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Prevalence of Immunodeficiency in Children With Invasive Pneumococcal Disease in the Pneumococcal Vaccine Era
A Systematic Review

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IMPORTANCE Despite increasing access to vaccination, invasive pneumococcal disease (IPD) is responsible for approximately 826 000 deaths worldwide in children younger than 5 years each year. To allow early identification and prevention, an improved understanding of risk factors for IPD is needed.

OBJECTIVES To review the literature on the prevalence of primary immunodeficiency (PID) in children younger than 18 years presenting with IPD without another predisposing condition and to inform guidelines for immunologic evaluation after the first episode of IPD based on published evidence.

EVIDENCE REVIEW A literature search of PubMed, Embase (inception [1974] to February 28, 2019), and MEDLINE (inception [1946] to February 28, 2019) was conducted using the terms *Streptococcus pneumonia*, *Streptococcus pneumoniae*, *pneumococcal infection*, *Streptococcus infection*, *pneumococcal meningitis*, *immunodeficiency*, *immune response*, *immunocompromised*, *susceptib**, *precursor*, *predispose**, *recurren**, *newborn*, *neonat**, *infan**, *toddler*, *child*, *preschooler*, *adolescen**, and *pediatric*. Publications reporting original data on immunodeficiency in children with microbiologically confirmed primary or recurrent IPD were included. Strength of clinical data was graded according to the 5-point scale of the Oxford Centre for Evidence-Based Medicine.

FINDINGS In 6022 unique children with primary IPD, 5 of 393 (1.3%) to 17 of 162 (10.5%) of all children and 14 of 53 (26.4%) of those older than 2 years had a PID identified. Higher rates of PID, up to 10 of 15 (66.7%), were found in children with recurrent IPD. Antibody deficiency was the most common immunodeficiency, followed by complement deficiency, asplenia, and rarer defects in T-cell signaling. The site of infection was a key indicator for the risk of underlying PID, with the greatest risk of PID in children with meningitis or complicated pneumonia.

CONCLUSIONS AND RELEVANCE Results of this study suggest that invasive pneumococcal disease, and particularly recurrent IPD, is an important marker of underlying PID in children without other risk factors. The findings also suggest that children older than 2 years with pneumococcal meningitis or complicated pneumonia and all children with recurrent IPD should be referred for an immune evaluation.

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Editorial

Supplemental content

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Streptococcus pneumoniae is an encapsulated gram-positive bacterium that can cause severe invasive disease, including pneumonia, meningitis, and sepsis. The advent of pneumococcal conjugate vaccine has changed the epidemiologic profile of invasive pneumococcal disease (IPD). The 7-valent pneumococcal conjugate vaccine (PCV7) was approved by the US Food and Drug Administration in 2000 and included in the European routine vaccination schedule from 2001. Introduction of PCV7, administered in 3 doses, was associated with a 70% reduction in IPD in vaccine-eligible children across continents.[1] Further gains were made with the introduction of the 3-dose 13-valent pneumococcal vaccine (PCV13), including provision of herd immunity to individuals older than 65 years and those too young to be vaccinated.[2-4] Despite these advances, IPD still accounts for approximately 11% of all deaths in children younger than 5 years, equating to 826 000 deaths annually worldwide.[5]

Even with optimal vaccine coverage, there remains a group of children who have increased susceptibility to IPD. Established risk factors include prematurity, malnutrition, and infection with HIV. Invasive pneumococcal disease may also be associated with primary defects in the immune system, comprising B-cell disorders, complement deficiency, congenital asplenia, and defects involving the Toll-like receptor (TLR) signaling pathway. Newly identified mutations in *MYD88* and *IRAK4* confer a high risk of infection with bacteria such as *S pneumoniae* (**Box 1**).[14,15]

In the era of pneumococcal vaccination, it is postulated that IPD with any serotype is a potential marker of primary immunodeficiency (PID).[16] However, there are no guidelines for immunologic evaluation after the first episode of IPD. Therefore, the aim of this study was to review the literature on the incidence of PID in children presenting with IPD without another predisposing condition.

Key Points

Question What is the frequency of primary immunodeficiency in children with invasive pneumococcal disease since the availability of pneumococcal vaccine?

Findings In this systematic review of 17 studies that included 6022 unique patients with primary invasive pneumococcal disease, children older than 2 years without a known predisposing condition presenting with their first episode of *Streptococcus pneumoniae* meningitis or pneumonia or recurrent invasive pneumococcal disease had rates of primary immunodeficiency as high as 26%.

Meaning This study's findings suggest that immune evaluation may need to be considered in all children older than 2 years presenting with invasive pneumococcal disease, including assessment for immunoglobulin deficiency, specific antibody deficiency, complement disorders, and asplenia.

Methods

This study followed the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) reporting guideline.[17] On February 28, 2019, we searched PubMed, Embase (inception [1974] to February 28, 2019), and MEDLINE (inception [1946] to February 28, 2019) using the OVID interface. The search strategy (**Box 2**) was developed by 2 of us (C.B. and A.G.) in conjunction with an expert medical librarian. Search terms included *Streptococcus pneumonia*, *Streptococcus pneumoniae*, *pneumococcal infection*, *Streptococcus infection*, *pneumococcal meningitis*, *immunodeficiency*, *immune response*, *immunocompromised*, *susceptib**, *precursor*, *predispose**, *recurren**, *newborn*, *neonat**, *infan**, *toddler*, *child*, *preschooler*, *adolescen**, and *pediatric* (Box 2).

The identified titles and abstracts were screened, and the full texts of all relevant articles independently reviewed by 2 of us (C.B. and L.K.P.). Discrepancies were resolved by discussion and, when necessary, review by another of us (A.G.). Hand searching was undertaken after reviewing references of the retrieved articles. Strength of clinical data was graded according to the 5-point scale of the Oxford Centre for Evidence-Based Medicine, which considers study type, inclusion criteria, heterogeneity, and comparison group.[18]

Included publications reported original data on immunodeficiency in those with primary or recurrent IPD. Additional inclusion criteria specified a sample size of 5 or more children younger than 18 years at the time of presentation and the isolation of *S pneumoniae* via culture or polymerase chain reaction from a sterile site (blood or pleural, synovial, or cerebrospinal fluid). Studies were excluded if specific pediatric data were not reported or were unavailable after contacting the corresponding author. Data including population demographics, vaccination rates, and immunologic evaluation were extracted from articles meeting the inclusion criteria.

