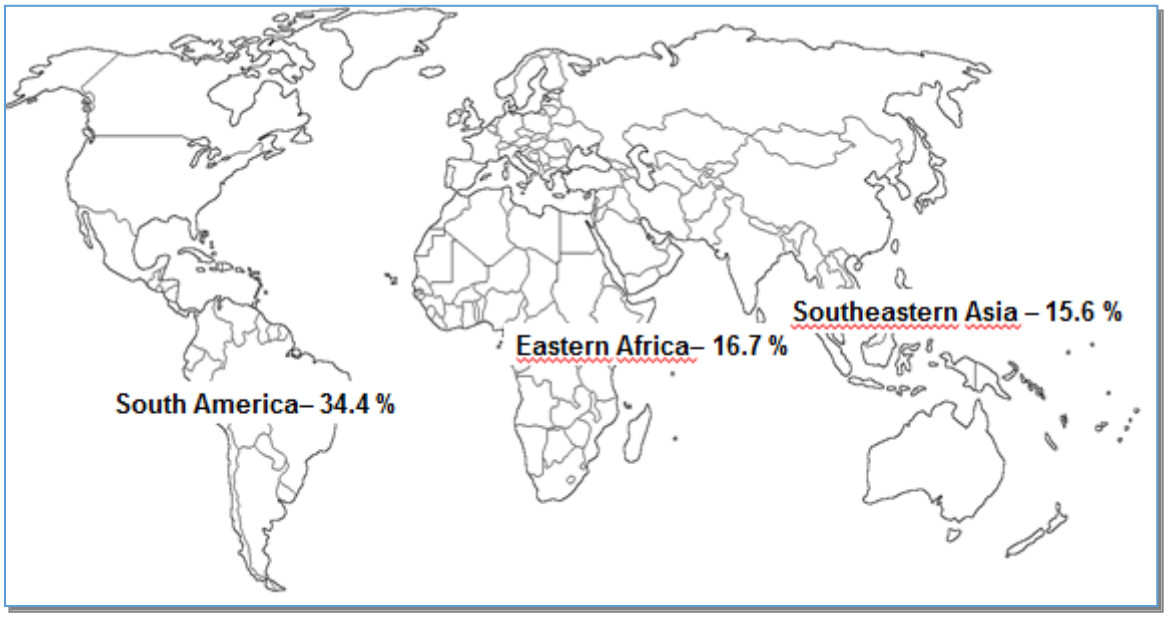


Figure 1L: Severe renal dysfunction/haemodialysis (n=44)

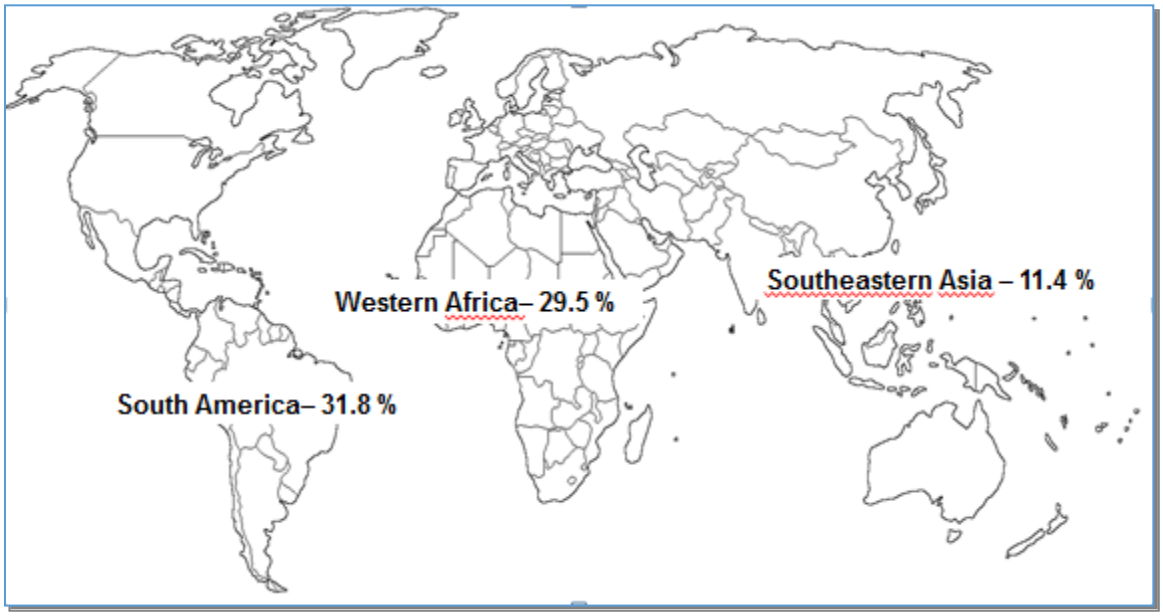


Figure 1M: Autoimmune disease (immunosuppressive therapy)(n=284)

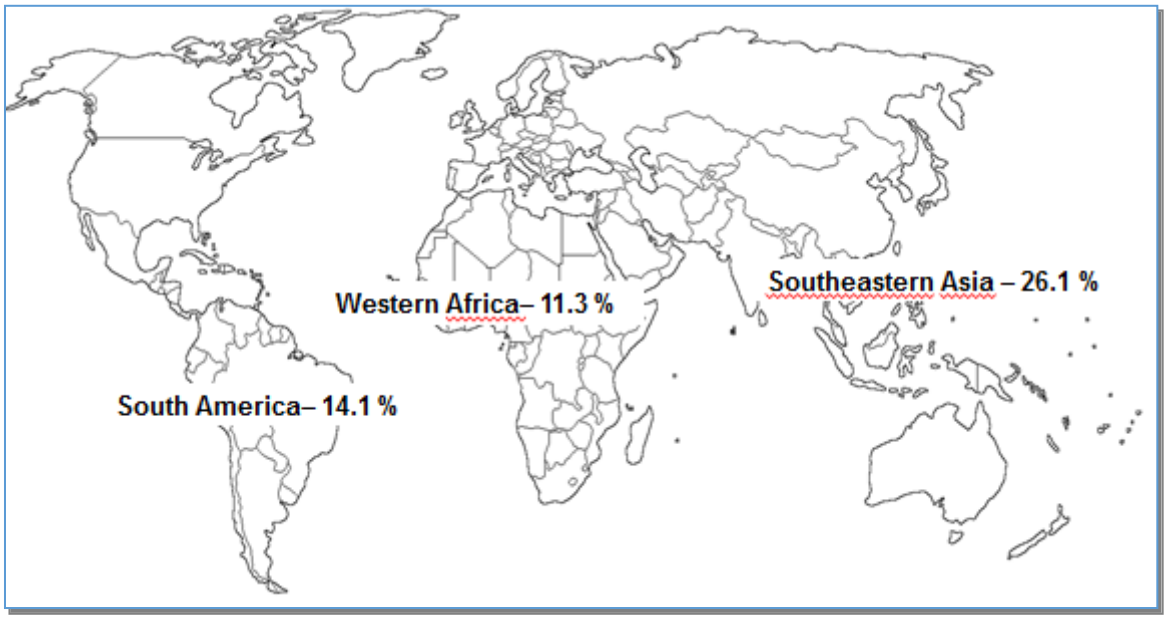
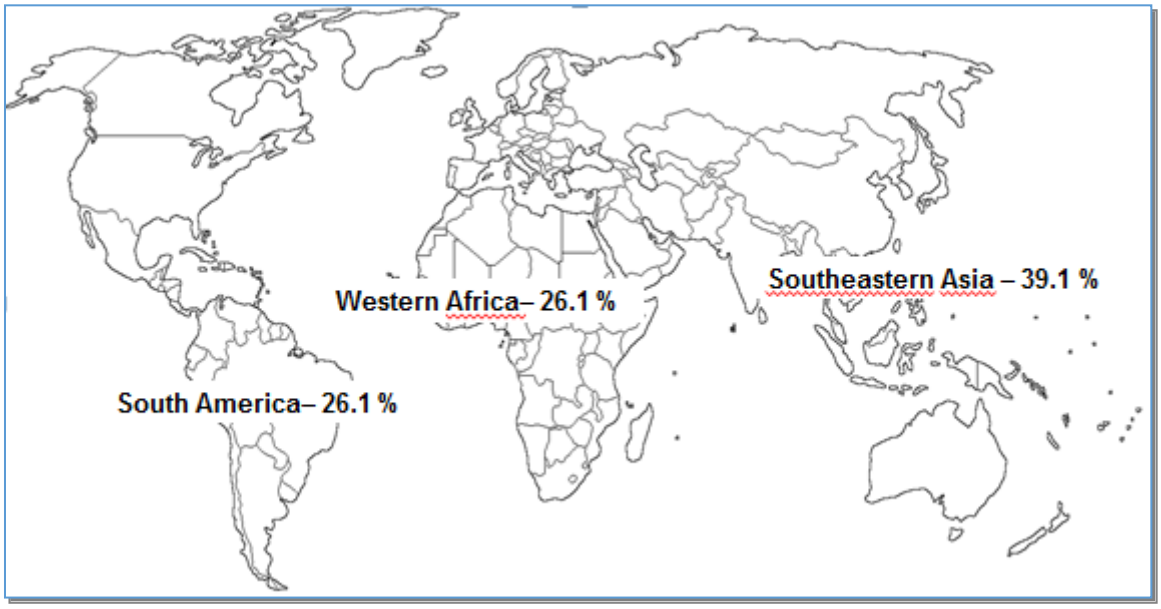


Figure 1N: Severe liver disease (n=23)



Vaccinations and malaria prophylaxis

P/E ratios differed widely between vaccines and patient categories (Figure 1).

Protection/exposure ratio ≥ 90%

P/E ratios were ≥ 90% for TF ("T1"), DTP, and hepA. Although overall P/E rates for these vaccinations were high, coverage was lower in certain subgroups. For DTP in ICCITs with immune disease and with vaccine allergy, P/E rates were ≤ 90% (P/E 78.3% (18/23) and 85.1% (80/94)), p= 0.003 and 0.000, respectively). The hepA vaccine P/E rate was ≤ 90% only in the vaccine allergy group (P/E 86.4% (83/95), p=0.001).

P/E rates for TF ("T1") were ≤ 90% in ICCITs with HIV (any CD4 count), (functional) asplenia, ICCITs on immunosuppressive treatment (solid-organ transplantation), and IDDM. However, differences were not significant.

Protection/exposure ratio ≥ 80%

Malaria chemoprophylaxis was prescribed for 84.4% (390/461) of participants travelling to "M1" countries. ICCITs with HIV (CD4>500) were more likely (P/E 92.0% (104/113), p=0.012), and ICCITs with a vaccine allergy less likely to receive malaria chemoprophylaxis (P/E 40.0% (10/25), p=0.000). Of all ICCITs travelling to T2 countries, 80.0% (369/461) received a TF vaccination.

Protection/exposure ratio ≤ 80%

YF vaccine P/E rate was 70.1% (498/710) for ICCITs travelling to "YF1" countries. Of ICCITs with HIV (CD4> 500), and with coagulation dysfunction, ≥ 90% were vaccinated against YF (P/E 93.0% (120/129) and 91.1% (21/23; p=0.000 and 0.025, respectively). ICCITs on immunosuppressive treatment (autoimmune disease or SOT) were less

likely to receive YF vaccination (P/E 32.9% (27/82) and 19.4% (7/36), p=0.000 and 0.000, respectively).
P/E rate for rabies was 8.6% (150/1597) and for Hep B 36.6% (730/1981). The latter was ≥ 50% among ICCITs with HIV (any CD4 count), severe liver disease, severe renal impairment/haemodialysis and among SOT recipients (Table 3; Supplementary File 1).

Hepatitis A and B antibody titres

ICCITs with an indication for post-vaccination antibody titre assessment were those with HIV, with a primary immune disease, those on immunosuppressive treatment, and with coagulation dysfunctions (because of subcutaneous, instead of intramuscular vaccination route) (11-13).
In those groups, hepA and hepB antibody titres were assessed at least once before travelling in 58.1% (551/944) and 75.7% (393/514), respectively.
ICCITs with HIV (CD4 200-500 and CD4>500) were more likely to undergo antibody titre checks. HepA A/I rates were 67.8% (160/236) and 71.6% (68/95; p=0.021 and 0.001, respectively). HepB A/I rates were 90.4% (66/73) and 90.5% (151/167; p=0.002 and 0.000, respectively).
ICCITs with coagulation dysfunctions were less likely to have antibody titres checked (hepA A/I rate 36.6%; 43/112) and hepB A/I rate (16.1%; 5/31); only the latter being statistically significant (p=0.000). SOT recipients had a significantly higher hepA A/I rate (73.1% (79/108, p=0.000)).

Standby antibiotics

ICCITs with an indication for prescription of standby antibiotics were those with: HIV (CD4 count< 500), (functional) asplenia, immune disease, immunosuppressive treatment, IDDM, and those with severe renal impairment/haemodialysis. Of those, 50.6% (579/1181) received such a prescription.
ICCITs with HIV (CD4 200-500), with immunosuppressive drugs (for autoimmune disease), or with severe renal impairment or haemodialysis were significantly less likely to receive a prescription for standby antibiotics (P/I rates in the last groups ≤ 30%, (P/I 38.8% (40/103) and 27.3% (12/44), p=0.013, 0.010 and 0.002, respectively)).
ICCITs with (functional) asplenia and solid organ transplant recipients were more likely to receive such a prescription (P/I rate 64.2% (88/137) and 61.3% (95/155), p=0.001 and 0.010, respectively) (Table 3 and Supplementary File 1).

Conclusion

Baseline and travel characteristics

We described baseline and travel characteristics, vaccination rates, antibody titre assessments and prescription of stand-by antibiotics for 2,104 travel episodes in 1826 ICCITs.
Differences in baseline characteristics across various ICCITs categories, such as age or male/female ratio are explained by disease specific intrinsic differences across categories, and are comparable to previous studies (2, 21).

