

Missed Opportunities? A Retrospective Study Into Adults Hospitalized With Invasive Infection From Airway Pathogens

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Background. Invasive disease caused by airway pathogens, including *Streptococcus pneumoniae*, *Haemophilus influenzae*, *Neisseria meningitidis*, and *Moraxella catarrhalis*, has high morbidity and mortality worldwide, with immunodeficiency being a known association with recurrent disease. The study aimed to describe the frequency of known immunodeficiency and predisposing factors in adult patients presenting with invasive infections and determine the frequency of screening for and detection of immunodeficiency.

Methods. A retrospective analysis was conducted at a large tertiary Australian health service, comprising multiple centers. Patients aged 18 years or older, in whom the above pathogens were isolated from sterile sites, were included as identified through a microbiology database, between 2015 and 2020. Using electronic medical records, patient demographics, medical history, outcomes of admission, and pathology results were captured and reviewed to address the aims.

Results. In 252 patients, *S pneumoniae* was the most common culprit, isolated in 73% (185/252), compared to 14.3% (36/252) and 11.5% (29/252) of infections caused by *H influenzae* and *N meningitidis*, respectively. Known diagnoses of secondary immunodeficiency were common (31% of patients). Of those presenting with invasive pneumococcal disease, 78% had at least 1 predisposing condition, though only 9 patients (6%) had previously received pneumococcal vaccination. Despite poor screening for immunodeficiency, 12 new diagnoses were made. While the commonest immunodeficiency was secondary, due to hematological and solid organ malignancies, 3 new primary immunodeficiency diagnoses were made.

Conclusions. Immunodeficiency is common in this patient population. Screening should be undertaken to ensure timely diagnosis and treatment of the underlying condition to avoid future morbidity and mortality.

Keywords. immunodeficiency; invasive; pneumococcal; vaccination.

Invasive diseases caused by airway pathogens, including *Streptococcus pneumoniae*, *Haemophilus influenzae*, *Neisseria meningitidis*, and *Moraxella catarrhalis*, are important due to their high morbidity and mortality with high prevalence worldwide [1, 2]. Apart from *Moraxella* species, they are also largely preventable with vaccination. Despite the availability of vaccines in Australia, 2014 cases of invasive pneumococcal disease (IPD) and 281 cases of invasive meningococcal disease were reported in 2018, with a mortality rate of approximately 6% for both pathogens [3, 4]. Case numbers are higher in the United

States (US), with >31 000 cases of IPD and approximately 350 cases of meningococcal disease diagnosed each year [5, 6].

Recurrent invasive infections have consistently been associated with immunodeficiency in adult and pediatric populations, predisposing to additional morbidity and mortality [7–12]. Predominantly antibody deficiencies, such as hypogammaglobulinemia, are relatively common, albeit underrecognized, in adults presenting with IPD [13]. Deficiencies in complement factors are an uncommon but important consideration in patients with invasive meningococcal disease [14]. Diagnosis of primary immunodeficiency (PID) can be challenging, particularly in adults, as it is rare and presents with variable clinical manifestations, both infective and noninfective. Multiple studies have highlighted issues with delayed diagnosis, emphasizing the importance of identifying patients who may benefit from screening [15–17].

Secondary immunodeficiency (SID), including human immunodeficiency virus (HIV), hematological malignancies, asplenia, and solid organ transplantation, has also been associated with risk of invasive infection [8, 18–20]. Furthermore, other chronic conditions including diabetes mellitus, chronic respiratory disease, and liver disease have been identified as

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increasing the risk of IPD [21–23]. Thus, assessing for these risk factors is important, as it allows for an opportunity to optimize vaccinations and reduce future morbidity risk. Various world health authorities, including the Australian Department of Health and the US Centers for Disease Control and Prevention (CDC), recommend immunization for at-risk groups as summarized in Appendix 1 [6, 24–28].

The primary aim of this study was to describe the frequency of known immunodeficiency and other risk factors in patients presenting to a large tertiary Australian health service with invasive infection caused by an airway pathogen. The secondary aim was to determine the frequency of screening and detection of new diagnoses of immunodeficiency or other risk factors for invasive disease. It was predicted that screening for PID and SID is rarely undertaken by healthcare practitioners. Furthermore, it aimed to determine rate of vaccination in patients presenting with invasive disease and if vaccination is being considered in the context of their invasive infection.

