Specific Antibody Deficiency (SAD / SPAD): A Comprehensive Disease Characteristics Report

Disease: Specific Antibody Deficiency (also Specific Polysaccharide Antibody Deficiency, SPAD) **Category as framed by request:** "Mendelian" — but see Summary; the disease is best classified as a **functional, largely idiopathic primary (predominantly) antibody deficiency**, not a single-gene Mendelian disorder. **Parent classification:** IUIS-2022 Group III — Predominantly Antibody Deficiencies (PAD) **Suggested MONDO/ontology anchors:** MONDO "specific antibody deficiency"; ICD-10 **D80.8/D80.9** (other/unspecified immunodeficiency with predominantly antibody defects); MeSH concepts under *Primary Immunodeficiency Diseases* / *Immunologic Deficiency Syndromes*.

Summary

Specific Antibody Deficiency (SAD), also termed Specific/Selective Polysaccharide Antibody Deficiency (SPAD), is a primary immunodeficiency recognized by the International Union of Immunological Societies and defined by an impaired IgG antibody response to polysaccharide antigens after 23-valent pneumococcal polysaccharide vaccine (PPSV23) challenge, in the setting of otherwise normal total IgG, IgA, IgM, and IgG subclass concentrations and normal responses to protein antigens (PMID: 32654695; PMID: 28588580). The core lesion is a functional failure of the **thymus-independent type-2 (TI-2)** antibody response to bacterial capsular polysaccharides — a response that normally matures only after ~2 years of age, forms no immunologic memory, and uses a restricted IgM/IgG2 isotype repertoire (PMID: 8167745). Because anti-capsular antibody is deficient, encapsulated bacteria (*Streptococcus pneumoniae*, *Haemophilus influenzae* type b) are poorly opsonized, producing the hallmark phenotype of **recurrent sinopulmonary infection** that can progress to bronchiectasis when diagnosis is delayed.

Despite the "Mendelian" label of the research template, SAD is **not a single-gene disorder**. It is a functionally defined, heterogeneous, and largely idiopathic condition — effectively a diagnosis of exclusion (PMID: 8167745; PMID: 28588580). The same laboratory picture

(impaired polysaccharide IgG with normal total IgG and normal protein-antigen responses) can arise secondarily within other defined immunodeficiencies (IgG subclass deficiency, selective IgA deficiency, Wiskott–Aldrich syndrome, DiGeorge anomaly) and acquired states (post-splenectomy, HIV, lymphoid malignancy), and rare **monogenic inborn errors of immunity (IEI) can phenocopy SAD** (PMID: 38933494). A mechanistic anchor is provided by the **TACI (TNFRSF13B)–NF-κB** pathway: a mouse model carrying the murine equivalent of the human CVID-associated *TNFRSF13B* A181E mutation shows selectively impaired TI-2 (TNP-Ficoll) antibody responses (PMID: 19605846).

Prognosis is generally good. In children the deficiency may resolve over time (PMID: 26454312). Management is tiered: prompt treatment of infections, **pneumococcal conjugate vaccination** (which bypasses the defect by presenting polysaccharide as a T-dependent conjugate), **antibiotic prophylaxis**, and — in refractory or severe cases — **immunoglobulin replacement therapy (IgRT)**, which in an adult SPAD cohort reduced antibiotic courses from a mean of 7.9 to 0.7 per year ($p < 0.001$) (PMID: 40097777; PMID: 32654695).

Section 1 — Disease Information

Overview. SAD/SPAD is an IUIS-recognized primary immunodeficiency in which patients experience recurrent respiratory infections with **normal immunoglobulins but diminished antibody responses to polysaccharide antigens after PPSV23** (PMID: 32654695). The defining laboratory phenotype is *normal IgA, IgM, total IgG and IgG subclass levels* combined with impaired anti-polysaccharide responses (PMID: 28588580). Diagnosis requires age ≥ 2 years (because the polysaccharide response is physiologically immature before then) and otherwise intact immunity.