The larger proportion of males among ICCITs with HIV is explained by a higher prevalence of HIV among persons of African origin and among men who have sex with men (MSM), and diagnosis of HIV often been established in middle age (22). The longer mean travel duration in this group and the majority travelling to Africa is explained by the fact that a considerable number is of African origin and returned for visiting friends and relatives (VFR). A previous study on HIV positive travellers found a higher proportion of males and a larger proportion travelling to Asia, probably due to a higher proportion of MSM travelling for the purpose of tourism (2).
Our study population comprised more HIV positive patients and patients on immunosuppressants, compared to a study from a national travel advice line the UK, which had a higher proportion of ICCITS with autoimmune disease without immunosuppressive treatment. This difference can be explained by the fact that our centre is a specialized referral clinic for TCDs, and ICTs specifically (23).

Vaccinations

P/E rates for DTP, TF, and hepA vaccination were comparable to P/E rates in the healthy population, whereas the YF vaccine P/E rate was lower (17). The latter is clarified by a contra-indication for this vaccination for most ICCITs. Vaccination before start of immunosuppressive therapy actually explains that YF P/E rates were not zero. Small ICCITs groups (2-31 participants) travelling to T1 countries made comparison between groups difficult and the low TF vaccine P/E rates (T1) in some groups are therefore unreliable. The lower TF P/E rate for ICCITs travelling to T2 countries, is explained by the fact that TF vaccination is only recommended under certain conditions, and the lower rabies P/E rate by the fact that patients often chose not to be immunised since immunoglobulins are routinely required as post-exposure treatment, regardless of pre-exposure vaccinations in ICTs.
ICCITs with a suspected adverse reaction against a vaccine component were mostly suspected of an egg yolk allergy, a contra-indication for YF vaccination. They were often referred to our centre for this vaccination specifically, explaining the lower P/E rates for the other vaccinations. The comparable YF vaccine P/E rate is illustrated by the high success rate of YF vaccination after an intradermal test dose, followed by a regular subcutaneous vaccination when no skin reaction occurred.
In ICCITs with immune diseases receiving immunoglobulin therapy such as for combined immunodeficiencies or major antibody deficiencies, vaccination is not routinely recommended, clarifying the lower DTP vaccine P/E rate (24, 25).

Antibody titres

Although comparable to the healthy population, the hep B vaccine P/E rate among ICCITs was considerably low, as was the hep B A/I rate (17). ICCITs with HIV, severe liver disease, and severe renal impairment or haemodialysis were more likely to have been vaccinated against hep B, and ICCITs with HIV to have a known post-vaccination antibody titre; possibly because clear guidelines exist regarding hepA (in case of certain risk factors) and hepB status in these patients (26, 27).

Since few guidelines exist regarding pre-travel care in ICCITs, a physician's decision on antibody titre assessments in certain risk groups is mainly based on expert opinion and may be influenced by variations in insurance-depending cost compensations, leading to heterogeneity in this decision, lower A/I rates and less protection, as shown by our findings. However, the low hep B P/E (certain groups) and A/I stipulate the question whether physicians should be more pro-active and move towards a low-threshold approach regarding this, and antibody titre assessments to demonstrate protection (28).

Standby antibiotics

P/I rates were considerably low; however, certain ICCITs, such as those with (functional) asplenia or on immunosuppressants for whom strict guidelines existed, had higher P/I rates than those with a theoretical indication for standby antibiotics. The very low P/I rate (<30%) in ICCITs with severe renal insufficiency can be explained by the existence of a national guideline, in which standby antibiotics are only recommended for ICCITs with nephrotic syndrome;(8) for ICCITs with severe renal insufficiency remain no specific recommendation exists, emphasizing the high need for uniform guidelines on pre-travel care for ICCITs.

However, since current studies showed travel related antibiotic use to be a risk factor for acquisition of antibiotic resistant enterobacteriaceae, more evidence is needed to establish the role of standby antibiotics in the prevention of severe complications of infection (29).

Strengths and limitations

A strength of this study is that, to the best of our knowledge, this is the largest study in this field up to now. The large number of ICCITs enabled us to divide the study population in patient groups characterised by their underlying disease; the latter being highly relevant for optimization of care and improvement of guidelines.

A limitation of this study was the retrospective design. Furthermore, the AMC TC is located in an area with a high immigrant percentage (VFR travellers), which may have led to other destinations in our study, compared to in the general population.

Future studies and recommendations

The findings of this study underscore the urgent need to develop uniform, international evidence-based travel guidelines for ICCITs.

The provided numbers on vaccination P/E rates, rates of antibody titre assessments and prescription of standby antibiotics in immunocompromised patients helped us to increase awareness concerning pre-travel care in ICCITs. However, to improve pre-travel care, uniform international pre-travel guidelines are highly needed, in the first place based on expert opinion, because the evidence base is often lacking. Such guidelines would reduce heterogeneity in management between physicians, allowing for research to vaccine immunology and travel advice regarding TCDs, and hopefully lead to measurable reductions in morbidity and mortality in this vulnerable population.

Table 3 A-K Level of statistical significance for protection/exposure (P/E); antibody titre assessment/indication (A/I); prescription of standby antibiotics/indication (P/I) ratio

Table 3A: DTP (P/E)

DTP	Protection/exposure (P/E)	%	Odds ratio 95% CI	p-value
All	1927/2020	95.3		
Sex, m vs f (498)	883/927	95.3	.90 (.59-1.38)	.383
Younger (18-29 yrs) vs other	224/237	94.5	.79 (.43-1.44)	.441
Older (>60 yrs)) vs others	489/511	95.7	1.01 (.65-1.74)	.066
1. HIV (CD4 count < 200) *	10/11	90.9	.47 (.06-3.71)	.399
2. HIV (CD4 count 200-500)	**92/101**	**91.1**	**.46 (.22-.94)**	**.029**
3. HIV (CD4 count > 500)	233/243	95.9	1.1 (.57-2.2)	.100
4. (Functional) asplenia	131/134	97.8	2.1 (.67-6.86)	.190
5. HSCT*	30/30	100	N a	.248
6. Primary immune disease*	**18/23**	**78.3**	**.2 (.06-.45)**	**.003**
7. Autoimmune disease (immunosuppressive therapy)	**270/275**	**98.2**	**2.8 (1.13-6.97)**	**.021**
8. SOT (immunosuppressive therapy)	148/153	96.7	1.4 (.57-3.58)	.593
9. Use of vitamin K antagonists/	110/116	94.8	.9 (.37-2.01)	.126
NOACs or coagulation dysfunction				
10. Allergy for any substance in the vaccine	**80/94**	**85.1**	**.3 (.13-.44)**	**.000**
11. IDDM	206/214	96.3	1.2 (.59-2.60)	.331
12. Severe renal impairment/haemodialysis*	41/44	93.2	.64 (.19-2.10)	.447
13. Severe liver disease*	22/23	95.7	1.0 (.14-7.80)	1.000
14. Remaining	363/380	95.5	1.01 (.59-1.73)	.970

Table 3B: Yellow fever (YF1) (P/E)

Yellow fever (YF1)	Protection/exposure (P/E)	%	Odds ratio 95% CI	p-value
All	498/710	70.1		
Sex, male vs female	219/308	71.1	1.1 (.77-1.48)	.696
Younger (18-29 yrs) vs others	42/63	66.7	.8 (.48-1.44)	.504
Older (>60 yrs)) vs others	**83/138**	**60.1**	**.56 (.38-.83)**	**.003**
1. HIV (CD4 count < 200) *	4/7	57.1	.56 (.12-2.52)	.429
2. HIV (CD4 count 200-500)	41/54	77.4	1.4 (.71-2.59)	.350
3. HIV (CD4 count > 500)	**120/129**	**93.0**	**7.09 (3.52-14.23)**	**.000**
4. (Functional) asplenia	53/69	76.8	1.44 (.81-2.39)	.215
5. HSCT*	0/2	0	Not applicable	1.00
6. Primary immune disease *	1/2	50.0	.42 (.03-6.76)	.506
7. Autoimmune disease (immunosuppressive therapy)	**27/82**	**32.9**	**0.16 (.10-.27)**	**.000**
8. SOT (immunosuppressive therapy)	**7/36**	**19.4**	**.09 (.04-.21)**	**.000**
9. Use of vitamin K antagonists/NOACs or coagulation dysfunction	**21/23**	**91.1**	**4.6 (1.01-19.7)**	**.025**
10. Allergy for any substance in the vaccine	36/45	80.0	1.7 (.83-3.7)	.143
11. IDDM	**80/97**	**82.5**	**2.2 (1.25-3.77)**	**.005**
12. Severe renal impairment/haemodialysis	17/26	65.4	.8 (.35-1.80)	.573
13. Severe liver disease*	6/8	75.0	1.3 (.25-6.34)	.772
14. Remaining	70/90	77.8	1.6 (.92-2.63)	.098

Table 3C: Typhoid fever (T1) (P/E)

Typhoid fever ("T1")	Protection/exposure (P/E)	%	Odds ratio 95% CI	p-value
All	148/162	91.4		
Sex, m vs f (498)	73/79	92.4	1.3 (.43-3.92)	.644
Younger (18-29 yrs)*	17/17	100	.9 (.84-.94)	.365
Older (>60 yrs)*	48/52	92.3	1.2 (.36-4.02)	1.000
1. HIV (CD4 count < 200)	Not applicable			
2. HIV (CD4 count 200-500) *	8/9	88.9	.7 (.09-6.41)	.566
3. HIV (CD4 count > 500) *	16/19	84.2	.4 (.11-1.76)	.215
4. (Functional) asplenia*	1/2	50.0	.1 (.01-1.50)	.166
5. HSCT*	1/1	100	1.0 (.98-1.01)	1.000
6. Primary immune disease *	1/1	100	1.0 (.98-1.01)	1.000
7. Autoimmune disease (immunosuppressive therapy) *	26/26	100	.8 (.77-.89)	.077
8. SOT (immunosuppressive therapy)*	15/17	88.2	.7 (1.14.-3.31)	.446
9. Use of vitamin K antagonists/NOACs or coagulation dysfunction*	15/16	93.8	1.5 (.18-12.0)	.586
10. Allergy for any substance in the vaccine*	2/2	100	1.0 (.97-1.01)	1.000
11. IDDM*	20/24	83.3	.4 (.11-1.37)	.132
12. Severe renal impairment/haemodialysis	Not applicable			
13. Severe liver disease	Not applicable			
14. Remaining*	29/31	93.5	1.5 (.31-6.90)	.475

Table 3D: Typhoid fever (T2) (P/E)

Typhoid fever (T2)	Protection/exposure (P/E)	%	Odds ratio 95% CI	p-value
All	369/461	80.0		
Sex, m vs f (498)	179/224	79.9	.9 (.59-1.49)	.064
Younger (18-29 yrs)	**46/65**	**70.8**	**.5 (.29-.96)**	**.035**
Older (>60 yrs)	**122/140**	**87.1**	**2.0 (1.13-3.46)**	**.016**
1. HIV (CD4 count < 200)	Not applicable			
2. HIV (CD4 count 200-500) *	16/18	88.9	2.0 (.45-8.83)	.546
3. HIV (CD4 count > 500)	25/31	80.6	1.0 (.40-2.56)	.971
4. (Functional) asplenia*	17/24	70.8	.6 (.23-1.42)	.287
5. HSCT*	**7/13**	**53.8**	**.3 (.09-.83)**	**.026**
6. Primary immune disease *	5/8	62.5	.4 (.09-1.70)	.193
7. Autoimmune disease (immunosuppressive therapy)	63/75	84.0	1.3 (.69-2.60)	.740
8. SOT (immunosuppressive therapy)	25/35	71.4	.6 (.27-1.26)	.165
9. Use of vitamin K antagonists/NOACs or coagulation dysfunction	30/33	90.9	2.6 (.77-8.61)	.114
10. Allergy for any substance in the vaccine*	7/11	63.6	.42 (.12-1.45)	.238
11. IDDM	36/41	87.8	1.8 (.70-4.83)	.210
12. Severe renal impairment/haemodialysis*	5/6	83.3	1.2 (.14-10.60)	1.00
13. Severe liver disease*	5/9	55.6	.3 (.08-1.12)	.079
14. Remaining*	80/103	77.7	.8 (.47-1.38)	.429

Table 3E: Rabies (P/E)

Rabies	Protection/exposure (P/E)	%	Odds ratio 95% CI	p-value
All	150/1597	8.6		
Sex, m vs f (498)	79/729	9.8	1.3 (.95-1.9)	.098
Younger (18-29 yrs)	**33/213**	**15.5**	**2.2 (1.47-3.37)**	**.000**
Older (>60 yrs)	44/434	10.1	1.3 (.89-1.86)	.182
1. HIV (CD4 count < 200) *	0/9	0	Not applicable	1.000
2. HIV (CD4 count 200-500) *	**2/96**	**2.1**	**.2 (.05-.89)**	**0.014**
3. HIV (CD4 count > 500)	19/222	8.6	1.0 (.60-1.65)	.990
4. (Functional) asplenia	6/106	5.7	.6 (.27-1.45)	.268
5. HSCT*	2/30	6.7	.8 (.18-3.21)	1.000
6. Primary immune disease *	1/22	4.3	.5 (.06-3.59)	.715
7. Autoimmune disease (immunosuppressive therapy)	22/236	9.3	1.1 (.69-1.79)	.191
8. SOT (immunosuppressive therapy)	**5/128**	**3.9**	**.4 (.17-1.03)**	**.050**
9. Use of vitamin K antagonists/NOACs or coagulation dysfunction	13/105	12.4	1.5 (.85-2.85)	.152
10. Allergy for any substance in the vaccine	8/78	5.3	1.2 (.58-2.61)	.292
11. IDDM	16/160	10.7	1.2 (.70-2.08)	.452
12. Severe renal impairment/haemodialysis*	0/30	0	Not applicable	.104
13. Severe liver disease*	**5/22**	**3.3**	**3.2 (1.17-8.82)**	**.017**
14. Remaining	36/341	10.6	1.4 (.90-1.99)	.146