METHODS

Study Design and Population

A retrospective analysis was conducted of patients, aged ≥ 18 years, who presented to Monash Health, a large health network comprising of 5 public hospitals in the southeast of Melbourne, Australia. The study was conducted over a 6-year period (2015–2020) and included admitted patients identified as having invasive infection with any of the following airway pathogens: *S pneumoniae*, *N meningitidis*, *H influenzae*, and *M catarrhalis*.

Data Collection

Participants were identified from the health service’s microbiology database, capturing invasive isolates (blood cultures or other sterile sites, including cerebrospinal fluid, pleural, and synovial specimens). Electronic medical records were reviewed, capturing patient demographics, outcome of hospital admission, and organism serotype. We evaluated records for documentation of known PID or SID, and other conditions associated with an increased risk of invasive infection. Additionally, records were reviewed for documentation of prior pneumococcal or meningococcal vaccination and where this was not documented, the Australian Immunisation Register was reviewed.

To determine whether underlying immunodeficiency or other risk factors were considered, pathology results were reviewed for relevant tests and imaging records were evaluated for evidence of asplenia or malignancy, within 3 months of patients’ admission. There are no available guidelines currently to guide screening of patients. Therefore, in screening for SID, we defined a minimum set of tests that we considered as important to perform for the exclusion of conditions known to be commonly associated with invasive infection, as summarized in

Table 1. Summary of Screening Investigations in Patients With Invasive Infection

| | |
|--|--|
| Initial Screening for Immunodeficiency and Other Risk Factors | |
| Full blood examination + peripheral blood film | |
| Urea, electrolytes, and creatinine | |
| Liver function tests | |
| HbA1c | |
| Lymphocyte subsets | |
| Serum immunoglobulins | |
| HIV serology | |
| Multiple myeloma screening: SFLC, SPEP, UPEP (in addition to immunoglobulins) | |
| Further Screening Dependent on Clinical History and Other Patient Factors | |
| Detailed primary immunodeficiency screen | Detailed secondary immunodeficiency screen |
| Neutrophil function testing | Examination or imaging to assess for underlying malignancy |
| Memory B cells | |
| Vaccine responses | |
| Complement factors (C3/C4) | |
| Complement function testing | |
| Other, more specialized immunophenotypic and functional tests | |
| Imaging to assess for presence of a spleen or splenomegaly (abdominal ultrasound) | |
| Abbreviations: HbA1c, glycated hemoglobin; HIV, human immunodeficiency virus; SFLC, serum free light chains; SPEP, serum protein electrophoresis; UPEP, urine protein electrophoresis. | |

Table 1. For PID screening, the tests were compiled to exclude immunodeficiencies commonly associated with infections caused by encapsulated organisms. We also searched for more detailed screening that may have been performed according to clinical history and findings from the initial screening investigations.

Statistical Analysis

Categorical variables were summarized using frequency and percentage. Continuous variables were summarized using median and range.

Ethics Approval

Approval to conduct the study was provided by the Monash Health Human Research Ethics Committee (RES-20-0000-522A). Patient consent was not required.

RESULTS

Over the 6-year study period, 266 patients were identified as having 1 of the 4 described respiratory pathogens isolated from a sterile site (Figure 1). Fourteen patients who were not admitted to the health service were excluded. The majority of patients had invasive infection with *S pneumoniae* (185/252 [73%]), with 14% (36/252) and 12% (29/252) of infections caused by *H influenzae* and *N meningitidis*, respectively.