> "Specific antibody deficiency is a primary immunodeficiency disease recognized by the International Union of Immunology Societies and defined by recurrent respiratory infections with normal immunoglobulins, but diminished antibody responses to polysaccharide antigens after vaccination with the 23 valent pneumococcal polysaccharide vaccine" (PMID: 32654695).

Key identifiers. - **ICD-10:** D80.8 / D80.9 (immunodeficiency with predominantly antibody defects, other/unspecified). - **MeSH:** indexed under *Primary Immunodeficiency Diseases* / *Immunologic Deficiency Syndromes* (no unique legacy MeSH term for SPAD specifically). -

IUIS-2022: Group III, predominantly antibody deficiencies. - **OMIM / Orphanet / MONDO:** No single OMIM phenotype number applies because the disorder is functionally (not molecularly) defined. Where a knowledge base requires a MONDO node, use the MONDO term for "specific antibody deficiency."

Synonyms / alternative names. Specific Antibody Deficiency (SAD); Specific/Selective Polysaccharide Antibody Deficiency (SPAD); Selective Anti-Polysaccharide Antibody Deficiency; Impaired Polysaccharide Responsiveness; Partial antibody deficiency with normal immunoglobulins.

Data source type. The evidence base is **aggregated disease-level** (case series, cohort studies, registry data, and expert reviews) rather than derived from a single EHR dataset; there is a recognized lack of consensus on case definition (PMID: 28588580).

Section 2 — Etiology

Primary causal mechanism. SAD is a **functional defect of the antibody response to capsular (TI-2) polysaccharide antigens** (PMID: 8167745). It is largely **idiopathic** and comprises multiple immunologic phenotypes with no single established causal gene (PMID: 28588580).

Genetic risk factors. No single Mendelian gene defines primary SAD. However: - The **TACI (TNFRSF13B)–NF-κB** axis is mechanistically implicated: *TNFRSF13B* is mutated in ~10% of CVID patients, and the murine A144E equivalent of human A181E selectively impairs TI-2 responses (PMID: 19605846). - Defined **monogenic IEI can phenocopy SAD**, presenting with impaired polysaccharide IgG but normal total IgG and normal protein/conjugate responses (PMID: 38933494).

Environmental / host risk factors. Age (immature < 2 years), and a strong association with **atopic/allergic disease** (asthma, allergic rhinitis) — see Section 3. Adult SPAD shows **female predominance (~75%)** (PMID: 40097777). Secondary causes that must be excluded include splenectomy, HIV/AIDS, and lymphoid malignancy (PMID: 8167745).

Protective factors. No germline protective variant is established. The strongest *acquired* protective intervention is **pneumococcal conjugate vaccination**, which converts the polysaccharide into a T-dependent antigen and restores protection (Section 12).

Gene–environment interactions. Not formally characterized. The clinical picture is best understood as a functional threshold phenomenon in which an intrinsically restricted TI-2 response, host age, and a co-existing allergic diathesis converge to produce recurrent encapsulated-bacterial infection.

Section 3 — Phenotypes

The dominant clinical phenotype is **recurrent sinopulmonary infection** with a striking co-association with allergic disease.

Phenotype	Type	Frequency	Suggested HPO
Recurrent pneumonia	Clinical sign / infection	91.7% in a pediatric SAD cohort (11/12)	HP:0006532 (Recurrent pneumonia)
Recurrent respiratory / sinopulmonary infection	Clinical sign	Defining feature	HP:0002205; HP:0011108 (Recurrent respiratory infections)
Recurrent otitis media	Clinical sign	Common	HP:0000403
Chronic/recurrent rhinosinusitis	Clinical sign	Common	HP:0011109 (Chronic sinusitis)
Asthma	Comorbid allergic disease	100% (12/12) in pediatric SAD cohort	HP:0002099
Allergic rhinitis	Comorbid allergic disease	11/12 pediatric SAD	HP:0003193
Bronchiectasis	Complication (delayed dx)	Associated with long diagnostic delay	HP:0002110
Impaired polysaccharide vaccine response	Laboratory abnormality	Defining	HP:0005425 (Abnormal antibody level) / functional

In a pediatric cohort of 12 children (mean age 6 y), **recurrent pneumonia predominated (91.7%)**, and **all patients had asthma with 11/12 having allergic rhinitis** (PMID: 27614984):

> "recurrent pneumonia predominated (91.7%) as well as other respiratory and invasive infections. All patients with SAD had associated asthma, 11 had allergic rhinitis" (PMID: 27614984).