Table 3F: Hepatitis A (P/E)

Hepatitis A	Protection/exposure (P/E)	%	Odds ratio 95% CI	p-value
All	1926/2028	95.0		
Sex, m vs f (498)	**873/925**	**94.4**	**.6 (.42-.97)**	**.035**
Younger (18-29 yrs)	229/237	96.6	1.4 (.68-2.96)	.353
Older (>60 yrs)	484/512	94.5	.8 (.49-1.21)	.253
1. HIV (CD4 count < 200)	10/11	90.9	.5 (.06-3.75)	.470
2. HIV (CD4 count 200-500)	92/98	93.9	.7 (.31-1.69)	.447
3. HIV (CD4 count > 500)	233/242	96.3	1.3 (.63-2.56)	.623
4. (Functional) asplenia	130/136	95.6	1.0 (.45-2.41)	.932
5. HSCT*	30/30	100	Not applicable	.398
6. Primary immune disease	22/23	95.7	1.1 (.14-7.89)	1.000
7. Autoimmune disease (immunosuppressive therapy)	267/275	97.1	1.7 (.81-3.53)	.158
8. SOT (immunosuppressive therapy)	147/153	96.1	1.2 (.51-2.76)	.155
9. Use of vitamin K antagonists/NOACs or coagulation dysfunction	113/116	97.4	1.8 (.58-5.93)	.294
10. Allergy for any substance in the vaccine*	**83/95**	**86.4**	**.3 (.16-.57)**	**.001**
11. IDDM	207/214	96.7	1.5 (.67-3.20)	.339
12. Severe renal impairment/haemodialysis*	40/44	90.9	.5 (.16-1.33)	.138
13. Severe liver disease	22/23	95.7	1.1 (.14-7.89)	.961
14. Remaining	**356/381**	**93.4**	**.6 (.38-.98)**	**.037**

Table 3G: Hepatitis A (A/I)

Hepatitis A	Titre/indication (A/I)	%	Odds ratio 95% CI	p-value
All with indication antibody titre	551/944	58.1		
Sex, m vs f (498)	Not applicable			
Younger (18-29 yrs)	Not applicable			
Older (>60 yrs)	Not applicable			
1. HIV (CD4 count < 200) *	7/10	70.0	1.3 (.39-4.59)	.765
2. HIV (CD4 count 200-500)	**68/95**	**71.6**	**1.7 (1.08-2.61)**	**.021**
3. HIV (CD4 count > 500)	**160/236**	**67.8**	**1.7 (1.24-2.28)**	**.001**
4. (Functional) asplenia	Not applicable			
5. HSCT	Not applicable			
6. Primary immune disease *	6/10	60.0	.8 (.22-2.63)	.448
7. Autoimmune disease (immunosuppressive therapy)	136/223	61.0	1.2 (.86-1.59)	.320
8. SOT (immunosuppressive therapy)	**79/108**	**73.1**	**2.1 (1.40-3.34)**	**.000**
9. Use of vitamin K antagonists/NOACs or coagulation dysfunction	**43/112**	**36.6**	**.4 (.26-.59)**	**.000**
10. Allergy for any substance in the vaccine	Not applicable			
11. IDDM	Not applicable			
12. Severe renal impairment/haemodialysis	Not applicable			
13. Severe liver disease	Not applicable			
14. Remaining	Not applicable			

Table 3H: Hepatitis B (P/E)

Hepatitis B	Protection/exposure (P/E)	%	Odds rati 95% CI	p-value
All	730/1981 (36.6)	36.6		
Sex, m vs f	**380/908**	**41.9**	**1.5 (1.24-1.79)**	**.000**
Younger (18-29 yrs)	**113/230**	**49.1**	**1.8 (1.35-2.34)**	**.000**
Older (>60 yrs)	**111/503**	**21.1**	**.4 (.31-.50)**	**.000**
1. HIV (CD4 count < 200) *	7/11	63.6	3.0 (.88-10.3)	.112
2. HIV (CD4 count 200-500)	**69/100**	**68.0**	**4.1 (2.66-6.34)**	**.000**
3. HIV (CD4 count > 500)	**165/241**	**68.5**	**4.5 (3.38-6.03)**	**.000**
4. (Functional) asplenia	52/129	40.3	1.2 (.81-1.68)	.397
5. HSCT	14/30	46.7	1.5 (.73-3.11)	.260
6. Primary immune disease	4/23	17.4	.4 (.12-1.05)	.053
7. Autoimmune disease (immunosuppressive therapy)	**76/271**	**28.0**	**.6 (.47-.83)**	**.001**
8. SOT (immunosuppressive therapy)	**78/143**	**54.5**	**2.2 (1.55-3.08)**	**.000**
9. Use of vitamin K antagonists/NOACs or coagulation dysfunction	**30/115**	**26.1**	**.6 (.38-.90)**	**.014**
10. Allergy for any substance in the vaccine	**24/93**	**25.8**	**.6 (.36-.94)**	**.024**
11. IDDM	**37/214**	**17.3**	**.3 (.22-.47)**	**.000**
12. Severe renal impairment/haemodialysis	**23/44**	**52.3**	**1.9 (1.05-3.46)**	**.039**
13. Severe liver disease	12/22	54.5	2.1 (.89-4.82)	.084
14. Remaining	**74/374**	**19.8**	**.4 (.27-.47)**	**.000**

Table 3I: Hepatitis B (A/I)

Hepatitis B	Titre/indication (A/I)	%	Odds ratio 95% CI	p-value
All	393/514	75.7		
Sex, m vs f (498)	Not applicable			
Younger (18-29 yrs)	Not applicable			
Older (>60 yrs)	Not applicable			
1. HIV (CD4 count < 200) *	6/7	85.7	1.8 (.22-15.60)	1.00
2. HIV (CD4 count 200-500)	**66/73**	**90.4**	**3.3 (1.47-7.37)**	**.002**
3. HIV (CD4 count > 500)	**151/167**	**90.49**	**4.1 (2.33-7.20)**	**.000**
4. (Functional) asplenia	Not applicable			
5. HSCT	Not applicable			
6. Primary immune disease	5/0	100	Not applicable	.596
7. Autoimmune disease (immunosuppressive therapy)	54/79	68.4	.6 (.36-1.04)	.065
8. SOT (immunosuppressive therapy)	**74/83**	**89.2**	**2.9 (1.40-5.96)**	**.003**
9. Use of vitamin K antagonists/NOACs or coagulation dysfunction	**5/31**	**16.1**	**.0 (.02-.13)**	**.000**
10. Allergy for any substance in the vaccine	Not applicable			
11. IDDM	Not applicable			
12. Severe renal impairment/haemodialysis	Not applicable			
13. Severe liver disease	Not applicable			
14. Remaining	Not applicable			

Table 3J: Malaria (P/E)

Malaria ("M1")	Protection/exposure (P/E)	%	Odds ratio 95% CI	p-value
All	390/461	84.4		
Sex, m vs f (498)	175/200	87.5	1.5 (.89-2.54)	.131
Younger (18-29 yrs)	29/34	85.3	1.1 (.40-2.84)	.907
Older (>60 yrs)	60/74	81.1	.7 (.39-1.41)	.360
1. HIV (CD4 count < 200) *	5/5	100	Not applicable	1.000
2. HIV (CD4 count 200-500)	42/47	89.4	1.6 (.61-4.18)	.340
3. HIV (CD4 count > 500)	**104/113**	**92.0**	**2.5 (1.20-5.22)**	**.012**
4. (Functional) asplenia	36/42	85.7	1.1 (.45-2.72)	.834
5. HSCT*	1/1	100	Not applicable	1.000
6. Primary immune disease*	2/2	100	Not applicable	1.000
7. Autoimmune disease (immunosuppressive therapy)	39/48	81.3	.8 (.35-1.66)	.461
8. SOT (immunosuppressive therapy)*	9/11	81.8	.8 (1.7-3.9)	.681
9. Use of vitamin K antagonists/NOACs or coagulation dysfunction*	16/19	84.2	1.0 (.28-3.41)	1.000
10. Allergy for any substance in the vaccine*	**10/25**	**40.0**	**.1 (.04-.23)**	**.000**
11. IDDM	45/50	90.0	1.7 (.66-4.50)	.262
12. Severe renal impairment/haemodialysis*	12/13	92.3	2.2 (.28-17.4)	.702
13. Severe liver disease*	6/7	85.7	1.1 (.13-9.22)	.706
14. Remaining*	49/58	84.5	1.0 (.46-2.12)	.979

Table 3K: Antibiotic use (P/I)

Antibiotic use	Prescription/indication (P/I)	%	Odds ratio 95% CI	p-value
All	579/1181	50.6		
Sex, m vs f (498)	273/515	53.0	1.2 (.95-1.51)	.135
Younger (18-29 yrs)	**93/157**	**59.2**	**1.50 (1.07-2.11)**	**.019**
Older (>60 yrs)	135/275	49.1	.9 (.71-1.21)	.574
1. HIV (CD4 count < 200) *	6/11	54.5	1.2 (.36-3.87)	.791
2. HIV (CD4 count 200-500)	**40/103**	**38.8**	**.6 (.39-.90)**	**.013**
3. HIV (CD4 count > 500)	Not applicable			
4. (Functional) asplenia	**88/137**	**64.2**	**1.9 (1.31-2.74)**	**.001**
5. HSCT*	Not applicable			
6. Primary immune disease	15/21	71.4	2.5 (.96-6.44)	.054
7. Autoimmune disease (immunosuppressive therapy)	**122/278**	**43.9**	**.7 (.53-.92)**	**.010**
8. SOT (immunosuppressive therapy)	**95/155**	**61.3**	**1.7 (1.17-2.34)**	**.004**
9. Use of vitamin K antagonists/NOACs or coagulation dysfunction	Not applicable			
10. Allergy for any substance in the vaccine*	Not applicable			
11. IDDM	97/210	46.2	.8 (.60-1.09)	.160
12. Severe renal impairment/haemodialysis*	**12/44**	**27.3**	**.4 (.18-.69)**	**.002**
13. Severe liver disease	Not applicable			
14. Remaining	Not applicable			

* Values of less than 5 in one of the cells of the contingency table. Fisher's Exact Test used.

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APPENDIX (AVAILABLE ONLINE)

Supplementary File 1 A-F:	Ratio of protection/exposure- (P/E); antibody titre assessment/indication- (A/I); prescription of standby antibiotics/indication (P/I)
Supplementary File 1A:	Yellow fever, invariably required, P/E (%)
Supplementary File 1B:	Typhoid fever, invariably required P/E (%)
Supplementary File 1C:	Hepatitis B P/E (%)
Supplementary File 1D:	Hepatitis B A/I (%)
Supplementary File 1E:	Heatitis A P/E (%)
Supplementary File 1F:	Hepatitis A A/I (%)
Supplementary File 1G:	Antibiotic use P/I (%)

Chapter 7

Travel-related health problems in the immunocompromised traveller: an exploratory study

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Abstract

BACKGROUND: Immunocompromised travellers (ICTs) are at increased risk of travel-related health problems. Therefore, they are advised to attend specialised pre-travel clinics for advice on vaccination, malaria chemoprophylaxis and on demand antibiotics. However, studies yield conflicting data regarding travel-related health problems encountered by ICTs; questioning the rationale for certain advises, and particularly the advice of on demand antibiotics.

OBJECTIVE: To evaluate self-reported travel-related health problems, antibiotic use, medical visits and risk behaviours in ICTs and controls.

METHODS: We conducted a questionnaire-based observational study with pilot character. We recruited participants from a (medical) pre-travel clinic. Telephone interviews were conducted 2-4 weeks post-travelling, applying a structured questionnaire.

RESULTS: We included 30 ICTs and 30 controls. More ICTs than controls reported travel-related health problems, antibiotic use and medical visits, although not statistically significant. Travellers' diarrhoea appeared to be more severe in ICTs. Furthermore one ICT was hospitalized post-travel due to pneumonia. Of ICTs, 2/30 (7%) used on demand antibiotics while not indicated (according to the protocol of the Dutch national coordinating centre for travel advice or prescribed by a physician). Reversely, 6/30 (20%) did not use on demand antibiotics while actually indicated according to this protocol.

DISCUSSION: Our findings substantiate the recommendation of on demand antibiotics. However, ICTs did often not use on demand antibiotics correctly; they therefore need very careful instructions.

KEYWORDS: Travel; Immunocompromised traveller; immunodeficiency; Travellers' Diarrhoea

Introduction

Medical care and treatment for immunocompromised patients has improved over the past decades. As a consequence, these patients feel healthier and more often travel to high-risk destinations (either defined as a destination with an increased risk of exposure to endemic infectious diseases (1) or as a destination where hepatitis A and typhoid fever vaccinations are recommended (2). An estimated 16-54% of immunocompromised travellers (ICTs) travel to such high-risk destinations (1, 2).

Due to their often complex medical situation, pre-travel advice in specialised pre-travel clinics is recommended (2-5), but there are apparent obstacles to achieve optimal coverage. In fact, almost 30% of the immunocompromised patients do not seek pre-travel advice at all (2, 5, 6), compared to 50-65% of travellers in general (7, 8). Yet, pre-travel advice has been proven effective in reducing malaria [9], which is, potentially, particularly dangerous in ICTs (10, 11). The components of pre-travel advice are: informing patients concerning precautions during travel, the administration of recommended and suitable vaccinations, and the prescription of malaria chemoprophylaxis and on demand antibiotics. Such on demand antibiotics can be required in certain groups of ICTs, because of an increased risk of infection and ensuing complications. An important example of the use of on demand antibiotics is in the prevention of complications of bacterial travellers' diarrhoea such as dehydration and sepsis (12, 13).

However, the evidence base for the prescription of on demand antibiotics for ICTs remains small. Several studies have emphasized the need for on demand antibiotics, on the basis of a higher reported incidence of travel-related disease and hospital admissions among ICTs, most frequently caused by gastrointestinal disease, fever and respiratory problems (4, 14). By contrast, a recent study demonstrated that ICTs did not suffer more frequently or severely from gastro-intestinal discomfort during travel (15). More importantly, antibiotic use during travel has recently been identified as an important predictor for acquisition of ESBL-producing enterobacteriaceae and for contracting *Clostridium difficile* infection, with immunocompromised patients being particularly at risk (17-19).