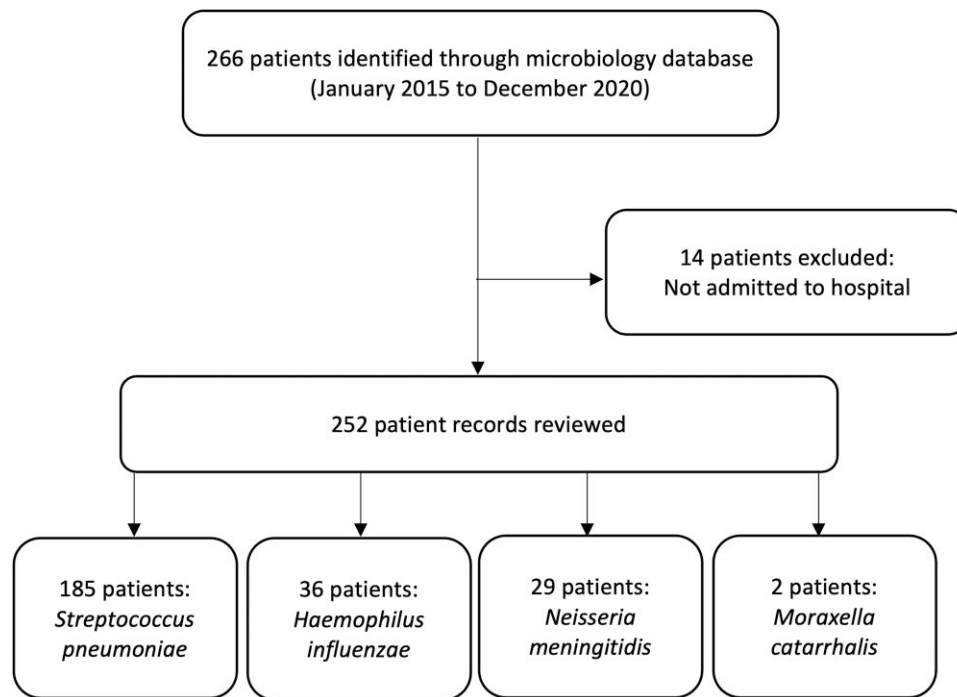


Figure 1. Flowchart describing identification and inclusion of data.

Moraxella catarrhalis accounted for infection in only 2 patients (0.8%).

Patient Demographics

Patient demographics are outlined in Table 2. Fifty-four percent of patients were female with a median age of 64 years (range, 18–95 years). Patients with meningococcal disease were younger on average (median, 54 years). Patients were predominantly Australian born (132/252 [52%]), with only 1 patient identifying as an Aboriginal or Torres Strait Islander.

Microbiology

The majority of organisms were isolated from blood, either by culture or polymerase chain reaction (PCR) testing (231/252 [92%]). Other sites of invasive disease included abdominal/peritoneal fluid culture (3 patients with *H influenzae*); joint tissue or fluid culture (most commonly from patients with *S pneumoniae*); and, more rarely, from pleural, pericardial, and corneal tissue/fluid culture.

Organism Serotypes

Serotyping was available for 178 of the *S pneumoniae* isolates. The majority of isolates were vaccine serotypes (121/178 [68%]), defined in Appendix 2. For the *N meningitidis* isolates, capsule group W predominated (15/29 [52%]).

Clinical Characteristics

Requirement for admission to the intensive care unit was common, occurring in 25% (63/252) of patients. Length of stay varied widely, with a median stay of 7 days. Mortality rate during hospital admission was high, particularly in those patients with pneumococcal infection (17/185 [9.2%]). Of the 2 patients with *Moraxella* infection, 1 had joint infection and the other had pneumonia with bacteremia. Both patients were discharged from the hospital, with 1 patient requiring extended rehabilitation (36 days).

Known Risk Factors for Invasive Disease

On admission, only 1 patient had a known diagnosis of a PID: congenital asplenia. SID was common (77/252 [30.6%]), with solid organ and hematological malignancy observed more commonly (Table 3). History of SID was less common in those with invasive meningococcal disease.

The majority of those presenting with IPD had at least 1 predisposing condition associated with a known increased risk of invasive disease. Age >65 years was the most common risk factor (94/185 [50.8%]), although there were high rates of diabetes mellitus (43/185 [23.2%]), chronic respiratory disease (40/185 [20.5%]), current cigarette smoking, and cardiac disease.

Three patients with known hematological malignancy and evidence of secondary hypogammaglobulinemia had 2 separate episodes of IPD during the study period. All 3 had a plasma cell dyscrasia. One patient had 4 months between episodes, both of

Table 2. Summary of Cases of Invasive Infection With Airways Pathogens Between 2015 and 2020 (N = 252)