Onset / severity / progression. Onset is typically **childhood** (but adult diagnosis is common, median age 45 years in an adult SPAD cohort). Severity is **variable**, ranging from mild recurrent infection to severe/invasive disease. Course is **episodic** (recurrent infections) and can be **progressive** toward bronchiectasis if untreated.

Impaired-persistence phenotype. Some children respond normally to PPSV23 acutely but lose protective titers over one year — an "impaired persistence" (memory) phenotype: at one year, **8/20 children showed deficient responses** (PMID: 25498324).

Quality of life. Primary antibody deficiencies impose substantial physical, psychological, and socioeconomic burden beyond infections and significantly reduce HRQOL (PMID: 42447994). In pediatric PID, lower child QoL correlates strongly with higher maternal caregiving burden ($r = -0.710$, $p < 0.001$) (PMID: 42119234). Validated instruments: SF-36, PedsQL, PROMIS, and disease-specific **PADQOL** and **CVID-QOL** (PMID: 42447994).

Section 4 — Genetic / Molecular Information

Causal genes. *None established for primary SAD.* The disorder is defined functionally and lacks a robust molecular case definition (PMID: 28588580).

Mechanistically implicated gene. TNFRSF13B (TACI) — HGNC:18153; encodes Transmembrane Activator and CAML Interactor. A CVID-associated mutation (A181E; murine equivalent A144E) impairs constitutive and ligand-induced **NF-κB** signaling and selectively degrades TI-2 antibody responses (PMID: 19605846). Variant type: **missense**; functional consequence: impaired signaling (hypomorphic / dominant-negative depending on allele). *TNFRSF13B* is mutated in ~10% of CVID patients.

Monogenic phenocopies. A 2024 review catalogs genetically defined IEI that initially present with impaired polysaccharide IgG, normal/near-normal IgG, and normal protein/conjugate responses — a picture indistinguishable from primary SAD (PMID: 38933494):

> "genetically defined IEI, that may initially present with an impaired IgG response to polysaccharide antigens, but normal or only slightly decreased IgG levels and normal responses to protein or conjugate vaccine antigens" (PMID: 38933494).

Modifier genes / epigenetics / chromosomal abnormalities. Not established for isolated SAD. Anti-polysaccharide deficiency does occur in chromosomal/syndromic disorders (e.g., DiGeorge/22q11) as a secondary phenomenon (PMID: 8167745). Allele frequency, somatic-vs-germline, and gnomAD data are not applicable to a functionally defined disease.

Section 5 — Environmental Information

- **Environmental/toxin factors:** No specific toxin, radiation, or occupational exposure is causally established.
- **Lifestyle factors:** Not defined; SAD is intrinsic/functional rather than lifestyle-driven.
- **Infectious agents (triggers of the clinical phenotype, not causes of the deficiency):** encapsulated bacteria, principally ***Streptococcus pneumoniae*** and ***Haemophilus influenzae*** **type b**, produce the recurrent pneumonia/meningitis/otitis phenotype when anti-capsular antibody is deficient (PMID: 8167745):

> "In infants and young children up to the age of 2 years the antibody response to capsular polysaccharides is inadequate resulting in an increased incidence of diseases such as pneumonia, meningitis, otitis" (PMID: 8167745).

Section 6 — Mechanism / Pathophysiology

Ordered causal chain

1. An **intrinsic/functional defect in the TI-2 (thymus-independent type-2) B-cell response** to bacterial capsular polysaccharides is present (largely idiopathic; in phenocopies, driven by a monogenic lesion such as *TNFRSF13B*/TACI–NF-κB signaling failure) → **leads to** inability to mount adequate anti-capsular IgG (especially IgG2/IgM).