These conflicting data led us to question the rationale for the prescription of on demand antibiotics. The objective of this study with pilot character for a future larger multi-centre study on this topic was to elucidate whether ICTs suffer more frequently from travel-related health problems compared to age- and sex-matched immunocompetent controls. Secondary objectives were to determine whether ICTs use antibiotics more often during travel and whether they know when and how to use these (on demand) antibiotics, to determine whether they seek medical care more often during and after travel, and to determine differences in risk behaviour regarding travel-related diseases between patients and controls.

Methods

Study setting

We performed an exploratory prospective questionnaire-based observational study on travel-related disease, travellers 'diarrhoea and antibiotic use in ICTs and sex- and age-matched immunocompetent travellers. We report according to STROBE (Strengthening the Reporting of Observational studies in Epidemiology) guidelines (20).

Participants were recruited from the outpatient department of the Centre of Tropical Medicine and Travel Medicine at the Academic Medical Centre (AMC) of the University of Amsterdam (UvA), the Netherlands, between October 2016 and June 2017. We included 30 participants in each group.

Data collection

For the purpose of this study, we developed a structured post-travel questionnaire (Supplementary File 1). Through the questionnaire, data on socio-demographic patient characteristics, travel-related health problems, travellers' diarrhoea, use of antibiotics during travel, need for medical care and risk behaviours during and after travel were collected. Informed consent was obtained during the pre-travel visit. A trained medical student conducted interviews by telephone 2-4 weeks after return from travel. Information on socio-demographic characteristics, vaccination status, the prescription of malaria chemoprophylaxis and standby-antibiotics was obtained during the pre-travel visit and from patient medical records.

In- and exclusion criteria

Inclusion criteria for eligibility to participate in this study were:

(a) Age ≥ 18 years;

(b) Travel destination outside Europe, the United States of America or Australia/New Zealand;

(c) Any of the following: treatment with immunosuppressive agents because of solid organ transplantation or auto-immune disease; asplenia (removal of spleen < 2 years ago); treatment with chemotherapy; autologous or allogeneic stem cell transplantation < 3 year ago; HIV infection with immunological damage (CD4 count < 500/mm^3); a primary immunodeficiency;

(d) Able and willing to provide written informed consent.

The control group consisted of immunocompetent sex- and age-matched clients from the same travel clinic. An immunocompromising condition potentially affects an individual ICT's choice of travel destination and duration. To be able to identify

differences in these aspects between ICTs and controls, the latter were not matched on basis of travel destination and duration.

Outcomes

The primary outcome of this study was the frequency of travel-related health problems in ICTs versus sex- and age-matched immunocompetent controls. Secondary outcomes were the percentage of participants who used on demand antibiotics during travel and the frequency of hospital and doctor's visits during and after travel. Qualitative outcomes of this study were the reasons subjects gave for the use of on demand antibiotics. In addition, the reported risk behaviour for travel-related diseases was studied: participants were asked whether they took into account the hygiene and quality of health care of a country when choosing the travel destination; the hygiene of the accommodation; and which measures they took to prevent disease.

Data analysis

We collected both quantitative and qualitative data of which the quantitative data were continuous or categorical. We performed the data-analysis of the quantitative data in SPSS version 23.0 for Windows®. We used a 0.05 alpha level for statistical significance. We compared baseline characteristics, the main and secondary objectives between ICTs and controls using the chi-square test for categorical, and the T-test for continuous normally distributed variables. We used Fisher's exact test if any of the values in the cells was ≤ 5. We reported mean and standard deviation for normally distributed variables, and median and the interquartile range for not-normally distributed variables. The Kolmogorov-Smirnov test was used to test for normality assumptions. The Mann-Whitney test was used for not normally distributed continuous variables. We ignored missing data and only handled available data.

Ethical approval

This data analysis did not require approval of the AMC ethics committee (written confirmation of the ethics committee with the authors).

Geographical destination

We grouped travel destinations into geographical regions as defined by the United Nations geoscheme (21).

Results

Study subjects

We included 30 ICTs and 30 age- and sex-matched immunocompetent controls in the study. Tables 1, 2 and Figure 1 provide baseline characteristics of the participants. The median age of both groups was 51 years. In both groups, 19 (63%) were male and 11 (37%) were female. Differences between body mass index, educational level and smoking habits were not significant. Alcohol consumption was significantly higher in the control group, with a median of 0.9 alcohol units per day (α 0.004).

Among ICTs, 26/30 (87%) were immunocompromised because of treatment with immunosuppressive agents of which 16/30 (53) had an autoimmune disease and 10/30 (33%) had a transplanted kidney; 3/30 (10%) were immunocompromised because of HIV with a CD4 count below 500 cells/mm^3, and 1/30 (3%) because of a malignancy treated with chemotherapy. Among ICTs, 19/30 (63%), had a non-immunocompromising condition such as arterial hypertension, asthma, depression and allergy. Among controls, this amounted to 11/30 (37%) participants.

The median travel duration was 21 and 22 days for ICTs and controls, respectively. Significantly more controls travelled to Southeast Asia; 14/30 (47%) ICTs versus 23/30 (77%) controls (p=0.019). Furthermore, although not significant, more ICTs travelled to Latin America; 7/30 (23%) ICTs versus 3/30 (10%) controls (p=0.177), and Africa; 5/30 (17%) ICTs versus 3/30 (10%) controls (p=0.452). (p=0.752). ICTs and controls differed in their purpose of travel; 7/30 (23%) of ICTs visited friends of relatives compared to 1/30 (3%) of controls. One control travelled with a business purpose while none of the ICTs travelled with this purpose. The remaining ICTs (23/30; 77%) and controls (28/30; 93%) travelled with the purpose of tourism.

Malaria chemoprophylaxis was prescribed to 6/30 (20%) of the controls and to 7/30 (23%) of ICTs. Mefloquine was prescribed to one participant in each group; all others received atovaquone/proguanil.

Table 1: Baseline characteristics

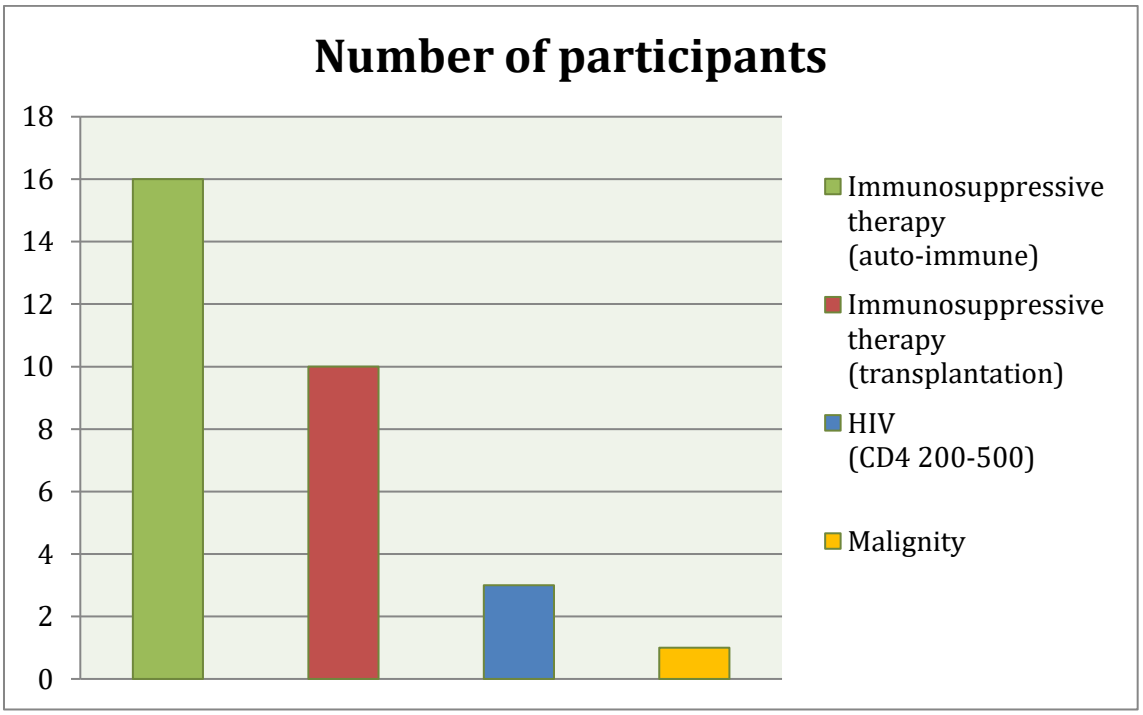
	ICTs	**Controls**	**P-value (95% CI)**
Total number	30	30	NA
Male *n* (%)	19 (63)	19 (63)	NA
Female *n* (%)	11 (37)	11 (37)	NA
Age [median]	51 [34-61]	51 [34-61]	0.695
Body Mass Index [median]	24.7 [22.7-27.2]	23.6 [22.3-25.5]	0.346
Highest education level *n* (%)			0.179
- University education	5 (17)	12 (40)	
- Higher professional education	14 (47)	12 (40)	
- Secondary vocational education or lower	9 (30)	6 (20)	
- Missing	2 (6)	0	
Smoking, pack years *n* (%)			0.245
- 0	20	21	

- 1-5 - 6-10 - > 10 - Missing	2 3 0 5	3 2 4 0	
Alcohol units/day [median]	0 [0-0.6]	0.9 [0.1-2]	0.004
Travel duration, days [median]	21 [14-29]	22 [15-30]	0.493
Travel destination			NA
- China (%)	2 (7)	1 (3)	
- South and Central America (%)	7 (23) *Bolivia, Peru, Surinam, Guatemala, Cuba*	3 (10) *Argentina, Surinam, Ecuador*	
- Southeast Asia (%)	14 (47) *Indonesia, Bali, Thailand, Sri Lanka, Cambodia, India, Malaysia, Pakistan*	23 (77) *Nepal, Bali, Thailand, Sri Lanka, Vietnam, Indonesia, Cambodia, India, Malaysia, Philippines*	
- West-Africa (%)	2 (7) *Ghana, Nigeria*	2 (7) *Cape Verde, Ghana*	
- South-Africa (%)	4 (13) *South Africa*	1 (3) *South-Africa*	
- East-Africa (%)	1 (3) *Zanzibar*		
Malaria prophylaxis			
- Atovaquone/proguanil	6 (20)	5 (17)	0.739
- Mefloquine	1 (3)	1 (3)	1.000
On demand antibiotic prescription *n* (%)		NA	NA
- Ciprofloxacin - Azithromycin - Other - None	13 (43%) 14 (47%) 0 3 (10)		

Table 2: Immunocompromising conditions and medications used

Immunocompromised group	
Auto-immune disease	Psoriatic arthritis, axial spondylarthritis, Crohn's disease, ulcerative colitis, neuromyelitis optica, psoriasis, rheumatoid arthritis, systematic lupus erythematosus
Transplantation	Kidney transplantation
Immunosuppressive medication (both for patients with an auto-immune disease and for patients with a transplantation)	Corticosteroids: prednisolone DMARDs: azathioprine, mercaptopurine, methotrexate Anti-TNFα: etanercept, adalimumab, infliximab Other: mycofenolic acid, cyclosporine, certoluzimab, tacrolimus, sirolimus, everolimus, tocilizumab, usketinumab
HIV	CD4 count 200-500
Antiretroviral therapy	Abacavir/lamivudine, emtricitabine/tenofovir, atazanavir, ritonavir, darunavir
Other medications	Antidepressants, inhalators, anti-epileptics, antihypertensive drugs, vitamin B12 injection, vitamin K antagonists, anti-histamines, proton-pump-inhibitors, laxatives, statin, glucose reducing medication, calcium carbonate, vitamin D, anti-arrhythmica, L-thyroxin, antiplatelet drugs, allopurinol, darbepoetin, folic acid.
Control group	
Other medications	Antidepressants, inhalators, anti-epileptics, antihypertensive drugs, vitamin B12 injection, vitamin K antagonists, anti-histamines, proton-pump-inhibitors, laxatives, statin, glucose reducing medication.

Figure 1: Numbers of participants with immunocompromising condition



A post-vaccination antibody titre of hepatitis A was assessed in 21/30 (70%) of ICTs. The antibody titre was positive in 16/21 (76%), and negative in 5/21 (24%) of ICTs for whom the titre was assessed. In case of a negative antibody titre, hepatitis A immunoglobulins, which give a 100% protection for several weeks depending on the immunoglobulin dose, are administered before travelling.
Ciprofloxacin was prescribed to 13/30 (43%) ICTs, azithromycin to 14/30 (47%) ICTs (corresponding with the number of ICTs travelling to Southeast Asia, as per protocol of the Dutch national coordinating centre for travel advice), and 3/30 (10%) ICTs did not receive a prescription for on-demand antibiotics. These three ICTs were HIV-patients with a CD4 count between 200-500 cells/mm^3, which is not a strict indication for prescription of on demand antibiotics, according to the protocol of the Dutch national coordinating centre for travel advice.

Travel-related health problems during and after travelling

During travel, 16/30 (52%) ICTs and 11/30 (37%) controls reported a health problem (p= 0.194) (Figure 2). Travel-related health problems were mainly gastrointestinal: 8/30 (27%) ICTs and 7/30 (23%) controls reported an episode of diarrhoea (unformed stools more than three times a day). Other reported gastrointestinal complaints were nausea, vomiting, loss of appetite and weight loss. Reported health problems other than gastrointestinal complaints were coughing, dyspnoea, nasal congestion, chest pain, fatigue and pruritus/urticaria. Although more ICTs than controls reported health problems, differences were not statistically significant (Figure 2). In the 2-4 weeks post-travel only 6/30 (20%) ICTs and 5/30 (17%) controls reported travel-related health problems (Figure 3).