| Characteristic | No. per Organism (%) | | | |
|------------------------------------|----------------------|--|--|---|
| | All | <i>Streptococcus pneumoniae</i> ^a | <i>Neisseria meningitidis</i> ^b | <i>Hemophilus influenzae</i> ^c |
| No. of cases | 252 (100) | 185 (73) | 29 (12) | 36 (14) |
| Site of isolation | | | | |
| Blood culture/PCR | 231 (92) | 173 (94) | 25 (86) | 32 (89) |
| CSF culture/PCR | 15 (6) | 11 (6) | 4 (14) | 0 (0) |
| Joint fluid or tissue culture | 13 (5) | 9 (5) | 2 (7) | 1 (3) |
| Abdominal/peritoneal fluid culture | 3 (1) | 0 (0) | 0 (0) | 3 (8) |
| Other | 1 (0) | 1 (0.5) | 0 (0) | 1 (3) |
| Patient demographics | | | | |
| Male sex | 116 (46) | 89 (48) | 10 (35) | 15 (42) |
| Female sex | 136 (54) | 96 (52) | 19 (65) | 21 (58) |
| Age, y, median (range) | 64 (18.3–91.5) | 63.7 (18.3–94.9) | 54.1 (18.4–79.2) | 69.4 (20.6–91.5) |
| Australian born | 132 (52) | 96 (52) | 17 (59) | 18 (50) |
| Hospital admission | | | | |
| LOS, d, median (range) | 7 (0–135) | 7 (0–135) | 8 (1–7) | 6 (0–70) |
| Required ICU care | 70 (28) | 50 (27) | 11 (38) | 8 (22) |
| Infectious diseases involvement | 113 (45) | 74 (40) | 17 (59) | 15 (42) |
| Outcome | | | | |
| Discharged home | 194 (77) | 140 (76) | 25 (86) | 28 (78) |
| Died in hospital | 19 (8) | 17 (9) | 0 (0) | 2 (6) |
| Discharged to rehabilitation | 29 (12) | 21 (11) | 2 (7) | 5 (14) |
| Self-discharged from hospital | 6 (2) | 5 (3) | 0 (0) | 1 (3) |
| Transfer to other acute hospital | 4 (2) | 2 (1) | 2 (7) | 0 (0) |

Only 2 cases of *Moraxella catarrhalis* infection were found in this cohort; therefore, data for those infections are not summarized in this table.

Abbreviations: CSF, cerebrospinal fluid; ICU, intensive care unit; PCR, polymerase chain reaction.

^aOrganism serotype for *Streptococcus pneumoniae*: vaccine type, 121 (65%); nonvaccine type, 57 (31%).

^bOrganism serotype for *Neisseria meningitidis*: B, 11 (38%), W, 14 (48%), Y, 4 (14%).

^cOrganism serotype for *Hemophilus influenzae*: type e, 2 (6%); nontypeable, 31 (86%).

which were caused by the same vaccine serotype (19A) and therefore may reflect relapsed or indolent infection. In the other 2 patients, the 2 episodes were 6 and 7 months apart, respectively, and caused by 2 different serotypes. None had documentation of immunoglobulin replacement therapy between episodes. Overall mortality rate was increased in those with SID (13% compared to 5% of patients without SID, $P = .06$).

Screening for Immunodeficiency and Other Risk Factors

Only 4 patients, all with pneumococcal disease, had all investigations of an initial screen as outlined in Table 1. Table 4 summarizes the screening undertaken in this cohort following a diagnosis of invasive infection. The majority of patients had a blood film performed. Two patients had presence of Howell-Jolly bodies. Further imaging was not performed to assess the spleen, nor was there an indication that the significance of this result was noted by the treating teams. Screening for diabetes mellitus by means of glycated hemoglobin (HbA1c) was undertaken in 43 patients without a prior diagnosis of diabetes (22%). Two of those patients had a new diagnosis of type 2 diabetes, both in the context of IPD.

Excluding those with a known diagnosis of hematological malignancy, a “comprehensive myeloma screen” was

performed in only 12 patients. Serum immunoglobulins were the most commonly requested. A new diagnosis of hematological malignancy or monoclonal gammopathy of uncertain significance (MGUS) was made in 6 patients, often as a result of multiple components of the screen being abnormal.

Screening for HIV was only performed in 34% of patients without a known diagnosis (84/249). It was performed in 69% (18/26) of those admitted under infectious diseases (ID), or in 48% of those admitted under a different unit but with ID input (54/113), compared with 11% (12/113) of those without ID involvement ($P < .001$). Computed tomography to assess for malignancy was performed at similar rates in all infection groups.

Only 6 patients underwent detailed PID screening, with ID involvement again resulting in increased screening (6/139 compared to 0/113 without ID involvement). Three new diagnoses of PID were made, all of which underwent detailed screening, following recovery from acute illness, and had abnormalities in several investigations.