Results

The search identified 691 articles in Embase, 108 in PubMed, and 54 in MEDLINE. After removal of duplicates, 746 records remained, of which 17 studies met the inclusion criteria (eFigure in the Supplement). Twelve articles studied children with primary IPD (**Table 1**) and 5 focused on those with recurrent IPD (**Table 2**).[19-35]

With exclusion of adult cases, there were 6022 cases of primary IPD. Among the 3851 infections where the site was recorded, bacteremia was the most frequent type, with 1731 cases (48.3%); followed by meningitis, with 1162 (32.5%); pneumonia, with 674 (18.8%); and septic arthritis or osteomyelitis, with 14 (0.4%). Occult bacteremia was differentiated from sepsis in 2 of the 12 studies of primary IPD.[23,26]

Vaccination rates varied between 8% and 75% in the included studies of primary IPD, reflecting differences in local vaccination policies during the study periods.[29,30] Two of the largest studies had high rates of vaccination, with 70% of participants receiving at least 3 doses of either PCV7 or PCV13.[25,26] For 3 studies, vaccine administration changed from PCV7 to PCV13 during the study period.[22,25,26] A standardized protocol for immunologic evaluation was used in 2 studies of primary IPD.[26,29]

Mannose-Binding Lectin Deficiency

Four studies examined the frequency of mannose-binding lectin (MBL) deficiency in a total of 1493 children with primary IPD.[22,24,27,28] All used amplification and typing of the *MBL* genotype at the time of IPD as a surrogate for measurement of serum MBL levels.

Observational studies of 2 unique cohorts of Spanish children with IPD reported a prevalence of MBL deficiency ranging from 41.2%

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Box 1. Risk Factors Associated With Invasive Pneumococcal Disease in Children[a]

- Complement deficiency
  - Complement deficiency (especially classic pathway)
  - C2 deficiency
  - C3 deficiency
- B-lymphocyte disorders
  - X-linked agammaglobulinemia
  - Autosomal recessive agammaglobulinemia
  - Common variable immunodeficiency
  - Specific antibody deficiency
  - Hyper IgM syndrome
  - CD21 deficiency
- T-lymphocyte and TLR-signaling disorders
  - Wiskott-Aldrich syndrome
  - Di George syndrome
  - Severe combined immunodeficiency
  - IRAK-4 deficiency
  - MyD88 deficiency
  - IKBKG/NEMO deficiency
- Asplenia
  - Congenital asplenia
  - Postsurgical asplenia
  - Hyposplenism related to medical disease
- Other risk factors
  - Young age
  - Elderly
  - HIV infection
  - Perinatal HIV exposure (without infection)
  - Malignant neoplasm
  - Bone marrow, hematopoietic stem cell, and solid organ transplant
  - Sickle cell disease
  - Prematurity
  - Chronic renal disease
  - Nephrotic syndrome
  - Chronic liver disease
  - Congenital heart disease
  - Chronic lung disease
  - Severe asthma
  - Insulin-dependent diabetes mellitus
  - Immunosuppression
  - Cochlear implant
  - Cerebrospinal fluid leak
  - Environmental tobacco smoke exposure
  - Air pollution

[a] This list was compiled from previously published studies.[6-13]

Box 2. Embase Search Strategy

1. *Streptococcus* pneumonia/ or exp *Streptococcus pneumoniae*/ or pneumococcal infection/ or *Streptococcus* infection
2. Pneumococcal meningitis
3. Immunodeficiency/ or immune response
4. Asplenia
5. (Deficien* or immuno-deficien* or immunocompromised or immuno-compromised).tw,kw,hw,fs
6. (Risk or susceptib* or precursor or predispos* or recurren*) .tw,kw,hw
7. (Newborn* or neonat* or infan* or toddler* or child* or preschooler* or pre-schooler* or adolescen* or pediatric* or pediatric*)
8. (1 or 2) and (3 or 4 or 5) and 6 and 7
9. Evidence-based medicine/
10. Cohort analysis
11. Follow-up
12. Clinical study
13. 8 and (9 or 10 or 11 or 12)

in children younger than 1 year to 31% in children younger than 2 years.[22,27] Both studies found a greater prevalence of MBL deficiency in children younger than 1 year, with 1 study reporting a 7-fold increased risk of MBL deficiency in infants (≤1 year) with *S pneumoniae* meningitis compared with children older than 1 year (41.1% vs 6.2%; $P < .01$).[22] Also, MBL deficiency in children younger than 2 years was associated with more severe disease as measured by admission to intensive care.[22,27]

In contrast, 2 case-control studies found no difference in the frequency of *MBL2* polymorphisms in children with IPD compared with control patients.[24,28] Vallès et al[28] found equal rates of MBL deficiency in children with *S pneumoniae* bacteremia and blood culture–negative febrile children (44.6% vs 43.5%). In the largest study, Lundbo et al[24] compared 1279 children with either *S pneumoniae* meningitis or bacteremia with 1263 age- and sex-matched control patients. *MBL2* polymorphisms were not associated with increased susceptibility to IPD or IPD-related 30-day mortality. Both studies included children with bacteremia without clinical evidence of sepsis.[24,28] Furthermore, one study was based in Mozambique and did not report the coexistence of HIV infection.[28]

Invasive pneumococcal disease can be caused by infection with serotypes included in the polyvalent vaccine (serotypes 1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F and 23F), defined as vaccine breakthrough, or from less invasive opportunistic serotypes outside the valency of current vaccines.[3] Overall, the studies suggest that *MBL2* polymorphisms may increase susceptibility to infection with specific *S pneumoniae* serotypes. In one study, in 11 children aged 1 year or younger with low-*MBL2* genotype, 6 (55%) had *S pneumoniae* meningitis due to opportunistic serotypes ($P < .01$ compared with children older than 1 year).[22] Similarly, a low-*MBL2* genotype was associated with increased odds of *S pneumoniae* bacteremia with an opportunistic serotype compared with a genotype associated with normal MBL levels (odds ratio [OR], 3.93; 95% CI, 1.1-14.5; $P = .04$).[28] In another study, among 13 children younger than 2 years with IPD due to an opportunistic *S pneumoniae* serotype, 6 (46.2%) had a low-*MBL2* genotype.[27] However, in a case-control study of children with meningitis and bacteremia, *MBL2* polymorphisms were not associated with *S pneumoniae* serotype. This study was performed in the era before the pneumococcal conjugate vaccine (pre-PCV era) and there was a predominance of vaccine serotypes.[24]