Figure 2: Numbers of participants with travel-related health problems during travelling

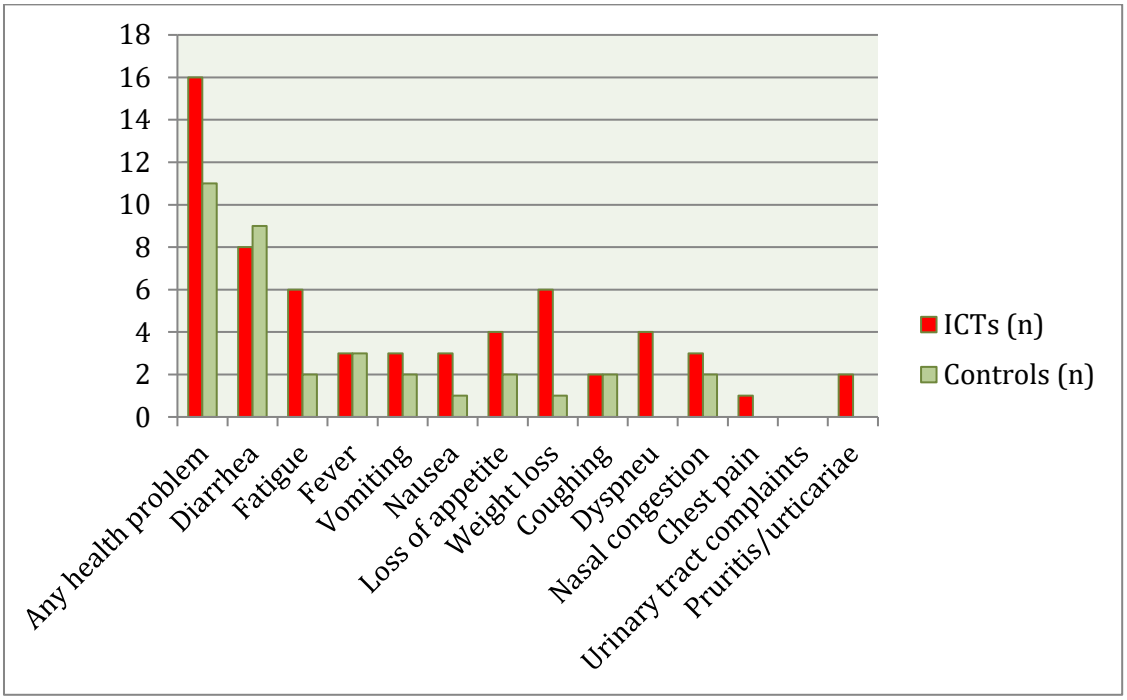
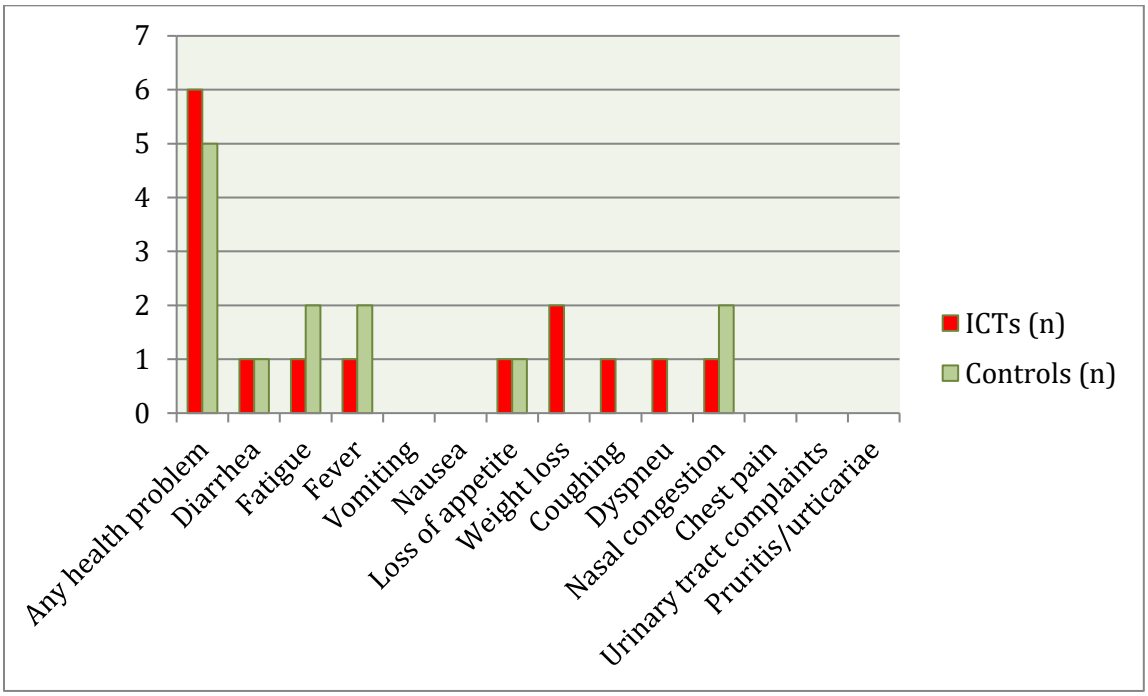


Figure 3: Numbers of participants with travel-related health problems post-travelling



Medical visits during and after travelling

Of 30 ICTs, 4 (13%) visited a physician or hospital during travel, versus none of the control participants. Reasons for these medical visits were severe diarrhoea (2 patients), severe coughing and respiratory tract symptoms in conjunction with fever (1 patients), and an INR control measurement (1 patient). Of the 2 (7%) ICTs with severe diarrhoea, 1 received a normal saline infusion; and 1 was advised to take Oral Rehydration Solution (ORS). The ICT with coughing and fever was advised to take antibiotics.

Post-travel, 2 (7%) ICTs visited a hospital: one was examined at the emergency department and discharged, and one was admitted. Of the control participants, 2 (7%) consulted a physician post-travel; none was referred to a hospital.

The ICT visiting the emergency department had a fever for > 3 days. This participant, who was known with psoriatic arthritis and treated with immunosuppressive combination therapy, was suspected of typhoid fever and received azithromycin orally; however a final diagnosis was not established. The admitted ICT, who was treated with immunosuppressive combination therapy because of a kidney transplantation, and also had a replaced mitral valve, had pneumonia and received intravenous moxifloxacin. Both ICTs recovered well. The two control participants visited because of fever and nasal congestion, and dizziness, respectively. Both recovered with spontaneous symptom resolution without further intervention (Table 3).

Table 3: Medical visits during and after travelling

	Immunocompromised patients	**Control group**	**P-value (95% CI)**
Medical visits during travelling *n* (%)	4	0	0.112
Reasons and advice	**-** Severe diarrhoea day (participant was advised to use ORS) - Severe diarrhoea and vomiting (participant received NaCl 0.9% infusion) - Severe coughing with fever (participant was advised to use AB) - INR measurement	NA	NA
Medical visits post-travelling *n* (%)	1	2	1.000
Reasons and advice	- Fever (participant received azithromycin)	- Fever and nasal congestion (participant was advised to wait and see) - Dizziness	
Hospital admissions during and post-travelling *n* (%)	1	0	1.000
Reasons	- Pneumonia (participant received moxifloxacin i.v.)	NA	NA

Antibiotic use

More ICTs than controls used antibiotics during and post-travel (6/30; 20% versus 1/30; 3%, p= 0.103). Reasons for antibiotic use among ICTs were coughing without fever (2/6; 33%), diarrhoea (2/6; 33%), pneumonia (1/6; 17%), and undifferentiated fever during and post-travel (1/6; 17%). The control participant had used antibiotics because of a dental treatment and prescription by his dentist.

Of the ICTs who had used antibiotics, 4/6 (13%) had a proper indication to do so (according to the protocol of the Dutch national coordinating centre for travel advice or prescribed by a physician), however 2/6 (33%) ICTs had used antibiotics without a clear indication i.e. coughing without fever. Reversely, 6/30 (20%) ICTs had an actual indication to use antibiotics (diarrhoea ≥ 3 times see [3, 22]), but did not do so (Table 4).

Table 4: Antibiotic use during and after travelling

	Immunocompromised patients	Control group	P-value (95% CI)
AB use during and post-travelling *n* (%)	6 (20)	1 (3)	0.103
Reasons for use	- Coughing without fever (n=2) - Diarrhoea (n=2) - Pneumonia post-travelling (n=1) - Fever e.c.i during and post-travelling (n=1)	Pre-travelling prescribed by dentist (n=1)	
Used AB with indication*	2 (7)	0 (0)	0.492
AB prescribed by physician	2 (7)	1 (3)	1.000
Used AB without indication	2 (7)	0	0.492
Did not use AB while indicated following guideline*	5 (17)	NA	NA

* Guideline recommendation: Start antibiotics (azithromycin or ciprofloxacin) after the first unformed stool (3, 22).

Risk behaviour

Participants were asked "whether they had taken into account the hygiene and quality of care of a country when they chose the visited country". Significantly more ICTs than controls answered this question positively (14/30; 47% versus 6/30; 20%, respectively: p= 0.028). ICTs explained that they "*did not want to visit a yellow fever endemic area"*, *"wanted to go to a safe country because of a bad experience during a previous journey"*, *"adjusted the immunosuppressive therapy before travel after consultation of their specialist"*, *"had fear of complaints of their chronic disease during travel and therefore wanted to visit a safe country", "had researched the quality of the hospitals in the visiting country"*, *"discussed the visiting country with their specialist before travel"*. Controls explained that they *"took [activated charcoal] and ORS with him",* "*wanted to go to a safe country because of illness during a previous journey".*

More ICTs than controls also took into account the type and hygiene of the accommodation where they stayed, (10/30; 33% versus 5/30; 17%, p= 0.136). ICTs explained that they *"did not want to camp anymore since the disease"* or *"wanted to stay in clean hotels because of the disease"*. Controls explained that they *"checked hygiene of the accommodation before staying there"* or *"chose a clean hotel because of the children".*

ICTs and controls exhibited similar risk behaviour during travel, with 20/30 (67%) ICTs versus 21/30 (70%) controls (p= 0.781) having taken measures to prevent travel-related illness. Measures that were taken in both groups were: drinking of bottled water; not eating food from street vendors; avoiding contact with stray dogs and cats; and not swimming in fresh water. Furthermore, some ICTs avoided malaria-endemic areas in the visiting countries (Table 5).

Table 5: Risk behaviour

	Immunocompromised patients	**Control group**	**P-value (95% CI)**
Took into account hygiene and risks when choosing the visited country *n* (%)	14 (47%)	6 (20%)	0.028*
Reasons and measures taken with regard to choice of country	*- "Did not want to visit a yellow fever endemic area."* *- "Went to a country where he had been before."* *- "Had a bad experience in the past, therefore, wanted to go to a 'safe' country."* *- "Adjusted immunosuppressive medication before travelling."* *- "Because of fear of IBD-complaints, wanted to visit a 'safe' country."* *- "Researched quality of hospitals in visiting country."* *- "Discussed visiting country with the nephrologist."*	*- "Took ORS/[an activated charcoal product with him."* *- "Because of illness/ hospital admission on previous journey, wanted to go to a 'safe' country."*	
Took into account type and hygiene of accommodation	10 (33%)	5 (17%)	0.136
Reasons and measures taken with regard to choice of accommodation	*- "Does not want to camp anymore since the disease."* *- "Stayed in clean hotels because of the disease."*	*- "Stayed in same hotel as always because that feels safe."* *- "Checked hygiene of accommodation."* *- "Chose a hygienic hotel because of the children."*	
Adjusted behaviour because of the risk of illness	20 (67%)	21 (70%)	0.781
Reasons and measures taken with regard to behaviour	*- "Only drinking bottled water."* *- "Did not buy food from the street food stalls."* *- "Avoided street dogs and cats."* *- "did not swim in fresh water."* *- "did not go to malaria-endemic areas."*	*- "Only drinking bottled water."* *- "Did not buy food from the streets."* *- "Avoided street dogs and cats."* *- "did not swim in fresh water."*	

*Statistically significant result ($p < 0.05$)

Discussion

In this exploratory study, we analysed self-reported travel-related health problems in ICTs compared to sex- and age-matched immunocompetent controls. We also evaluated antibiotic use, medical help seeking and risk behaviours in ICTs compared to controls.

Post-vaccination antibody titres

In our study, nearly 25% of ICTs had a negative hepatitis A titre. Titres were assessed to check whether an ICT who had received two hepatitis A vaccinations up to 25 years before still had an adequate titre; and to check whether an ICT who was vaccinated during the pre-travel visit, mounted a sufficient immune response and reached protection as defined by a positive titre. However, the data show that vaccination is probably less effective and that the duration of post-vaccination protection is probably shorter. This underscores the importance of antibody titre assessments during the pre-travel consult. Furthermore, the administration of an extra priming dose of hepatitis A should be considered, as this has been shown to be successful in the study by Rosdahl et al. (23)

Travellers' diarrhoea

In our limited-size cohort, ICTs did not have significantly more travel-related health problems than controls. Travellers' diarrhoea was comparable in both groups (8 ICTs vs 7 controls). However, particularly weight loss and fatigue were reported more frequently by ICTs. Our sample size was too small to draw firm conclusions, but the findings are suggestive for a trend towards more travel-related health problems in ICTs, except travellers' diarrhoea.

This is supported by the findings of Wieten et al. (14), who reported more travel-related health problems in ICTs in comparison to healthy controls, and by the findings of and of Baaten et al. (15, 16), who reported slightly higher, however not significantly different, frequencies and severity of travellers' diarrhoea in ICTs and in patients with diabetes mellitus (15, 16). Like our study, this study of Wieten et al. (14), evaluated travel-related health problems in ICTs. Their study, however, was performed retrospectively so that bias in self-reported health problems by a delay in time could not be excluded. Furthermore, our study focused more on antibiotic use, the reasons participants gave for this use and risk behaviours during travel while their study was primarily focused on infectious causes of travel-related health problems (14).