2. Because the TI-2 response normally **develops late in ontogeny, forms no memory, and uses a restricted IgM/IgG2 isotype repertoire** (PMID: 8167745), the defect **results in** low or non-durable serotype-specific anti-pneumococcal IgG on PPSV23 challenge.
3. Deficient anti-capsular antibody **leads to** impaired opsonization and complement-mediated clearance of encapsulated bacteria (*S. pneumoniae*, Hib).
4. Impaired opsonophagocytosis **results in** recurrent/severe **sinopulmonary and invasive infections** (pneumonia, otitis, sinusitis, meningitis) (PMID: 8167745; PMID: 27614984).
5. Repeated/chronic airway infection, if diagnosis is delayed, **leads to** airway wall damage and **bronchiectasis** (diagnostic delay 122 vs 24 months in patients with vs without bronchiectasis, p = 0.0042) (PMID: 40097777).

Branch (therapeutic bypass): Presenting the polysaccharide as a **protein-conjugate vaccine** converts the antigen to a **T-dependent** stimulus → germinal-center help → memory + higher-affinity IgG → **restores protection**, bypassing the TI-2 defect (PMID: 34290713; PMID: 27614984).

Molecular / cellular detail

- **Molecular pathway:** TACI (TNFRSF13B) → **NF-κB** signaling supports T-independent antibody responses; impaired signaling degrades TI-2 responses (PMID: 19605846).
- **Cell types (CL terms):** B lymphocyte (CL:0000236); marginal-zone B cell (CL:0000844) — the principal responders to TI-2 antigens; plasma cell (CL:0000786); memory B cell (CL:0000787). Neutrophils modulate conjugate-vaccine responses by restraining Tregs (mouse/human data) (PMID: 42565624).
- **Immune process (GO terms):** GO:0002374 (immunoglobulin production); T-independent B cell activation / humoral response; GO:0006954 (inflammatory response); GO:0045087 (innate immune response); GO:0007249 (canonical NF-κB signal transduction).
- **Immune system involvement:** immunodeficiency (humoral, functional), with prominent **allergic comorbidity** (asthma, allergic rhinitis) (PMID: 27614984).

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[TI-2 / TACI–NF-κB defect]
        │ leads to
        ▼
[Deficient anti-capsular IgG2/IgM] ── bypassed by ──► [Conjugate vaccine → T-dependent response
        │ results in
        ▼
[Impaired opsonization of S. pneumoniae / Hib]
        │ results in
        ▼
[Recurrent sinopulmonary + invasive infection]
        │ (if diagnosis delayed) leads to
        ▼
[Bronchiectasis / chronic lung damage]
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Section 7 — Anatomical Structures Affected

- **Primary organs / systems (respiratory):** paranasal sinuses (UBERON:0001825), middle ear (UBERON:0001756), lungs/bronchi (UBERON:0002048 lung; UBERON:0002185 bronchus). Body system: **respiratory system** (UBERON:0001004).
- **Secondary/complication:** bronchiectatic airways; potential invasive spread (meningitis — meninges UBERON:0002360; bloodstream).
- **Immune tissue:** spleen (UBERON:0002106) and marginal zone are central to TI-2 responses; splenectomy is a recognized secondary cause of anti-polysaccharide deficiency (PMID: 8167745).
- **Tissue/cell level:** respiratory epithelium (repeated infection); B-lymphocyte/marginal-zone B-cell compartment (functional defect).
- **Subcellular (GO cellular component):** plasma membrane receptor signaling (TACI at plasma membrane, GO:0005886); nucleus (NF-κB nuclear translocation, GO:0005634).
- **Lateralization:** typically **bilateral** sinopulmonary involvement (not lateralized).