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Table 1. Summary of Studies Concerning Primary IPD

Source	Country	Study Group	Median Age (Range, y)	Disease No. (% of Total)[a]	Vaccination Status, %	Investigation	Key Results
Prospective Studies							
Hénaff et al,[19] 2017	France	315 Children >5 y with culture- and/or Ag-positive *S pneumoniae* meningitis from 2001 to 2013	9 y (5-15)	Meningitis, 315 (100%)	23.5% Children received ≥1 dose of PCV[b]	Investigations determined by treating clinician[c]	• 108/315 (34%) Had an underlying risk factor: • 11/315 (3.5%) Had primary immunodeficiency (1 with C3 deficiency, 10 unspecified) • 11/315 (3.5%) Had secondary immunodeficiency (4 HIV, 2 cancer, 5 unspecified) • 28/315 (8.9%) Had a predisposing condition (eg, SS, CAH, T21, prematurity, asplenia) • 70/315 (22.2%) Had breach of the BBB
Gaschignard et al,[26] 2014	France	162 Children with culture-, PCR- or Ag-positive IPD from 2005 to 2011	13 mo (0.1-15)	• Meningitis, 141 (87%) • Pneumonia, 11 (6.8%) • Sepsis, 6 (3.7%) • OM/SA, 2 (1.2%) • Mastoiditis, 1 (0.6%) • Endocarditis, 1 (0.6%)	• 71% Had ≥2 doses (either PCV7 or PCV13, data missing for 2 cases). • PCV13 introduced in the last year of study	• Blood smear, abdominal US, complement studies (CH50 or AP50), IgG subclasses, total IgG antibody against 23 pneumococcal serotypes, IL-6 production +/− genetic testing. • All children with recurrent meningitis underwent MRI. • 35 patients did not have complete immune workup.	• 17/162 (10.4%) Had PID: SPAD (4 children), hypogammaglobulinemia (4), complement deficiency (3), XLA (2), IgG2 deficiency (2), congenital asplenia (1), and MyD88 deficiency (1). • PID more common in those >2 y (26% vs 3%; *P* < .001), male (16% vs 3%, *P* < .01) and those from consanguineous families (40% vs 9%, *P* = .01) • The number needed to investigate to identify 1 child with PID was 3.8 in children <2 y, compared with 9.6 in children <18 y[d]
Muñoz-Almagro et al,[27] 2014	Spain	147 Patients (102 children) with culture- and/or PCR-positive IPD from 2011 to 2013	35 mo (0.1-18)	• Meningitis, 12 (8.2%) • Pneumonia, 59 (40.1%) • Complicated pneumonia, 66 (44.9%) • Bacteremia, 10 (6.8%)	30.6% Received ≥1 dose of PCV	DNA extraction, amplification and genotyping of *MBL2*	• 23/147 (15.6%) Patients (children and adults) had a low-*MBL* genotype • 9/29 (31%) Children <2 y had a low-*MBL* genotype • 4/45 (8.9%) Children ≥2 and <5 y had a low-*MBL* genotype • Higher frequency of low-*MBL* genotypes in children <2 y with IPD caused by opportunistic serotypes compared with children >2 y (46.2% vs 13.2%, *P* = .02) • Higher frequency of low-*MBL* genotypes in children <2 y with *S pneumoniae* meningitis (42.9%, *P* = .19) • Low-*MBL* genotypes not associated with PICU admission (*P* = .83)
Retrospective Studies							
Bautista-Rodriguez et al,[22] 2017	Spain	48 Children with culture- and/or Ag-positive *S pneumoniae* meningitis from 2001 to 2016	19 mo (0.1-18)	Meningitis, 48 (100%)	31.2% Had received ≥2 doses of vaccine (PCV7 or PCV13) at time of diagnosis	DNA extraction, amplification and genotyping of *MBL2*	• 9/48 (18.8%) Had a low-*MBL* genotype • Children <12 mo had a 7-fold increased risk of low-*MBL* genotype compared with those >12 mo (41.1% vs 6.2%; *P* = .03) • *MBL2*-deficient genotype not significantly associated with sex, ethnicity, or admission to PICU
Yildirim et al,[25] 2014	USA	1052 Children with culture-positive IPD (of which information on comorbidities was available for 1008) from 2002 to 2014	27 mo (0.1-18)	• Meningitis, 75 (7.1%) • Pneumonia, 366 • (34.8%) • Bacteremia, 590 (56.1%) • Other, 21 (2%)[e]	70.1% had received ≥2 doses of vaccine (PCV7 or PCV13) at time of diagnosis	Investigations determined by treating clinician[c]	• 223/1008 (22.1%) Had ≥1 predisposing condition; mostly immunosuppression (32.7%), and chronic respiratory diseases such as asthma (22.4%) • 73/1008 (32.7%) Had immunodeficiency, either primary or acquired • 13/1008 (1.3%) Had PID[f] • Higher case fatality rate compared with those with no comorbidities (aOR, 3.7; 95% CI, 1.50-8.39; *P* = .001) after adjusting for age, sex, year of diagnosis and *S pneumoniae* vaccination status

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Table 1. Summary of Studies Concerning Primary IPD (continued)