New Diagnoses of Immunodeficiency

New diagnoses made as a result of screening are summarized in Table 5. Nine new diagnoses of SID were made with

Table 3. Prevalence of Known Immunodeficiency and Other Predisposing Conditions for Invasive Infection per Organism

| Immunodeficiency/Predisposing Condition | All (N = 252)* | Pneumococcus (n = 185) | <i>Haemophilus</i> (n = 36) | Meningococcus (n = 29) |
|--|----------------|------------------------|-----------------------------|------------------------|
| History of primary immunodeficiency | | | | |
| Congenital asplenia | 1 (0.4) | 1 (0.5) | 0 (0.0) | 0 (0.0) |
| History of secondary immunodeficiency | | | | |
| Any | 77 (31) | 59 (32) | 14 (39) | 4 (14) |
| Solid organ malignancy | 39 (15) | 29 (16) | 6 (17) | 4 (14) |
| Hematological malignancy | 23 (9) | 17 (9) | 5 (14) | 1 (3) |
| Other immunosuppressive medication | 32 (13) | 20 (11) | 11 (31) | 1 (3) |
| Functional asplenia/splenectomy | 7 (3) | 7 (4) | 0 (0) | 0 (0) |
| Renal transplant | 5 (2) | 3 (2) | 2 (6) | 0 (0) |
| HIV | 3 (1) | 2 (1) | 1 (3) | 0 (0) |
| Other predisposing conditions | | | | |
| Any | 190 (75) | 144 (78) | 28 (78) | 16 (55) |
| Age >65 y | 127 (50) | 94 (51) | 24 (67) | 8 (28) |
| Diabetes | 55 (22) | 43 (23) | 7 (19) | 5 (17) |
| Chronic respiratory | 51 (20) | 36 (21) | 11 (38) | 3 (10) |
| Current smoker | 47 (19) | 37 (20) | 5 (14) | 5 (17) |
| Cardiac disease | 43 (17) | 30 (16) | 11 (31) | 1 (3) |
| CKD (at least stage 4) | 30 (12) | 24 (13) | 6 (17) | 0 (0) |
| Harmful alcohol intake | 14 (6) | 12 (7) | 1 (3) | 1 (3) |
| Chronic liver disease | 13 (5) | 11 (6) | 1 (3) | 1 (3) |
| CSF leak | 2 (1) | 2 (1) | 0 (0) | 0 (0) |

Data are presented as No. (%).

*The two cases of *Moraxella* are not detailed separately in the table.

Abbreviations: CSF, cerebrospinal fluid; CKD, chronic kidney disease; HIV, human immunodeficiency virus.

hematological malignancy being the most common. Two patients were also diagnosed with solid organ malignancies (vulval cancer and cholangiocarcinoma). One patient had an acquired complement deficiency, secondary to a clinical picture and serology consistent with Sjogren syndrome. Of those with new SID diagnoses, 7 (78%) had been either admitted under or reviewed by the ID team.

Three new diagnoses of PID were made. The patients' age ranged from 38 to 62 years. Two patients had IPD and described recurrent otitis media throughout their childhood. Key findings that led to the diagnosis and were common among both patients were persistent, mildly reduced immunoglobulin G levels and absent pneumococcal vaccine responses, resulting in a diagnosis of an antibody deficiency. Both were eligible for intravenous immunoglobulin therapy. One patient also had absent C2 complement levels with reduced classical pathway function on 2 occasions, consistent with a primary complement deficiency.

The third case presented with *H influenzae* bacteremia and pneumonia and was subsequently diagnosed with 22q11 deletion syndrome at 38 years of age, despite having a number of previous medical conditions including autoimmune hemolytic anemia, congenital heart disease, fertility issues, and recurrent sinopulmonary infections. Investigations for immunodeficiency were markedly abnormal with significant hypogammaglobulinemia, reduced B cells with marked depletion of switched memory B cells, and reduced natural killer cells.

Vaccination Status

Data regarding prior vaccination status were missing for 76 patients, with 75 patients known to be unvaccinated. Of the 155 patients with IPD and at least 1 predisposing condition, only 9 had documentation of previous vaccination (9/155 [6%]). Meanwhile, only 3 of 121 patients with vaccine serotype pneumococcus had documentation of prior pneumococcal vaccination, indicating 118 possible events of preventable IPD. Of the 29 patients with meningococcal disease, none had prior vaccination against meningococcal serotype B, 5 had been vaccinated against meningococcal C, and 4 had been vaccinated with the quadrivalent vaccine (serotypes ACWY).

Of the 185 patients with IPD, all were eligible to receive both conjugated and polysaccharide pneumococcal vaccinations. At least 1 vaccine was administered and documented in 54 patients (29.2%). Of the 29 patients with meningococcal disease, 10 had subsequent vaccination. Patients who were reviewed in the ID clinic following invasive infection were more likely to receive subsequent pneumococcal vaccination (32/52 [61.5%] vs 31/175 [18%] of those not attending the ID clinic; $P < .001$).