Interestingly, although the incidence of travellers' diarrhoea was almost equal, consequences seemed more severe in ICTs compared to controls. Of ICTs, two sought medical help because of diarrhoea while none of the controls did.

Standby-antibiotics are prescribed to prevent ICTs from such complications. Previous studies have demonstrated that a significant amount of ICTs never receives a prescription of standby-antibiotics (24, 25). Our study demonstrates that 20% (6/30) of ICTs did not use the prescribed standby-antibiotics while this was actually indicated according to current Dutch guidelines (start after the first unformed stool) (3, 22). Reversely, 7% (2/30) of ICTs used the prescribed standby-antibiotics while this was

not indicated. Both can be potentially dangerous: not taking antibiotics increases the risk of complications of travellers' diarrhoea whereas injudicious use of antibiotics increases the risk of acquisition of ESBL-producing enterobacteriaceae and of contracting *Clostridium difficile* infection (17-19). Arcilla et al. (17) found that antibiotic use was an important predictor for the acquisition of enterobacteriaceae in healthy travellers. Therefore, careful instructions are important when on demand antibiotics are prescribed to ICTs. Although beyond the context of this study, it would be interesting to investigate whether e-health can contribute to improvement of care for ICTs during travel.

Risk behaviours

With regard to travel-related health problems other than travellers' diarrhoea, ICTs seemed to be more severely affected, with one post-travel admission of an ICT who had contracted pneumonia and another ICT visited the emergency department with an acute febrile illness, who was empirically treated with oral antibiotics under suspicion of typhoid fever, but without final diagnosis. Although there is no one-size-fits-it-all solution, physicians caring for ICTs should be aware of this vulnerability and be very careful instructing these patients. However, also ICTs should be aware of their situation and, for example, take into account their health status when choosing to which country to travel.

Our study evaluated risk behaviours with regard to the chosen country and accommodation, and which hygienic measures were taken. Our findings on this subject are encouraging. We showed that indeed significantly more ICTs compared to controls took into account the hygiene and quality of health care of a country when choosing their destination, which is encouraging. They more often consulted their physician before travel, did not risk travelling to yellow fever endemic areas because the yellow fever vaccination is contra-indicated, or they wanted to travel to a country to where they had travelled before.

Strengths and limitations

Our study is one of few studies to date evaluating behaviour and health problems of travelling immunocompromised patients. Furthermore, our study is the first study evaluating antibiotic use and medical visits, and evaluating motivations of ICTs on their behaviours. The main limitation of this study was its pilot character due to its small sample size. However, this study was performed in preparation of a larger multi-centre study; providing us with useful information concerning the sample size calculation, study design and questionnaire. A second limitation is the limited generalisation of our results, because up to 30% of ICTs do not visit a pre-travel clinic. In future, more research with larger sample sizes is needed to gain a better insight in travel-related health problems in ICTs, in (on demand) antibiotic use, and in risk behaviours. Novel web-designed applications and/or questionnaires could help receiving more specific information from participants travelling to remote countries. At last, since antibiotic use during travel has recently been recognised as a risk factor for acquisition of resistant

enterobacteriaceae, incidences and consequences of such acquisition in ICTs, particularly when having used (on demand) antibiotics, need further investigation.

Conclusions and recommendations

This exploratory study demonstrates that ICTs tend to have more travel-related health problems, tend to use (on demand) antibiotics more often and tend to consult a physician more often during and post-travel compared to immunocompetent controls. However, ICTs showed to have difficulties to use on demand antibiotics correctly (as proposed in the protocol of the Dutch national coordinating centre for travel advice); in certain cases thus increasing the risk of acquisition of resistant enterobacteriaceae. It is encouraging that more ICTs took into account the hygiene and quality of health care of a country when choosing the travel destination. Pending on further research, we recommend that ICTs are advised and instructed at a travel clinic specialised in ICTs. However, even then careful instruction is needed.

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APPENDIX (AVAILABLE ONLINE)

Supplementary File 1: Questionnaire on travel-related health problems, antibiotic use, medical visits and risk behaviours

Section 3

Epilogue

Chapter 8

Summary and General Discussion

Central to this thesis is the immunocompromised patient (ICPs), and more specifically, infection prevention by vaccinations in these patients. Specific vaccination recommendations exist for ICPs (1). The recommendation of pneumococcal vaccination is one of the more important aspects of vaccination guidelines for ICPs. However, although ICPs are recognized as being at an increased infection risk, a key question is whether this also holds true for pneumococcal infections. This is of particular relevance since unawareness of the importance of this vaccination by physicians and patients is identified as a significant factor for a low pneumococcal vaccination coverage worldwide (2-5).

Summary

In **Chapter 2**, we therefore studied the incidence rate of invasive pneumococcal disease (IPD) in ICPs. We demonstrated that the incidence rate of IPD is increased in all studied ICP conditions, but particularly in HIV-positive patients and in those who underwent a solid organ or stem cell transplantation. This underpins the importance of current pneumococcal vaccination recommendations. However, paradoxically, precisely in ICPs, immune responses are impaired and vaccinations are not as immunogenic as in immunocompetent individuals (6-10). In **Chapter 3** we showed that immunosuppressive medication in patients with autoimmune disease mitigated the response to both pneumococcal conjugate vaccine (PCV) and pneumococcal polysaccharide vaccine (PPSV). Furthermore, in **Chapter** 4 we showed that immunosuppressive medication in patients with inflammatory bowel disease (IBD) mitigated the response to the sequential pneumococcal vaccination schedule with PPSV administered two months after administration of PCV. In both studies conventional immunomodulators (cIMs) e.g. oral prednisolone >10mg/d, thiopurine or methotrexate, also often called disease-modifying antitheumatic drugs (DMARDs), and combination therapy with a cIM and a biological immunomodulator (bIM) had most severe effects on the immune response to pneumococcal vaccination, whereas the effect of monotherapy with bIMs was milder. In **Chapter 5,** pneumococcal vaccination in allogeneic HSCT recipients was studied. Nearly 15% of HSCT recipients did not reach seroconversion after pneumococcal vaccination.

A problem of note throughout our research on the immunogenicity of pneumococcal vaccinations in ICPs was the lack of internationally uniform definitions of seroconversion and correlates of protection. Nonetheless, these studies emphasized that more research is needed; applying uniform and internationally accepted definitions and correlates of protection, and investigating the immunogenicity of innovative vaccination schedules. Until then, post-vaccination antibody concentrations should be assessed to check whether seroconversion has been reached in ICPs.

Vaccination recommendations and other recommendations in the context of travelling ICPs were studied in **Chapter 6**. Antibody concentrations were not measured in a large proportion, nearly 45% and 25% for hepatitis A (hepA) and B (hepB) respectively, of ICPs with an indication for such an antibody concentration measurement. Half of all travelling ICPs in a specialised travel clinic did not receive a prescription of on-demand

antibiotics, while these were actually indicated. This is of particular importance, since it is demonstrated in **Chapter 7** that travelling ICPs tended to have more frequent, and more severe travel-related health problems compared to immunocompetent travellers, and that ICPs had difficulties with using on-demand antibiotics correctly (i.e. used per recommendation by the protocol of the Dutch National Coordinating Centre for Travel Advice (LCR) (11). These findings call for internationally uniform guideline recommendations for travelling ICPs, and for an increased awareness of the importance of complete and careful instructions, among physicians in the field of travel medicine.

The findings and conclusions of this thesis support existing vaccination recommendations for ICPs with scientific evidence, and contributed to their improvement; e.g. we proposed a new pneumococcal vaccination schedule for allo-HSCT recipients (**Chapter 5**). Furthermore, the importance, and need for implementation in current vaccination guidelines, of antibody concentration measurements post-vaccination is underscored. However, most importantly, further research in this field, using uniform definitions and correlates of protection, is needed. Until then, physicians should be aware of the vulnerability of ICPs and should give careful instructions according to current recommendations and evidence.

Section 1: Pneumococcal infections and vaccination in immunocompromised patients

Incidence rate of invasive pneumococcal disease

Infection with *Streptococcus pneumoniae* is a considerable threat, putting the very young, the elderly and ICPs at particular risk (12-16). IPD including invasive pneumonia, bacteraemia, and meningitis, are alarming manifestations, which carry substantial morbidity and mortality (12, 14-17). Therefore, pneumococcal vaccination is recommended in infants, the elderly, and risk groups (18, 19). Since immune responses are less robust in ICPs, they are advised to adhere to a sequential schedule with PCV followed by PPSV two months later (reviewed by Lopez et al. (18)). However, such vaccination programmes come with high costs and a high burden for ICPs. Therefore, they should be well-considered and evidence-based. The frequency at which an infection occurs, thus the incidence rate, is one of the fundamental building blocks at which such a vaccination recommendation should be built. In **Chapter 2**, by means of a systematic review and meta-analysis, we demonstrated that the IPD incidence rate was increased compared to healthy control cohorts, in all studied immunocompromising conditions.

In HSCT recipients, the IPD incidence was 60-fold higher in autologous HSCT recipients and 80-fold higher in allogenic HSCT recipients, compared to the IPD incidence in healthy control cohorts.

We showed that the IPD incidence in HIV patients decreased since the introduction of ART; however, the incidence was still more than 30-fold higher in the advanced cART in both African and non-African countries. These findings are supported by studies that show that adequate ART and a high CD4 count are associated with a lower IPD risk,

and by studies that show that inadequate ART and a low CD4 count are associated with a higher IPD risk (20-28); and by studies that demonstrate that humoral immune defects in HIV are persistent regardless of ART (29), which put HIV patients at persistent risk of infection.
In patients with chronic inflammatory disease, the IPD was only slightly increased, approximately 6-fold higher.
However, IPD is not always confirmed by culture. Therefore, since in this systematic review, IPD was defined by isolation of *S. pneumoniae* from a normally sterile site; we interpret these incidence rates as an underestimation of the total burden of pneumococcal infections in ICPs.

Pneumococcal vaccination in ICPs

Based on the findings of the systematic review on IPD in ICPs, we conclude that the recommendation for pneumococcal vaccination in ICPs is well substantiated. Thus, that ICPs should indeed receive pneumococcal vaccination. However, the next question that arises is which vaccination schedule ICPs should receive. We performed several immunogenicity studies in ICPs to answer this question.

Patients with an autoimmune disease

In a systematic review and meta-analysis (**Chapter 3)**, we studied seroconversion rates to serotypes 6B, 23F or both following vaccination with either PCV or PPSV in patients with autoimmune disease. In included studies seroconversion was most often defined as a two-fold increase in antibody concentrations pre- and post-vaccination. We showed that treatment with immunosuppressive agents impair immune responses to both PCV and PPSV in these patients. Treatment with cIMs (referred to as DMARDS in **Chapter 3**) or combination therapy (treatment with TNFα blocking agents and cIMs) led to a worse immune response as compared to the immune response when treated with monotherapy TNFα blocking agents. The same applied to our prospective cohort study (**Chapter 4**) evaluating the immune response to the currently recommended sequential schedule (administration of PPSV two months after administration of PCV) in IBD patients. In this study we measured serotype-specific pneumococcal IgG concentrations pre- and post-vaccination in IBD patients of all serotypes present in PCV13 and PPSV23 vaccines, except for serotype 17F. We defined seroconversion as a post-immunisation antibody concentration of ≥1.3 µg/mL for ≥70% of all measured serotypes (30, 31). Since TNFα blocking agents act more specifically on the immune system than cIMs (32-35), this is in line with our hypothesis.
Post-vaccination GMCs were lower in patients receiving immunosuppressive therapy (**Chapter 3)**. However, the relation between pre- and post-vaccination GMCs is subject of debate. One meta-analysis in immunocompetent individuals showed no relation between pre- and post-vaccination antibody concentrations (36). However, in the elderly and in patients with primary immunodeficiencies, high pre-vaccination GMCs were related to a lower ratio of pre- and post-vaccination GMCs (31, 37). Findings are, thus, bifurcated, precluding the drawing of conclusions.

Against our hypothesis, our systematic review showed that PPSV elicited a stronger immune response than PCV in ICPs, but not in controls (**Chapter 3**). We speculate that immunosuppressive treatment precludes the T-cell mediated immune response, which is provoked by PCV in immunocompetent individuals, and which induces a strong memory response and the production of high-affinity long-lived plasma cells (38). However, the results of this study only apply to short-term immunogenicity. Up to date, few studies were devoted to long-term immunogenicity (39-41). Published studies showed that antibody concentrations decreased to lower levels in patients with AD than in immunocompetent controls (39-41). We concluded that immunosuppressive treatment negatively affects intervals of protection after pneumococcal vaccination. Therefore antibody concentration measurements and possibly a booster vaccination in the years after pneumococcal vaccination are needed. However, hyporesponsiveness, by which an initial dose of pneumococcal vaccination limits the number of responding B-cells after subsequent doses of pneumococcal vaccination, has been described (42, 43). Thus, research on new vaccination schedules is necessary.

In this light, we studied the immune response to the currently recommended pneumococcal vaccination schedule in IBD patients in **Chapter 4**. This prospective cohort study was one of the first studies that evaluated immunogenicity of the currently recommended schedule in patients receiving immunosuppressive therapy. This study is therefore very relevant for contemporary practice.

From this study we concluded that the currently recommended schedule for ICPs is safe and immunogenic in the majority of IBD patients. IBD patients receiving immunosuppressive therapy had lower SCRs compared to IBD patients not on immunosuppressive therapy (SCR to all evaluated serotypes was 59% versus 81%, respectively). However, compared to the findings in our systematic review on immunogenicity, the sequential vaccination schedule was still more immunogenic compared to single vaccination with PCV or PPSV (a reported SCR of 26% and 37%, respectively, in patients with AD on immunosuppressive therapy).
Surprisingly, SCRs were lower for serotypes present in both vaccines (50%) compared to SCRs for serotypes exclusive to PPSV (70%). This exclusively applied to IBD patients using immunosuppressive medications and not to IBD patients not using these medications. This finding implicates that hyporesponsiveness can indeed play a role in the immunogenicity of vaccination schedules with subsequent pneumococcal vaccinations. However, further research is needed to draw firm conclusions on this phenomenon.
The results of this prospective study in IBD patients combined with the results of our systematic review, led us to conclude that at this moment the sequential schedule of PCV, followed by PPSV two months later, should be advised in patients with an AD. Furthermore, vaccination should best be administered before the start of immunosuppressive therapy. However, since intervals of protection after pneumococcal vaccination are probably shorter, antibody titres should regularly be

assessed. In case of waning titres, a booster vaccination could be considered. However, more research is necessary on this topic, particularly, the phenomenon of hyporesponsiveness should be better understood.