Source	Country	Study Group	Median Age (Range, y)	Disease No. (% of Total)[a]	Vaccination Status, %	Investigation	Key Results
Schutze et al,[30] 2002	USA	2498 Children with culture-positive IPD from 1993 to 1999	13 mo (0.3-5.7)	• Meningitis, 9 (30.8%) • Bacteremic pneumonia, 2 (7.7%) • Bacteremia, 17 (46.2%)	Pre-PCV	Investigations determined by treating clinician	• 22/2498 (0.9%) Children had asplenia. Of these: • 12 Had congenital asplenia (9 with associated CHD) • 10 Had surgical splenectomy • 9/22 (40.9%) died, the majority (6/9) with congenital asplenia • 4/22 (18.2%) had asplenia diagnosed at presentation
Venetz et al,[31] 1998	Switzerland	393 Cases with culture and/or Ag positive IPD in 378 children from 1985 to 1994	24 mo (0-17)	• Meningitis, 165 (41.9%) • Bacteremic pneumonia, 102 (26%) • Empyema, 7 (1.8%) • Bacteremia, 102 (26%) • Peritonitis, 3 (0.8%) • OM/SA, 2 (0.5%) • Other, 2 (0.5%)[g] • Unknown, 10 (2.5%)	Pre-PCV	Investigations determined by treating clinician	• 28/393 (7.1%) Cases had a known predisposing condition: • 5/393 (1.3%) Had any immunodeficiency recorded[f] • 13/165 (3.6%) Of children with meningitis had an underlying skull fracture • 14 Children (3.6%) had recurrent IPD
Case-Control Studies							
Gowin et al,[21] 2018	Poland	14 Children with culture- and/or PCR-positive *S pneumoniae* meningitis from 2012 to 2016 compared with healthy family members	Not reported	Meningitis, 14 (100%)	*S pneumoniae* vaccination not available during the study period	DNA extraction and genotyping of 11 SNPs involved in the immune response (complement factor, MBL2, TLR, TIRAP)	• SNPs in 11 genes more common in cases than controls • Carriage of 2 risky alleles associated with increased risk of meningitis (OR, 4.9; 95% CI, 1.17-20.48; $P = .035$) • Carriage of ≥6 MAF of studied SNPs associated with an increased risk of meningitis (OR, 8.4; 95% CI, 1.9-36.7; $P = .006$)
Carrasco-Colom et al,[23] 2015	Spain	60 Children with culture- and/or PCR-positive IPD and systemic inflammatory response syndrome in 2010 compared with healthy volunteers	3.1 y (0.1-10)	• Pneumonia, with effusion 36 (60%) • Pneumonia, 12 (20%) • Meningitis, 9 (15%) • Septic arthritis, 2 (3.3%) • Sepsis, 1 (1.7%)	38.3% Had received ≥3 doses of PCV7 at time of diagnosis	DNA extraction and genotyping of 10 SNPs involved in TLR signaling pathway proteins IRAK1, IRAK4, IRAKM, and MyD88	• PID screening by a clinical immunologist normal in all cases • Some SNPs associated with greater risk of developing IPD: • rs1059701 (*CC* genotype) in *IRAK1* (OR, 1.43; 95% CI, 1.14-1.80; $P = .007$) • rs4251513 (*CC* genotype) in *IRAK4* (OR, 2.18; 95% CI, 1.58-3.02; $P < .001$) • rs1461567 (T allele) in *IRAK4* (OR, 1.50; 95% CI, 1.13-1.98; $P = .016$) • rs6853 (*AA* genotype) in *MyD88* (OR, 2.13; 95% CI, 1.79-2.53; $P < .001$) • G allele from rs1624395 and C allele from rs13701128 associated with pleuropneumonia (OR, 1.83; 95% CI 1.23-2.74; $P = .015$ and OR, 2.06; 95% CI, 1.37-3.11; $P = .006$) • Non-*AA* genotypes and G allele from rs6853 associated with death (OR, 16.09; 95% CI, 3.34-77.57; $P = .005$ and OR, 8.39; 95% CI, 2.47-28.46; $P = .006$)

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Table 1. Summary of Studies Concerning Primary IPD (continued)

Source	Country	Study Group	Median Age (Range, y)	Disease No. (% of Total)[a]	Vaccination Status, %	Investigation	Key Results
Lundbo et al,[24] 2014	Denmark	1279 Children <5 y with culture-positive IPD from 1982 to 2007 compared with age- and sex-matched healthy controls (stored newborn dried blood spot)	13 mo (0.1-5)	• Meningitis, 372 (29%) • Bacteremia, 907 (71%)	Pre-PCV	DNA extraction and genotyping of 4 SNPs involved in MBL2 function	• 196/1192 (16.4%) Children with IPD had a low-MBL genotype compared with 173/1180 (14.7%) of healthy controls (P = .15) • No increased risk of *S pneumoniae* meningitis or bacteremia in children with low-MBL genotype compared with children with intermediate or "normal" MBL genotype (OR, 0.85; 95% CI, 0.56-1.28 and OR, 0.89; 95% CI, 0.68-1.15, respectively) • No difference in frequency of genotypes in children with recurrent IPD (n = 12) compared with controls (OR, 0.46; 95% CI, 0.06-3.56) • No increased 30-day mortality after *S pneumoniae* meningitis or bacteremia compared with children with normal MBL genotype (OR, 1.65; 95% CI, 0.41-6.62 meningitis and OR, 1.81; 95% CI, 0.33-10.01 bacteremia) • Defective MBL genotype did not influence *S pneumoniae* serotype distribution
Vallès et al,[28] 2010	Mozambique	64 Children <5 y with positive BC for *S pneumoniae* matched with 121 BC-negative controls from 2001 to 2003	26 mo (0.1-5) mo	Bacteremia, 64 (100)	Not recorded	DNA extraction, amplification and genotyping of *MBL2*	• 24/55 (44.6%) Cases and 46/106 (43.4%) controls had a low-MBL genotype (P = .40) • 19/161 (12%) Had a severe MBL deficient genotype • Low-MBL genotypes were associated with IPD due to opportunistic serotypes (OR, 3.93; 95% CI, 1.1-14.5; P = .04) • All children <1 y with IPD due to an opportunistic serotype had a low-MBL genotype (100% vs 40%, P = .001)
Hirschfeld et al,[29] 2006	Canada	50 Children with culture-positive IPD matched with 28 healthy controls	(0.3-18)[h]	• Meningitis, 1 (2%) • Bacteremic pneumonia, 13 (26%) • Bacteremia, 34 (68%) • Septic arthritis, 1 (2%) • Complicated sinusitis, 1 (2%)	8% of Children received ≥1 dose of PCV7	Focused in vitro assay of TLR signaling using TLR ligands and measurement of cytokine production	No significant difference in TLR function between cases and controls (P > .05)