DISCUSSION

This study highlights potentially missed opportunities when caring for patients presenting with invasive infections, throughout all stages of patient care, pre- and postinfection.

Table 4. Screening Undertaken to Assess for Immunodeficiency or Other Risk Factors for Invasive Infection and the Number of New Diagnoses Arising From These Tests

| Screening Investigation | No. of Patients Tested (%) | No. With an Abnormal Result With New Diagnoses (% of Those Tested) |
|--|----------------------------|--|
| Initial screening | | |
| Peripheral blood film ^a | 218 (87) | 2 (1) ^b |
| Lymphocyte subsets | 36 (14) | 0 (0) |
| Serum immunoglobulins ^a | 73 (32) | 7 (10) |
| HIV serology ^a | 84 (34) | 0 (0) |
| HbA1c ^a | 43 (22) | 2 (5) |
| Multiple myeloma screen ^a | 12 (5) | 6 (50) |
| SPEP ^a | 49 (21) | 6 (12) |
| UPEP ^a | 13 (6) | 0 (0) |
| SFLC ^a | 31 (14) | 3 (10) |
| Detailed immunodeficiency screen | | |
| Complement factors (C3/C4) | 42 (17) | 1 (2) |
| Functional complement testing | 17 (7) | 2 (12) |
| Neutrophil function testing | 13 (5) | 1 (8) ^c |
| Memory B cells | 14 (6) | 4 (29) |
| Vaccine responses | 9 (4) | 3 (33) |
| Imaging of the spleen (abdominal ultrasound) | 37 (15) | 0 (0) |
| Imaging to assess for underlying malignancy | 64 (25) | 2 (3) |

Full blood examination, urea creatinine, electrolytes, and liver function were assessed in all 252 patients and are excluded from the table.

Abbreviations: HbA1c, glycated hemoglobin; HIV, human immunodeficiency virus; SFLC, serum free light chains; SPEP, serum protein electrophoresis; UPEP, urine protein electrophoresis.

^aFor these screening tests, patients with a known diagnosis of the condition were excluded. Proportions of those tested are calculated based on the number of patients tested without a known diagnosis. Known splenectomy (n=2), known HIV (n=3), known hematological malignancy (n=23), known diabetes mellitus (n=55).

^bIncludes 2 patients with detected Howell-Jolly bodies, without further investigation to confirm hyposplenism.

^cReduced phagocytosis with normal production of reactive oxygen species on testing.

While also highlighting the burden of invasive airway pathogen infections within an Australian setting, it confirms the potential for underlying primary immunodeficiencies, as well as secondary immunodeficiencies as common predispositions, particularly solid organ and hematological malignancies, in keeping with previous studies [29].

Additionally, other premorbid chronic conditions were also common, and yet, despite eligibility for pneumococcal vaccination, vaccination rates were low in this cohort. With many of the isolates being vaccine serotypes, this presents as a potentially missed opportunity to prevent morbidity and mortality from invasive disease for 181 patients. Thus, this study highlights the need to consider pneumococcal vaccine eligibility, across all settings of healthcare and upon each patient encounter. Efforts to incorporate pneumococcal vaccination alerts into patients' electronic medical records would likely be beneficial in

increasing physician awareness to this issue. It is important to consider that vaccination rate may have been underestimated due to inadequate documentation of vaccination status. While attempts were made to cross-reference vaccination records in the AIR, mandatory reporting of vaccination did not begin until early 2021 [30].

In line with Australian data, invasive meningococcal disease was relatively uncommon [4], with patients being younger and less likely to have an underlying immunodeficiency compared to patients with IPD. In contrast, SID occurred frequently in patients with *H influenzae* infection, in particular solid organ malignancy. Meningococcal vaccination rates were relatively low, acknowledging that meningococcal ACWY vaccination was only added to the Australian schedule in 2017, approved for those aged 15–19 years, and meningococcal B vaccine (Bexsero) being made routine in 2020 [31]. Our study did not capture *H influenzae* type b vaccination data. However, outside scheduled childhood vaccines, Australian guidelines only recommend vaccination for patients with asplenia and hematopoietic stem cell transplants [24].