Allogeneic HSCT-recipients

In **Chapter** 5 we investigated the immune response to pneumococcal vaccination in allogeneic HSCT recipients. Allogeneic HSCT recipients who did not receive immunosuppressive therapy during vaccination were vaccinated ≥1 year post-HSCT with three doses of PCV at a one-month interval and one dose of PPSV six months after the last PCV. We investigated seroconversion of all serotypes present in either the PCV or PPSV vaccine, except from serotype 17F. Seroconversion was defined as a post-immunization antibody concentration ≥ 0.35-1.0 µg/mL for ≥7/13 serotypes. The SCR was 33/39 (85%) for serotypes present in both vaccines. For the 10 serotypes that were only covered by PPSV, SCRs varied between 55 and 85%, except for serotype 12F for which the SCR was below 20% (**Chapter 5)**. The systematic review we performed on this topic (**Chapter 5**) showed similar results. Although pneumococcal vaccination was generally immunogenic in allogeneic HSCT recipients, seroconversion of serotypes present in both vaccines was still not reached in 15% of patients. Therefore, we concluded that in HSCT recipients routine measurements of post-vaccination antibody concentrations are very important so that, if necessary, a booster vaccine can be administered. Vaccination guidelines recommend to repeat administration of PPSV every 5 years (44, 45). However, these booster vaccinations are debatable, since the study of Cordonnier et al. (46) showed no beneficial effects of a PPSV booster 2-10 years after the initial complete revaccination schedule. We therefore conclude that, as in patients with AD, also in allogeneic HSCT recipients, hyporesponsiveness could play a role; however, it needs to be emphasized that this phenomenon needs further research (42, 43).

The literature review of this study aimed to study differences between early (3 months post-HSCT) and late (9 months post-HSCT) start of the revaccination schedule. Short-term immune responses were similar; however, two years post-HSCT SCRs of late starters were significantly higher compared to SCRs of early starters. In this light, late start of the revaccination schedule post-HSCT seems more advantageous, but also puts unprotected HSCT-recipients at risk of life-threatening IPD in the first year-post HSCT when they are the most vulnerable (47, 48). Therefore, we proposed a new vaccination schedule combining advantages of early and late starting of the revaccination schedule post-HSCT. In this schedule, revaccination starts 4-6 months post-HSCT with three PCVs at a one-month interval; a fourth PCV is administered 6 months after the previous (3rd PCV), followed by PPSV 2 months later.

Definitions and correlates of protection

A recurrent limitation in our immunogenicity studies was that internationally used uniform definitions and correlates of protection are flawed. For pneumococcal serotypes, the WHO recommends a cut-off value of 0.35 µg/mL, but this value is based on three clinical studies in children who received PCV7 (for adults PCV13 is

recommended) and is not serotype-specific [16-18]. The real protective concentration might be higher for several serotypes, which has recently been shown in a study in adults [19]. The more conservative American Academy of Allergy, Asthma & Immunology (AAAAI) defined seroconversion as a post-immunization antibody concentration of ≥1.3 µg/mL for ≥70% of all measured serotypes. In the literature, a wide variety of definitions of seroconversion were used in different studies (10). Cut-off values as correlates of protection were either based on an absolute GMC concentration post-vaccination, on an absolute increase between pre- and post-vaccination GMCs, or on the ratio between pre- and post-vaccination GMCs. The minimal antibody GMC level differed between studies. Furthermore, studies differed in the number of serotypes for which the antibody concentrations were assessed, and the number of required seroconverted serotypes as a definition for seroconversion; some studies even assessed a total antibody concentration of all assessed serotypes together.

These mixed definitions precluded us from inclusion of a large number of studies in our systematic review on immunogenicity, and it furthermore hampers the use of results from (our) studies in a broad group of physicians or researchers. We therefore call for a uniformly and internationally used definition of seroconversion for pneumococcal serotypes.

Section 2: Immunocompromised travellers

International travelling has become an integral part of an affluent lifestyle over the past decades (49). Numbers show that the number of international flights increased exponentially and are expected only to increase further (49). It is imaginable that, in the past, ICPs were not able to travel because of their impaired health; however, treatment improvements and novel therapies enabled patients to lead normal lives including travelling (50, 51). During travel, ICPs are exposed to a variety of exotic and non-exotic pathogens increasing infection risks. Often, health care is of inferior quality compared to health care at home (52). Furthermore, vaccinations are generally less effective in ICPs than in healthy individuals, and live-attenuated vaccines, e.g. Yellow Fever (YF) vaccination, are contra-indicated (11, 53).

These factors put travelling ICPs at heightened risks (54-57). Therefore, they are advised to visit a specialised pre-travel clinic in advance of travelling (50, 55, 58, 59). Antibody concentration measurements for hepatitis A and B and the prescription of stand-by antibiotics are indicated (11, 58). Few studies evaluated pre-travel care data of travelling ICPs. In **Chapter 7**, we evaluated characteristics of pre-travel care for 2,104 travel episodes in 1,826 travelling ICPs. We described P/E, P/I and A/I rates in ICPs and compared P/E rates to rates in the healthy population (**Chapter 7**). P/E was defined as the number of protected (P) travellers divided by the total number of travellers to disease endemic (E) countries where vaccination is recommended (as per LCR protocol (11)) (60). P/I was defined as the number of patients who received a prescription (P) for a standby antibiotic during travelling, divided by the total number of

patients with an indication (I) for this prescription. A/I was defined the number of patients in whom an antibody (A) concentration was measured, divided by the total number of patients with such an indication (I).
For most vaccinations, P/E rates were ≥ 90%, and as high as in the healthy population (60). As expected, the P/E rate of the YF vaccine was lower (70%) because this vaccine is contra-indicated in ICPs (11, 53). However, vaccination before start of immunosuppressive therapy most likely explains this relatively high P/E rate. P/E rates of the rabies vaccine were lower. Many ICPs chose not to be vaccinated against rabies because in ICPs immunoglobulins are routinely required as post-exposure treatment, irrespective of pre-exposure vaccinations (11, 61).
A/I and P/I rates were lower than expected, demonstrating that a substantial number of travelling ICPs does not receive optimal pre-travel care. The A/I rate was 57% and 76% for hepA and B, respectively. ICPs with a higher hepB A/I rate were those with HIV, severe liver disease, severe renal impairment or haemodialysis. For these patients, particularly for haemodialysis patients, strict guidelines exist with regard to hepB vaccination (62). The P/I rate was 51%. P/I rates were higher for patients with (functional) asplenia and for patients treated with immunosuppressive agents.
In our observational pilot study on travel-related health problems and antibiotic use (**Chapter 8**), we furthermore show that 20% (6/30) of travelling ICPs did not use prescribed standby antibiotics in situations in which current Dutch guidelines recommend to use these antibiotics. Reversely, 7% (2/30) used stand-by antibiotics while guidelines not strictly indicated their use. The prescription of stand-by antibiotics is encouraged because they should prevent severe complications of travellers' diarrhoea (11, 58). However, recently published studies recognized antibiotic use as a risk factor of acquisition of antibiotic resistant enterobacteriaceae and for *Clostridium difficile* infection, which made the role of standby-antibiotics in travelling ICPs erratic (63-65).
In **Chapter 8**, we also elaborate on travel-related health problems and risk behaviours in ICPs. Although results on travel-related health problems were not statistically significant due to the small sample size, the findings of this study pointed towards a trend of more travel-related health problems, and more consultations of a physician in ICPs during travelling as compared to immunocompetent controls. Furthermore, in ICPs, consequences of travel-related health problems such as travellers' diarrhoea appear to take a more serious disease course than in immunocompetent controls.
With regard to risk behaviours in travelling ICPs, our data showed that significantly more ICPs than controls considered a country's general hygiene and quality of health care in the decision-making on the travel destination. For example, a considerable number of ICPs consulted their physician before travelling, or did not risk travelling to a yellow fever endemic area without a valid vaccination.

From our studies on travelling ICPs, we conclude that the role of standby antibiotics demands further evaluation. However, until then, instructions with concern to standby antibiotics, and other pre-travel advices such as the measurement of antibody concentrations post-vaccination, should be carefully given. Therefore, increased

awareness concerning pre-travel care in ICPs among health care workers in the field of pre-travel medicine is needed.

The future

This thesis demonstrated that infections risks and vaccine immunogenicity are different in ICPs. The paradox that ICPs are at increased infection risk whilst benefitting less from vaccinations was the main topic of this thesis. We showed that immune responses to pneumococcal vaccination in patients with an AD receiving immunosuppressive therapy, and in allogeneic HCT recipients were impaired. We also showed that pre-travel care for ICPs is suboptimal, and that detailed instructions concerning standby antibiotics are needed. However, many questions remain and new questions arise.

First, we stress the need for internationally uniform definitions of seroconversion and correlates of protection of pneumococcal vaccinations. With regard to immunogenicity studies, we studied immune responses in patients with an AD receiving most commonly prescribed immunosuppressive agents; however, novel biological treatments are continuously developed and integrated in the care for patients with AD. The effects on vaccine immunogenicity of these novel therapies need evaluation. A compelling idea would be that some of these biological treatments target the immune system so specifically, and thus minimally, that live-attenuated vaccines can be administered safely.

We studied immunogenicity of existing pneumococcal vaccination schedules, which failed to achieve seroconversion in a considerable number of ICPs. However, as a next step, studies should be performed evaluating different schedules in order to figure out which is most optimal in ICPs.

Furthermore, we studied short-term immunogenicity and because few studies evaluated long-term immunogenicity, we underscored the importance of routine, and regularly repeated post-vaccination antibody concentration measurements. Future studies, however, should devote to long-term immunogenicity of the pneumococcal vaccination. The measurement of antibody concentrations and application of internationally uniform definitions and correlates of protection, as we propose, would help performing these studies.

Although this thesis was devoted to immunogenicity studies of pneumococcal vaccination, a next step would be to perform studies on cost-effectiveness and efficacy in ICPs, as defined by the number of prevented pneumococcal infections by pneumococcal vaccination. Our systemic review on IPD incidence rates in ICPs could help to design such studies.

Our studies on travelling ICPs paved the path for a larger multi-centre study to evaluate travel-related health problems, antibiotic use and risk behaviours in ICPs. To study these characteristics truly prospectively, e-health applications, which travelling ICPs and controls can use during travelling would help collecting data that are more accurate. The role of standby antibiotics in travelling ICPs needs to be further

established with respect to the recently found association between antibiotic use and the acquisition of antibiotic resistant enterobaceriaceae.

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prevent human rabies: recommendations of the advisory committee on immunization practices. MMWR Recomm Rep. 2010;59(Rr-2):1-9.
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Nederlandse Samenvating

Nederlandse samenvatting

Immuungecompromitteerde patiënten hebben een hoger risico op infecties door de verminderde werking van hun immuunsysteem. Voor hen is infectiepreventie door middel van vaccinaties van groot belang. Echter, juist in immuungecompromitteerde patiënten is de immuunrespons op vaccinatie verminderd. Dit leidt tot de klinische paradox dat diegenen die vaccinaties het hardste nodig hebben, hier het minst waarschijnlijk voordeel van hebben. Dit doet veel vragen oprijzen op wetenschappelijk, maar belangrijker nog, op klinisch gebied. Omdat het onmogelijk is om alle vragen met betrekking tot dit onderwerp te behandelen in één proefschrift, kozen wij ervoor om de, vanuit klinisch oogpunt, meest relevante onderwerpen te behandelen. Dat zijn: pneumokokkeninfectie en –vaccinatie en de reizigersgeneeskunde voor immuungecompromitteerde patiënten.

In **Hoofdstuk 2** beschreven wij in een systematisch literatuuronderzoek de incidentie van invasieve pneumokokkeninfecties onder immuungecompromitteerde patiënten.
Hoewel pneumokokkenvaccinatie wordt geadviseerd in internationale richtlijnen, zijn deze richtlijnen vaak schaars onderbouwd met betrekking tot incidentie studies van pneumokokkeninfecties in deze populatie. Om die reden, zochten wij op systematische wijze naar beschikbare literatuur hierover en includeerden in totaal 45 relevante artikelen.
Meta-analyse van 38 van deze 45 artikelen toonde een incidentie onder HIV patiënten vanaf het jaar 2000 van 331/100.000 persoonsjaren in niet-Afrikaanse landen en in Afrikaanse landen van 318/100.000 persoonsjaren. Onder patiënten met een autologe en allogene stamceltransplantatie was de incidentie 696/100.000 respectievelijk 812/100.000 persoonsjaren. Onder patiënten met een orgaantransplantatie werd een incidentie berekend van 465/100.000 persoonsjaren en onder patiënten met een chronische inflammatoire ziekte van 65/100.000 persoonsjaren. Deze aantallen zijn fors verhoogd in vergelijking tot de immuun-competente populatie waar een incidentie van 10/100.000 persoonsjaren werd berekend en onderbouwen daarom de huidige vaccinatierichtlijnen voor immuungecompromitteerde patiënten.