Abbreviations: Ag, antigen; aOR, adjusted odds ratio; BBB, blood-brain barrier; BC, blood culture; BJI, bone and joint infection; BSI, bloodstream infection; CAH, congenital adrenal hyperplasia; CHD, congenital heart disease; Ig, immunoglobulin; IL, interleukin; IPD, invasive pneumococcal disease; MAF, minor frequency alleles; *MBL*, mannose-binding lectin; OM, osteomyelitis; OR, odds ratio; PAD, primary antibody deficiency; PCR, polymerase chain reaction; PCV, pneumococcal conjugate vaccine; PICU, pediatric intensive care unit; PID, primary immunodeficiency; SA, septic arthritis; SNP, single-nucleotide polymorphism; SPAD, specific-antibody deficiency; SS, sickle cell anemia; TIRAP, toll-interleukin 1 receptor domain containing adaptor protein; TLR, toll-like receptor; T21, trisomy 21; US, ultrasonography; WBC, white blood cell; XLA, X-linked agammaglobulinemia.

[a] Percentages may not total 100 because of rounding.

[b] The proportion completing 3 doses of PCV was not recorded.

[c] The number of children undergoing immune investigation was not recorded.

[d] This was calculated using data extracted from the published article.

[e] Not otherwise specified.

[f] Comorbidities were not recorded for 44 of 1052 cases. The type of PID was not recorded.

[g] Including a case of cellulitis and cerebellar abscess.

[h] Median age was not recorded.

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Table 2. Summary of Studies Concerning Recurrent IPD

Source	Country	Study Group	Study Type	Recurrent Disease, No. (% of Total Episodes)[a]	Vaccination Status	Investigation	Key Results
Ingels et al,[20] 2015	Denmark	2128 Children with culture positive IPD from 1980 to 2008	Retrospective cohort	• Bacteremia, 25/33 (75.8%) • Meningitis, 8/33 (24.2%)	1/15 (6.7%) Received ≥1 dose of PCV before testing	• Plasma concentrations of Ig classes and subclasses, T-cell, B-cell and NK-cell counts, complement studies, MBL genotypes, specific antibody response to PPV23 vaccine, and TLR-signaling functional assay. Testing for *MYD88*, *IRAK4*, and *NEMO* gene mutations. • 6 Patients declined investigation and 1 died before evaluation.	• 54/2128 (2.5%) Had recurrent IPD • Underlying cause identified in 42/54 (77.8%) children • 15/54 (27.8%) Children underwent analysis, with 10/15 (66.7%) found to have an immunodeficiency: • 6/15 (40%) C2-deficiency • 3/15 (20%) Selective antibody deficiency • 1/15 (6.7%) TLR-signaling defect • No mutations in *IRAK4*, *NEMO*, or *MYD88* • The number needed to investigate to identify 1 child with PID was 1.5[b]
Alsina et al,[32] 2015	Spain	583 Children with culture- and/or PCR-positive IPD from 2004 to 2011	Prospective cohort	• Meningitis, 10/23 (43.5%) • Pneumonia with empyema, 7/23 (30.4%) • Bacteremic pneumonia, 1/23 (4.3%) • Bacteremia, 3/23 (13%) • Septic arthritis, 2/23 (8.7)	3/10 (30%) Received PPV23 before first episode of IPD	• Medical record review with stepwise evaluation including plasma concentrations of Ig classes and subclasses, T-cell, B-cell and NK-cell counts, CH50, C3 and C4 levels, Howell-Jolly bodies in blood smear. • (+/− Abdominal US), antibody response to PPV23 vaccine and TLR-signaling functional assay. • Brain MRI in all patients with meningitis.	• 7/583 (1.2%) Surviving patients had recurrent IPD with an underlying cause identified in 5/7 (71.4%) Patients: • 3/7 (42.9%) CSF leakage • 1/7 (14.3%) MYD88 mutation • 1/7 (14.3%) Malignancy • 1/5 (20%) Patients investigated had a PID • 1 Patient had suspected PID with 3 episodes of SBI but normal immune testing results.
Gaschignard et al,[26] 2014	France	162 Children with culture-, PCR-, or Ag-positive IPD from 2005 to 2011	Prospective cohort	• Meningitis, 13/17(76.5%) • Pneumonia, 2/17 (11.8%) • Sepsis, 2/17 (11.8%)	11/17 (64.7%) Received ≥1 dose of PCV7 or PCV13 before presentation	• Blood smear, abdominal US, complement studies (CH50 or AP50), IgG subclasses, total IgG antibody against 23 pneumococcal serotypes, IL-6 production +/− genetic testing. • Brain MRI in all patients with meningitis.	• 17/162 (10.5%) of Children had recurrent disease • 2/16 (12.5%, *P* = .68) Children undergoing investigation had a PID (both children had XLA)
Mason et al,[33] 2007	United States	3986 Children with culture- and/or Ag-positive IPD from 1993 to 2006	Prospective cohort	• Bacteremia, 67/108 (62%) • Pneumonia, 25/108 (23.1%) • Meningitis, 10/108 (9.3%) • Other, 6/108 (5.6%)[c]	25/90 (27.8%) Received PPV23 before presentation	1 Child with 3 episodes of IPD had detailed immune testing, otherwise not reported.	• 90/3986 (2.3%) Children had recurrent IPD with an underlying cause identified in 71/90 (78.9%) patients • An immunodeficiency was identified in 8/90 (8.9%): • 5/90 (5.6%) Asplenia • 1/90 (1.1%) SCID • 1/90 (1.1%) Complement factor D deficiency • 1/90 (1.1%) T-cell abnormality[d]
Einarsdóttir et al,[34] 2005	Iceland	819 Children and adults with culture- and/or Ag-positive IPD from 1975 to 2004	Retrospective observational	• Bacteremia, 13/28 (46.4%) • Meningitis, 6/28 (21.4%) • Bacteremic pneumonia, 5/28 (17.9%) • Peritonitis, 3/28 (10.7%) • Septic arthritis, 1/28 (3.6%)	6/22 (26%) Children eligible for vaccine received ≥1 dose of PCV[e]	Investigations determined by treating clinician.	• 36/819 (4.4%) Surviving patients had recurrent IPD (12 children) with an underlying cause identified in 11/12 (91.7%) children: • 1/12 (8.3%) Asplenia • 5/12 (41.7%) Immunoglobulin disorder, including 2 children with SPAD and 3 children with Ig deficiency
Orlicek et al,[35] 1997	United States	394 Children with blood or CSF culture-positive IPD from 1991 to 1994	Retrospective observational	• Bacteremia, 14/21 (66.7%) • Pneumonia, 5/21 (23.8%) • Meningitis, 2/21 (9.5%)	Not recorded	Measurement of Ig, hemoglobin electrophoresis/sickle cell screen, CH100, tetanus antibody levels, HIV testing, and splenic imaging in some patients.	• 16/394 (4%) Were repeated infections (recurrent or relapse) • 6/16 Underwent any immunologic evaluation with no immunodeficiency identified