Screening for immunodeficiency was relatively uncommon or incomplete. Despite this, several new diagnoses with significant clinical implications were noted. Screening for PID yielded 3 new diagnoses, with hypogammaglobulinemia, which is associated with both IPD and invasive *H influenzae* infection [13, 32], featuring in 2 patients. Newly diagnosed PID patients were >35 years of age and mostly with little relevant medical history. Furthermore, screening for hematological malignancy, in particular plasma cell dyscrasias, yielded 4 new diagnoses plus 2 patients with MGUS. It is unclear whether a specific aspect of the patients' medical history prompted screening in those particular patients, with 1 shortcoming of this study being its retrospective nature and heavy reliance on clinician documentation of all aspects of history, thus resulting in possible documentation bias. Nonetheless, this study demonstrates that where undertaken, screening with an easy and inexpensive test such as serum immunoglobulins led to diagnosis of immunodeficiency (PID or SID) in approximately 10% of tested patients. Thus, this study highlights the potential for diagnosing immunodeficiency with even basic screening and prompts the need for education and increasing awareness among physicians.

Screening for HIV, previously shown to be low in this patient cohort [33], remained low throughout 2020. While no new HIV cases were detected, overall screening was modest and universal screening in all episodes of invasive infection may indeed detect new HIV diagnoses. One important finding highlighted by this study is the usefulness of ID unit involvement, which led to increased screening for immunodeficiency and improved vaccination rates. This may reflect a more focused approach and better understanding of the significance of these infections. The resultant outcome is greater detection of immunodeficiency, with implications to improved patient care.

Table 5. Summary of New Diagnoses of Immunodeficiency

| Patient | Sex, Age | Clinical Disease | Investigations | Final Diagnosis |
|---------|----------|--|--|---|
| 1 | F, 52 y | Pneumococcus: meningitis | Decrease in memory B cells Poor/absent vaccine responses Normal immunoglobulins | Specific antibody deficiency |
| 2 | M, 62 y | Pneumococcus: meningitis and bacteremia | Abnormal vaccine responses, reduced phagocytosis, reduced functional complement, reduced immunoglobulins Normal C3/C4 | Complement deficiency (C2) + specific antibody deficiency |
| 3 | F, 38 y | <i>Haemophilus</i> : bacteremia | Abnormal immunoglobulins, memory B cells, lymphocyte subsets | 22q11 deletion syndrome |
| 4 | M, 75 y | Pneumococcus: bacteremia and bone/joint infection | Abnormal immunoglobulins, SPEP, and SFLC | Multiple myeloma |
| 5 | F, 44 y | Pneumococcus: bacteremia and otitis media | Abnormal immunoglobulins and SPEP Normal SFLC | Multiple myeloma |
| 6 | M, 73 y | Pneumococcus: bacteremia and bone/joint infection | Abnormal immunoglobulins, SPEP, and SFLC | Waldenstrom macroglobulinemia |
| 7 | M, 68 y | Pneumococcus: bacteremia and bone/joint infection | Abnormal immunoglobulins and SPEP | Lymphoplasmocytic lymphoma |
| 8 | F, 63 y | Pneumococcus: meningitis and bacteremia | Abnormal SPEP Normal immunoglobulins and SFLC | MGUS |
| 9 | M, 63 y | Pneumococcus: bacteremia | Abnormal immunoglobulins, SPEP, and SFLC | MGUS |
| 10 | M, 81 y | <i>Haemophilus</i> : bacteremia and gastrointestinal | Abnormal CT imaging and MRCP | Cholangiocarcinoma |
| 11 | F, 74 y | Pneumococcus: bacteremia | Abnormal examination | Vulval cancer |
| 12 | F, 59 y | Pneumococcus: bacteremia | Abnormal memory B cells, vaccine responses, complement factors Normal neutrophil function and immunoglobulins | Complement deficiency secondary to Sjogren syndrome |

Abbreviations: CT, computed tomography; F, female; M, male; MGUS, monoclonal gammopathy of uncertain significance; MRCP, magnetic resonance cholangiopancreatography; SFLC, serum free light chains; SPEP, serum protein electrophoresis.

Finally, this study demonstrates that invasive infections with airway pathogens, while not uncommon, may commonly be associated with immunodeficiency, in particular SID. A primary screen may also yield surprises in an adult population, where diagnosis of PID is often delayed. Here, further weight is thus added to the importance of screening in the context of invasive infection, as an opportunity for early detection, which may expedite treatments and prevent morbidity and mortality. Although there are no specific guidelines that stipulate which investigations to undertake, this study outlines some basic and readily accessible ones, and supports input from ID in the care of these patients. Assessing the cost-benefit of these screening measures and benefits of a defined set of criteria to help guide clinicians at the bedside in deciding whom to screen, and what investigations to perform, would be useful. Further research is required to determine these factors.