In **Hoofdstuk 3** beschreven wij in een systematisch literatuuronderzoek het effect van immunosuppressiva op de immunogeniciteit van pneumokokkenvaccinatie in patiënten met een auto-immuunziekte. Ook hier geldt, dat ondanks de aanbeveling voor pneumokokkenvaccinatie, weinig bekend is over het effect van de vaccinatie bij gebruik van immunosuppressiva. We includeerden 22 artikelen met in totaal 2.077 patiënten, van wie 1623 immunosuppressiva gebruikten en 454 patiënten tot de controlegroep behoorden.
Meta-analyse toonde aan dat zowel het polysacharide als het geconjugeerde vaccin minder goed werkten in patiënten die immunosuppressiva gebruikten vergeleken met controles. Het effect van TNFα remmers was milder ten opzichte van het effect van DMARDS of wanneer een combinatie van beiden werd gebruikt. Verder, toonden wij aan dat het polysacharide vaccin (PPSV) onder patiënten die immunosuppressiva gebruikten, beter werkte dan het geconjugeerde vaccin (PCV). Bij controles was er

geen verschil in de werking van beide vaccins. Een verklaring hiervoor is dat de stimulus die het immuunsysteem krijgt doordat door de conjugatie van het vaccin ook T cellen worden betrokken bij de immuunreactie, wegvalt bij gebruik van immunosuppressiva. Deze bevindingen onderbouwen het huidige vaccinatiebeleid waarbij zowel het geconjugeerde als het polysacharide vaccin worden toegediend.

In **Hoofdstuk 4** onderzochten wij in een prospectief cohort patiënten met IBD de immuunrespons op het huidige aanbevolen vaccinatieschema waarbij eerst het geconjugeerde vaccin en 2 maanden daaropvolgend het polysacharide vaccin wordt toegediend. Vóór 2012 werd alleen het polysacharide vaccin aanbevolen, zodat de meeste studies op dit gebied gericht zijn op een vaccinatieschema met ofwel het polysacharide ofwel het geconjugeerde vaccin, maar niet op de combinatie van beiden. We maakten onderscheid tussen vier groepen, namelijk patiënten op 1) DMARDS, 2) anti-TNFα monotherapie, 3) combinatietherapie, 4) controles (IBD patiënten die geen immunosuppressiva gebruiken). De antistofconcentratie werd gemeten voorafgaand aan en 4-8 weken nadat beide vaccinatie waren toegediend.
Het vaccinatieschema was veilig en over het algemeen immunogeen in patiënten met IBD. Echter, patiënten die één of meer immunosuppressiva gebruikten hadden een significant slechtere respons op het vaccinatieschema dan controle patiënten: een adequate respons werd gemeten in 59% (61/104) van de patiënten die een immunosuppressivum gebruikten in vergelijking tot 81% (30/37) van de controle patiënten. Patiënten die meer dan één immunosuppressiva gebruikten hadden de minst goede immuunrespons op het vaccinatieschema; 52% (15/29) had een adequate respons. Om die reden adviseren wij om het vaccinatieschema te starten vóórdat immunosuppressieve therapie wordt gestart.

In **Hoofdstuk 5** onderzochten wij in een retrospectief cohort patiënten na allogene stamceltransplantatie de immuunrespons op pneumokokkenvaccinatie. Ook verrichten wij een systematisch literatuuronderzoek naar pneumokokkenvaccinatie in deze patiëntencategorie. Antifstofconcentraties werden gemeten in 42 van 103 patiënten die tussen 2009-2017 de vaccinatie-polikliniek van het AMC bezochten. Van deze patiënten had 85% een goede respons op serotypes die gedekt worden door zowel het geconjugeerde als het polysacharide vaccin en 62% op serotypes die alleen gedekt worden door het polysacharide vaccin.
Het systematisch literatuuronderzoek omvatte zes relevante studies; 64-98% van allogene stamceltransplantatie patiënten had een goede respons op pneumokokkenvaccinatie in deze studies. Ook toonde dit literatuuronderzoek geen verschil aan in succespercentages tussen het vroeg (3-6 maanden) en het laat starten (≥1 jaar) na transplantatie. Echter wel was de respons op lange termijn beter indien laat gestart werd met het vaccinatieschema. Om die reden stellen wij een nieuw vaccinatie schema voor waarbij het vaccinatieschema opgestart wordt 3-6 maanden, en een extra polysacharide vaccinatie wordt toegediend ≥1 jaar na transplantatie. Op die manier worden de voordelen van vroeg en laat starten gecombineerd,

respectievelijk het eerder bereiken van bescherming en het beter behouden van deze bescherming op de lange termijn.

In **Hoofdstuk 6** onderzochten wij in een retrospectieve cohortstudie karakteristieken van het reizigersadvies voor immuungecompromitteerde en chronisch zieke reizigers. Deze categorie patiënten zijn kwetsbare reizigers. Immuungecompromitteerde patiënten zijn vatbaarder voor infecties, tijdens een reis worden zij blootgesteld aan een velerlei 'vreemde' pathogenen. Reizigersadvies voor deze patiënten omvat daarom naast de standaardadviezen, onder andere ook het verrichten van een antistofmeting na hepatitis A en B vaccinatie en het voorschrijven van een 'on demand antibioticakuur', te gebruiken in geval van diarree.
Wij analyseerden gegevens van 2.104 immuungecompromitteerde en chronisch zieke reizigers en vonden dat de vaccinatiegraad van benodigde vaccinaties ≥90% was; dat het percentage van patiënten met een daadwerkelijke antistofmeting als deze werd aanbevolen, na hepatitis A vaccinatie 56.6% was en na hepatitis B vaccinatie 75.7%; en dat het percentage van patiënten aan wie 'on demand antibiotica' werd voorgeschreven als dit geïndiceerd was, 50.6% was.
Hiermee toonden wij aan dat meer aandacht nodig is voor reizigersadviezen speciaal bedoeld voor immuungecompromitteerde en chronisch zieke reizigers.

In **Hoofdstuk 7** onderzochten wij in een case-control studie reisgerelateerde klachten, antibiotica gebruik, gebruik van medische zorg en risicogedrag onder immuungecompromitteerde reizigers en vergeleken deze bevindingen met bevindingen onder op geslacht en leeftijd gematchte controles.
Hoewel wordt aanbevolen 'on demand antibiotica' voor te schrijven aan immuungecompromitteerde reizigers ter preventie van reizigersdiarree, is het de vraag hoeveel vaker dit voorkomt in deze patiëntencategorie en in hoeveel gevallen er sprake is van een gecompliceerd beloop.
Ondanks dat immuungecompromitteerde reizigers vaker reis gerelateerde klachten, antibioticagebruik en gebruik van medische zorg rapporteerden, waren verschillen in bovengenoemde karakteristieken niet significant. Wel toonde dit onderzoek aan dat 2 van de 30 immuungecompromitteerde reizigers de antibiotica gebruikten zonder een strikte indicatie en dat 6 van de 30 geen antibiotica gebruikten terwijl hier op basis van de aanbevelingen wel een indicatie voor was. Tot slot, toonde dit onderzoek dat significant meer immuungecompromitteerde reizigers dan controles voorzorgsmaatregelen namen met betrekking tot de keuze voor hun bestemming.
Op basis van deze bevindingen is de aanbeveling voor het gebruik van 'on demand antibiotica' gegrond, maar is uitgebreide en zorgvuldige instructie door de voorschrijvende arts noodzakelijk.

Hoofdstuk 8 omvat de Engelse samenvatting en discussie van de verschillende hoofdstukken uit dit proefschrift. De grootste limitaties in dit proefschrift werden besproken en ook aanbevelingen voor nieuw en/of aanvullend onderzoek werden gedaan.

Centraal in dit proefschrift stond infectiepreventie door vaccinatie in de immuungecompromitteerde patiënt/reiziger. Het eerste deel van dit proefschrift richtte zich op de aanbeveling voor pneumokokkenvaccinatie bij immuungecompromitteerde patiënten. Het tweede deel richte zich op het reizigersadvies voor immuungecompromitteerde reizigers en de gezondheidsrisico's gedurende het reizen in deze groep.

Curriculum vitae

Curriculum vitae

Work experience

2016-2018	PhD Candidate, Centre of Tropical Medicine and Travel Medicine; Academic Medical Centre, Amsterdam.
2015-2016	House Officer emergency department; OLVG-Oost, Amsterdam.
2014-2015	House Officer internal medicine; Groene Hart Ziekenhuis, Gouda.

Research

2016-2018	PhD Candidate, Center of Tropical Medicine and Travel Medicine; Academic Medical Center, Amsterdam.
2015	Contribution to medical research, Title: Analysis and improvement of the usage of an interactive internet platform for optimising management of cardiovascular risk factors in older persons; Department of Neurology, Academic Medical Centre, Amsterdam.
2014	MD Scientific Elective (Master Report), Title: Qualitative research on the motivation of women on Sint Maarten to illegally terminate an unplanned pregnancy; Medical Sociology, department of Medical Humanities, VU medical centre, Amsterdam; Bush Road Clinic, Sint Maarten.
2010-2011	Student research assistant, research on gastric cancer; Department of Pathology, VU medical centre, Amsterdam.

Electives and clinical rotations abroad

2014	Extracurricular Internship; Medisch Contact, Utrecht, the Netherlands.
2014	Elective Tropical Medicine; Kawolo Hospital, Uganda.
2013	General Practitioning; Bush Road Clinic, Sint Maarten.
2011	Voluntary internship paediatrics; Tel-Aviv, Israel.
2007-2010	Language courses Spanish in Ecuador; Mexico and Spain.
2007-2011	Voluntary work at orphanages; Ecuador and Mexico.

Education

2007-2014	Bachelor’s and Master’s degree in Medicine; Free University of Amsterdam, Amsterdam.
2010-2011	Spanish Language and Culture, propaedeutics, *Cum Laude*; University of Amsterdam, Amsterdam.
2001-2007	Gymnasium, *Cum Laude*; Groene Hart Lyceum, Alphen aan den Rijn.

PhD Portfolio

General courses

Year	*Course*	*Hours/ECT*
2016	Academic Englisch Writing UvA Talen	80/2.9
2016	BROK (Basiscursus Klinisch Onderzoekers)	28/1
2016	Pubmed Basics	2.5/0.1
2016	Searching for a CAT (Critical Appraisal Topic)	2.5/0.1
2016	Searching for a systematic review	2.5/0.1
2016	Practical biostatistics	40/1.4
2016	Systematic review	20/0.7
2016	Scientific Writing in English for Publication	42/1.5
2016	Oral Presentation in English	22/0.8
2016	The AMC world of sciences	20/0.7
2016	Clinical data management	9/0.3
2016	OpenClinica Training	12/0.4
2017	Project management	16/0.6
Total		296.5/10.6

Specific courses

Year	*Course*	*Hours/ECT*
2016	Infectious Diseases	36/1.3
2017	Advanced Immunology	80/2.9
2017	Biupama (Basiscursus Infectieziekten en Uitheemse Pathologie)	80/2.9
Total		196/7.1

Seminars, workshops and master classes

2016-2018 Weekly department seminars

Presentations / Congresses / Symposia

2016 Apr Symposium on the Emergence and Spread of multidrug Resistant Bacteria in an Era of Globalization; Utrecht. No presentation.

2016 Sep IBD evening training for physicians and nurses of the Amsterdam region.

2017 Apr IBD lunch and learn meeting.

2017 May Oral presentation at The 15th Conference of the International Society of Travel Medicine; Pre-travel care for immunocompromised and chronically ill travellers: a retrospective study.

2017 May 5th network meeting of MIA 's-Hertogenbosch The Netherlands**;** No presentation.

2017 Oct Oral presentation at PhD retreat Amsterdam Infection and Immunity; Immunity against measles before and after allogeneic stem cell transplantation

2017 Oct Poster presentation at ECTMIH Antwerp**;** Pre-travel care for immunocompromised and chronically ill travellers: a retrospective study

2017 Oct Oral presentation at ECTMIH Antwerp; Travel-related health problems in the immunocompromised traveler (pIMMUNOTRAV): a questionnaire based case control Study. (Prepared by M. van Aalst, presented by A. Goorhuis)

Awards and Prizes

2017 Young Investigator Award; by the *International Society of Travel Medicine*.

List of co-authors

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List of publications

Publications in this thesis

1. Van Aalst M, Verhoeven R, Omar F, Stijnis C, van Vugt M, de Bree GJ, et al. Pre-travel care for immunocompromised and chronically ill travellers: A retrospective study. Trav Med Infect Dis. 2017;19:37-48.

2. Van Aalst M, van Ruissen MCE, Verhoeven R, de Bree GJ, Goorhuis A, Grobusch MP. Travel-related health problems in the immunocompromised traveller: An exploratory study. Trav Med Infect Dis. 2018;25:50-7.

3. Van Aalst M, Lotsch F, Spijker R, van der Meer JTM, Langendam MW, Goorhuis A, et al. Incidence of invasive pneumococcal disease in immunocompromised patients: A systematic review and meta-analysis. Trav Med Infect Dis. 2018;24:89-100.

4. Van Aalst M, Langedijk AC, Spijker R, de Bree GJ, Grobusch MP, Goorhuis A. The effect of immunosuppressive agents on immunogenicity of pneumococcal vaccination: A systematic review and meta-analysis. Vaccine. 2018;36(39):5832-45.

5. Langedijk AC, van Aalst M, Meek B, van Leeuwen EMM, Zeerleder S, Meijer E, et al. Long-term pneumococcal vaccine immunogenicity following allogeneic hematopoietic stem cell transplantation. Vaccine. 2019;37(3):510-5.

6. van Aalst M, Garcia Garrido HM, van der Leun J, Meek B, van Leeuwen EMM, Löwenberg M, et al. Immunogenicity of the currently recommended pneumococcal vaccination schedule in patients with inflammatory bowel disease. Clinical Infectious Diseases. 2019. *Epub ahead of print.*

Other publications

7. Van Aalst M, Nelen CM, Goorhuis A, Stijnis C, Grobusch MP. Long-term sequelae of chikungunya virus disease: A systematic review. Trav Med Infect Dis. 2017;15:8-22.

8. Grobusch MP, van Aalst M, Goorhuis A. Yellow fever vaccination - Once in a lifetime? Trav Med Infect Dis. 2017;15:1-2.

Dankwoord

De top is bereikt!!! Eindelijk en onverwacht toch snel!
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