Abbreviations: CH, classic hemolytic complement test; CSF, cerebrospinal fluid; IPD, invasive pneumococcal disease; IRAK4, interleukin-1 receptor-associated kinase 4; MRI, magnetic resonance imaging; *MYD88*, myeloid differentiation primary response gene 88; NEMO, nuclear factor κ B essential modulator (*IKBKG* gene); NK, natural killer; PCV, pneumococcal conjugate vaccine; PPV23, 23-valent polysaccharide vaccine; SBI, serious bacterial infection; SCID, severe combined immunodeficiency; SPAD, specific antibody deficiency; TLR, toll-like receptor; XLA, X-linked agammaglobulinemia.

[a] Percentages may not total 100 because of rounding.

[b] This was calculated using data extracted from the published article.

[c] This included nonsterile sites such as peritonitis (n = 3), cellulitis (n = 1), endocarditis (n = 1), and infected facial cystic hygroma (n = 1).

[d] Not otherwise specified.

[e] PCV was introduced in 1991.

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Table 3. Frequency of Immunodeficiency in Children Presenting With Primary IPD

Condition	Reported Incidence of Immunodeficiency	Evidence Level
Meningitis	3.5% (108/315) Children >5 y[a]	4
	10.6% (15/141) Children <15 y[b]	2
Pneumonia	8% (2/11) Children[b]	4
Bacteremia	No immunodeficiency identified[b,c]	2
All IPD	1.3% of All children in retrospective review[d,e]	3
	10.4% (17/162) of All children and 26% (14/53) of children 2-16 y undergoing systematic evaluation[b]	2

Abbreviation: IPD, invasive pneumococcal disease.

[a] Data from Hénaff et al.[19]

[b] Data from Gaschignard et al.[26]

[c] Data from Hirschfeld et al.[29]

[d] Data from Yildirim et al.[25]

[e] Data from Venetz et al.[31]

Primary Immunodeficiency

The overall frequency of PID in children presenting with IPD without another predisposing condition varied between 5 of 393 (1.3%) and 14 of 53 (26.4%) (**Table 3**).[19,25,26,31] Gaschignard et al[26] prospectively evaluated 162 children with primary IPD for immunodeficiency across a 7-year period. One hundred twenty-seven children (78.5%) completed immune evaluation (Table 1). The overall frequency of PID in children younger than 16 years presenting with primary IPD was 17 of 162 (10.4%). Children older than 2 years were significantly more likely to have PID than children younger than 2 years (14 of 53 [26%] vs 3 of 109 [3%]; $P < .001$). Based on these data, the number needed to investigate to identify 1 child with PID was 3.8 in children younger than 2 years compared with 9.6 in children aged 2 to 18 years. After the introduction of PCV13 in France in 2010, the proportion of children with abnormal immune testing results was higher (6 of 22 [27.3%]) compared with the pre-PCV13 era (20 of 96 [20.8%]).[26]

In the French cohort,[26] the most commonly diagnosed immunodeficiency was primary antibody deficiency (12 of 17 [71%]), consisting of hypogammaglobulinemia (4 children), specific pneumococcal antibody deficiency (4 children), X-linked agammaglobulinemia (2 children), and IgG2 deficiency (2 children). Other diagnoses included complement deficiency (3 of 17 cases [21%]) and 1 case each of congenital asplenia and MyD88 deficiency (1 of 17 [6%]). Ten of 162 children (6.2%) were from consanguineous families, with higher rates of PID in these children compared with those from nonconsanguineous families (4 of 10 [40%] vs 13 of 152 [9%]; $P = .01$).[26] Rates of PID were similar in children with meningitis and pneumonia (15 of 141 [11%] vs 2 of 11 [18%]; $P = .35$). Although not reported by Gaschignard et al,[26] the majority of patients with pneumonia and an identified PID had complex pneumonia with empyema or pleural effusion at presentation (Capucine Picard, MD, PhD, written communication, January 2, 2019).[26]

These results contrast the findings of a small case-control study of 14 children (13 children with *S pneumoniae* pneumonia with bacteremia and 1 child with meningitis) that reported no difference in TLR function and cytokine production between children presenting with IPD and healthy control patients.[29]

Of the 3 retrospective studies included in this review, none systematically examined for immunodeficiency and 2 did not specifically exclude children with occult bacteremia. In those studies, the frequency of PID ranged from 13 of 1008 (1.3%) in children with all types of IPD to 11 of 315 (3.5%) in children older than 5 years with *S pneumoniae* meningitis.[19,25,31]

Hénaff et al[19] reviewed data for 315 children with *S pneumoniae* meningitis and found that approximately one-third (108 patients [34%]) had a predisposing condition, most commonly an anatomical breach in the blood-brain barrier (70 [22.2%]). Eleven of the children (3.5%) had a PID. One child had C3 deficiency; the remaining children with PID were not described in the article, and further information was not received after contacting the corresponding author. In addition, 69 of 294 children with recorded vaccination status (23.5%) received 1 or more doses of pneumococcal vaccine.[19]