Notes

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manuscript. C. D.: Providing input to drafts of manuscript. S. O.: Study concept and design, and reviewing drafts of the manuscript.

Potential conflicts of interest. S. O. sat on the CSL-Behring advisory board meeting on secondary immunodeficiency. All other authors: No reported conflicts.

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Appendix 1. Summary of Recommendations of Vaccination for At-Risk Conditions of Invasive Airway Pathogens

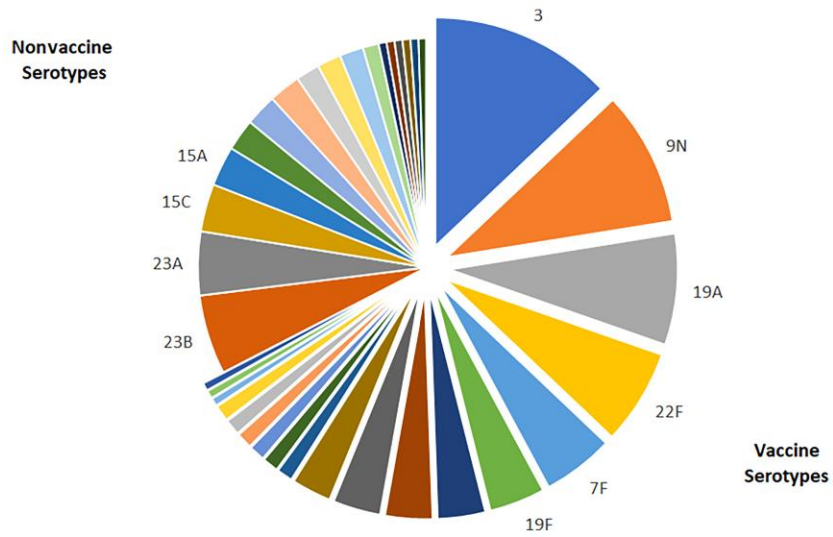
| Organism | Risk Groups Recommended for Vaccination |
|--|--|
| <i>Streptococcus pneumoniae</i> | Aged ≥65 y (United States) |
| | Age ≥70 y (non-Indigenous Australians) |
| | Age ≥50 y (Indigenous Australians) |
| | Solid organ or hematological malignancy |
| | Congenital/anatomical/acquired asplenia |
| | Congenital immunodeficiency |
| | Proven/presumptive CSF leak |
| | HIV infection |
| | Chronic respiratory disease |
| | Chronic renal disease (stage 4/5) |
| | Diabetes mellitus |
| | Chronic liver disease |
| | Immunosuppressive medications |
| | Cardiac disease |
| Harmful use of alcohol | |
| Current smoker | |
| Previous episode of IPD | |
| Cochlear implants ^a | |
| Nephrotic syndrome ^a | |
| Sickle cell disease or other hemoglobinopathies ^a | |
| <i>Neisseria meningitidis</i> | Congenital/anatomical/acquired asplenia |
| | Hematopoietic stem cell transplant ^b |
| | Defects or deficiencies within the complement pathways |
| HIV infection | |
| Current or future treatment with complement inhibitor | |
| <i>Haemophilus influenzae</i> type B | Congenital/anatomical/acquired asplenia |
| | Hematopoietic stem cell transplant |

Adapted from recommendations from the United States Centers for Disease Control and Prevention and the Australian Immunisation Handbook.^[6, 24–2824–28]

Abbreviations: CSF, cerebrospinal fluid; HIV, human immunodeficiency virus; IPD, invasive pneumococcal disease.

^aOnly recommended in the United States.

^bOnly recommended in Australia.



Appendix 2. Pie chart to show the distribution of serotypes in the *Streptococcus pneumoniae* isolates ($n = 178$). Serotype data were missing for 7 patients. The most common serotypes are labeled for both vaccine and nonvaccine serotypes. Vaccine serotypes are those included in the pneumococcal polysaccharide vaccination (Pneumovax 23): 1, 2, 3, 4, 5, 6B, 7F, 8, 9N, 9V, 10A, 11A, 12F, 14, 15B, 17F, 18C, 19F, 19A, 20, 22F, 23F, 33F.