Yildirim et al[25] found a similar rate of immunodeficiency in a large study of 1052 children with IPD. Of the 1008 children with recorded comorbidities, 223 (22.1%) had a predisposing condition and 13 (1.3%) had PID. Children with comorbidities had a higher fatality rate (4.8% vs 1.7%; $P < .001$) and were more likely to have infection with an opportunistic serotype compared with those with no comorbidities (32.1% vs 18.3%; $P < .001$).[25] The frequency of predisposing conditions was higher in both studies than recorded by Venetz et al[31] in a retrospective study of 393 cases of IPD in which 28 (7.1%) had a predisposing condition and 5 (1.3%) had a PID. There are a number of explanations for these differences: the latter study included younger children and those with occult bacteremia, and data were collected before introduction of pneumococcal vaccine.[31]

Genetic Factors

Two studies examined how single-nucleotide polymorphisms (SNPs) in genes associated with the immune response increase susceptibility to IPD.[21,23] In a study of 14 children with *S pneumoniae* meningitis in the pre-PCV era, there was a cumulative increased risk of IPD with SNPs in 7 genes involved in MBL2, complement, and TLR function. Carriers of risky alleles had an 8.4-times greater risk of developing pneumococcal meningitis compared with healthy family members.[21]

A case-control prospective study including 1279 children also demonstrated an association between SNPs in *IRAK1*, *IRAK4*, and *MYD88* in the sickest children with IPD compared with healthy volunteers. The inclusion criteria were IPD and evidence of systemic inflammatory response syndrome. Twenty-three of 60 cases (38.3%) had received complete vaccination with PCV7 (≥3 doses), yet 25 children (41.7%) were admitted to the intensive care unit. Results of functional PID screening, directed by a clinical immunologist, were normal in all children. The greatest risk of IPD was associated with SNPs in *IRAK1* (OR, 1.43; 95% CI, 1.14-1.8; $P = .007$), whereas SNPs in *IRAKM* were associated with complicated pneumonia (OR, 1.83; 95% CI, 1.23-2.74; $P = .02$ vs OR, 2.06; 95% CI, 1.37-3.11; $P = .006$). Single-nucleotide polymorphisms in *MYD88* were associated with an increased risk of death (OR, 16.09; 95% CI, 3.34-77.57; $P = .005$).[23]

Asplenia

Gaschignard et al[26] screened for asplenia in 162 children with primary IPD by using peripheral blood smear. Patients with abnormal results on the blood smear then underwent abdominal ultrasonog-

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raphy and splenic scintigraphy. A single case of congenital asplenia was identified (0.6%).[26] These results are similar to those of Schutze et al,[30] who retrospectively reviewed 2498 cases of IPD. Overall, 22 patients (0.8%) were asplenic at presentation, and 50% of patients with congenital asplenia died at presentation. However, because the approach to screening and the number of children investigated for asplenia were not reported, the denominator is unclear.[30] Both studies are limited by lack of consensus on the most sensitive approach to screening for asplenia or hyposplenism.[26,30]

Recurrent Invasive Pneumococcal Disease

Five studies, 2 prospective and 3 retrospective, studied rates of immunodeficiency in children with recurrent IPD.[20,26,32-34] The 3 studies that clearly described inclusion criteria defined recurrence as 2 separate episodes 30 days apart or 2 or more episodes within 30 days owing to different serotypes.[20,32,34] Rates of pneumococcal vaccination varied from 6.7% to 64.7%.[20,26] The 2 largest studies identified a predisposing condition in most children (42 of 54 [77.8%] and 71 of 90 [78.9%]) with recurrent IPD.[20,33] Overall, the most common predisposing conditions included anatomical breach in the blood-brain barrier, sickle cell disease, cancer, and PID.[20,32-34] The rate of recurrent IPD in children surviving an initial episode was between 1.7% and 4.4%.[20,32,34] Again, a limitation of all included studies was the lack of differentiation between occult bacteremia and sepsis.[20,26,32-34]

The 3 studies that systematically screened for immunodeficiency found a PID in 17 of 162 [10.5%] to 10 of 15 [66.7%] of children with recurrent IPD.[20,26,32] Ingels et al[20] prospectively evaluated 54 Danish children with no underlying risk factors for IPD. Fifteen patients consented to immune evaluation, of whom 10 (67%) had a PID identified. The most common conditions were complement deficiency (6 children [40%]) followed by pneumococcal antibody deficiency (3 [20%]) and a single case of TLR-signaling defect (1 [7%]). Based on these data, the number needed to investigate to identify 1 child with PID is 1.5. Gaschignard et al[26] found a similar rate of antibody deficiency, identifying 2 cases of X-linked agammaglobulinemia in a subset analysis of 10 children with recurrent IPD (20%).

Mason et al[33] prospectively audited 90 children with recurrent IPD and recorded an immunodeficiency in 8 (9%) at the time of discharge, including 1 child each with immunoglobulin deficiency, complement deficiency, and T-cell abnormality and 5 children with asplenia. In contrast, a retrospective audit by Einarsdóttir et al[34] identified immunoglobulin disorders in 5 of 12 children (42%) with recurrent IPD; however, the immunodeficiency was not further characterized. Both studies are limited by lack of a specified protocol for immune evaluation.[33,34] Another retrospective audit of 6 children younger than 25 months with recurrent IPD who had standardized immune evaluation identified no cases of PID.[35]

Rates of asplenia in children with recurrent IPD ranged from 0% to 8.3%.[26,32-34] Two small prospective studies did not identify any children with asplenia despite screening with peripheral blood smear and abdominal ultrasonography.[26,32]

Discussion

The widely published "warning signs of primary immunodeficiency" have been shown to be neither sensitive nor specific for identifying PID.[36] The diagnosis known as *primary immunodeficiency* has evolved into a broad and complex group of disorders requiring a new paradigm for screening and diagnosis.[37] Delayed diagnosis of PID leads to late referral to integrated specialist services, augmented stress for families, and increased health care costs.[38]

Currently, we are not aware of any consensus guidelines recommending an approach to the immunologic evaluation of children with IPD; therefore, there is significant variation in practice.[20,39,40] To our knowledge, this is the first systematic review evaluating the risk of PID in children with IPD. Our study has highlighted that IPD, and particularly recurrent IPD, is an important marker of antibody deficiency, complement disorders, TLR-signaling defects and asplenia. Immunologic evaluation of children with IPD enables early diagnosis of PID, resulting in timely provision of genetic counseling, treatment, and prophylaxis to reduce the risk of death and the chronic, lifelong implications of recurrent infection.[41-43] The benefit of early identification is well established for immunoglobulin deficiency and has recently been demonstrated for newer disorders such as IRAK-4 and MyD88 deficiency.[15,43]

Primary Invasive Pneumococcal Disease

In settings with high vaccine uptake, IPD in children due to vaccine serotypes is unusual in the absence of comorbidities. In a population with more than 70% pneumococcal vaccination, every fifth child with IPD and every third child younger than 3 years had an underlying comorbidity.[25] In children with primary IPD, 1.3% to 10.4% of all children and 26% of children older than 2 years had a PID identified (Table 3).[25,26,31] Immunoglobulin deficiency and pneumococcal antibody deficiency were the most common immunodeficiencies, followed by complement deficiency and rarer defects in T-cell signaling. The site of infection was an important determinant of the likelihood of underlying PID, with the greatest likelihood in children with meningitis.[19,26] *Streptococcus pneumoniae* pneumonia was also a presenting feature of PID in several studies, although the definition of pneumonia was heterogeneous across the studies.[25,26,31] No studies found *S pneumoniae* bacteremia to be a presenting feature of PID, and the results of 2 key studies were likely shaped by an overrepresentation of *S pneumoniae* bacteremia.[26,28] Age was also an important risk factor: the risk of PID in children older than 2 years was 8 times that of children younger than 2 years at the time of presentation.[19,22,26-28] This may reflect waning protection from maternal antibody or changes in the innate immune system between infancy and childhood.[6]

The data on the frequency of asplenia in IPD are limited owing to the poor sensitivity of the combination of abdominal ultrasonography and the presence of Howell-Jolly bodies as a screening tool for asplenia and hyposplenism.[26,30,33,44] In one study, 1% of all children with primary IPD had asplenia; in these children, the mortality rate of IPD was as high as 50%.[30] Further studies are needed that use newer, more sensitive screening techniques, such as technetium Tc 99m–labeled erythrocyte scintigraphy and measurement of pitted erythrocytes.[44-46]

This systematic review identified several studies suggesting high rates of MBL deficiency in children, especially children younger than 2 years with meningitis or pneumonia due to opportunistic *S pneumoniae* serotypes.[22,24,27,28] Mannose-binding lectin is a serum protein crucial to the innate immune system. It recognizes carbohydrate moieties and acts as a preantibody through activation of the complement system via the lectin pathway or direct opsonophagocytosis.[47] It is important to recognize the limitations of genotyping, as performed in these

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studies, as a surrogate marker for MBL deficiency. Children with identical genotypes may have 10-fold differences in MBL level.[48] None of the studies we reviewed proved causality, and larger studies are required to better understand the contribution of variations in serum MBL levels to pneumococcal disease. Furthermore, the implications of MBL deficiency for long-term risk of invasive infection are not clear.[6,47]

The interaction between genetic factors, the immune system, and susceptibility to IPD remains complicated. Although the included studies found that SNPs in genes associated with the innate immune response increased the risk of IPD,[21,23,24] there are many limitations to genetic association studies, such as the potential for genotyping errors, the need to carefully match cases and controls, and ethnic differences in gene expression that may limit the applicability of results.[49] Hence, these genetic variations require further study to fully understand the implications for screening and treatment.

Recurrent Invasive Pneumococcal Disease

As we expected, children with recurrent IPD were more likely to have an underlying immunodeficiency than those with primary IPD.[20,26,32-34] More than 75% of patients had a condition predisposing them to recurrent IPD.[20] This was especially true for children with recurrent meningitis who commonly had a cerebrospinal fluid leak identified.[32] In children with recurrent IPD with no known comorbidities, between 12.5% and 66.7% had a PID identified. This variability likely reflects a heterogeneous approach to immune evaluation and generally small sample size.[20,26,32-34] Complement deficiency was most common, followed by antibody deficiency, pneumococcal antibody deficiency, and defects in T-cell signaling.[20,26,32] Rates of asplenia were higher in children with recurrent compared with primary IPD (6% vs 0.5%); however, few studies screened systematically for asplenia.[26,32-34] These data support routine evaluation for a predisposing condition in children presenting with recurrent IPD.

Limitations

This review is limited by the observational design of most studies. Three of the 17 studies prospectively applied immune evaluation, and in other studies the approach and completeness of immune evaluation differed.[20,26,32] Because children with preexisting comorbidities were excluded from evaluation, we were unable to draw conclusions about rates of PID in this broader group. There may also be inherent survival bias because most of the studies only performed immune evaluation for patients surviving to follow-up.

It is postulated that rates of PID would be higher in a population with more comprehensive pneumococcal vaccination because cases would represent either vaccine failure or would be attributed to opportunistic nonvaccine serotypes. Heterogenous vaccination rates and differences in use of PCV7 or PCV13 limit the applicability of some results to settings with high vaccination rates.

Recently, there have been advances in whole-exome sequencing as a means to identify the contribution of genetic factors, including monogenic inborn errors of immunity, to IPD at a population level.[50,51] In the future, whole-exome sequencing could characterize an individual's immune system and aid in predicting the risk of recurrent IPD or severe infection to allow a personalized approach to secondary prevention and treatment.

Conclusions and Implications for Clinical Practice

This review's findings suggests that existing data support the immune evaluation of children older than 2 years without a known predisposing condition who present with their first episode of *S pneumoniae* meningitis, pneumonia, or recurrent IPD. Immune evaluation should include assessment for immunoglobulin deficiency, pneumococcal antibody deficiency, complement disorders, and asplenia. Data to support testing for MBL deficiency based on the currently available evidence are lacking. Further studies, beginning with prospective cohort studies, are required to further delineate the predisposing factors for IPD in the era of pneumococcal vaccine. This should also include assessment of the public health economics of immune evaluation in all children with IPD balanced against the potential for preventing the significant complications and mortality associated with PID.

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