Section 8 — Temporal Development

- **Onset:** Typically **childhood**; the polysaccharide response is physiologically inadequate before ~2 years, so diagnosis requires age ≥ 2 (PMID: 8167745; PMID: 32654695). Adult presentation is common (median diagnosis age 45 y in an adult cohort) (PMID: 40097777).
- **Onset pattern:** insidious/chronic recurrent infection.
- **Course:** episodic infections; may be **stable, self-resolving, or progressive** to bronchiectasis.
- **Duration / remission:** In children the deficiency **may resolve over time** (PMID: 26454312); a distinct "impaired persistence" subset loses titers by one year (PMID: 25498324).
- **Critical period / window of opportunity:** early diagnosis prevents bronchiectasis (delay strongly associated with bronchiectasis) (PMID: 40097777).

Section 9 — Inheritance and Population

Epidemiology. Precise SAD-specific incidence/prevalence is not well established because diagnosis depends on vaccine-challenge testing and case definitions vary; SAD is frequently under-recognized. Its parent category — **predominantly antibody deficiencies** — is consistently the **largest IEI group** across registries: 41.3% (38/92) in a Colombian tertiary cohort (PMID: 39836844) and 46.3% of 24,879 patients across 30 J-Project countries (PMID: 36605210). Among adults with unexplained recurrent/severe encapsulated-bacterial infection, PID was found in 39.8% (95% CI 30.4–48.8), and **SPAD was the most frequent diagnosis (37/47 = 78.7%)** (PMID: 36285530):

> "SPAD was the most frequent diagnosis by far (n = 37/47, 78.7%)" (PMID: 36285530).

Inheritance. No Mendelian inheritance pattern for primary SAD (functional, largely idiopathic). Phenocopying monogenic IEI follow their own (AD/AR/X-linked) patterns (PMID: 38933494). Penetrance, expressivity, anticipation, founder effects, and carrier frequency are **not applicable** to a non-Mendelian functional diagnosis.

Demographics. - **Sex ratio:** adult SPAD is **female-predominant (~75% female; ~3:1 F:M)** (PMID: 40097777). - **Age:** bimodal recognition — childhood onset and adult diagnosis (median 45 y in adults). - **Geographic/ethnic distribution:** no specific predilection documented; recognition depends on access to vaccine-challenge testing.

Section 10 — Diagnostics

Core diagnostic test — PPSV23 vaccine challenge. Measure **serotype-specific IgG before and 4–6 weeks after PPSV23** in patients ≥ 2 years with recurrent infection and otherwise intact immunity. An adequate response to an individual serotype is conventionally **post-immunization titer ≥ 1.3 µg/mL or a ≥ 4-fold rise over baseline** (PMID: 9723664):

> "An adequate IgG antibody response to an individual serotype was arbitrarily defined as a postimmunization antibody titer of 1.3 microg/ml or greater or at least four times the baseline value." (PMID: 9723664)

Age-adjusted proportion-of-serotypes criteria (pediatric). A response above 1.3 µg/mL for > **50% of serotypes** is normal for ages 2–5 years, and for > **70% of serotypes** in children older than 5 years (PMID: 25498324). Responses rise sharply in adults versus all pediatric age groups (7 months–16 years) (PMID: 9723664).

Diagnostics in the conjugate-vaccine (PCV) era. Widespread PCV13/15/20 reduces the number of *unique* PPSV23 serotypes available for interpretation (11 unique after PCV13; only 4 after PCV20), yet **PPSV23 challenge retains 81–84% diagnostic accuracy** in patients aged 2–65 (PMID: 39681261). A validated **18-plex electrochemiluminescence (ECL) assay** benchmarked against WHO ELISA in 164 sera showed **sensitivity 95%, specificity 84%, PPV 84%, NPV 95%** for SPAD (PMID: 40637813):

> "the 18-plex ECL assay for SPAD diagnosis showed a sensitivity of 95% and specificity of 84%, positive and negative predictive values of 84% and 95%, respectively" (PMID: 40637813).

Supporting labs. Normal total IgG, IgA, IgM and IgG subclasses (definitional); consider IgM/IgA anti-pneumococcal assays as adjuncts (do not replace serotype-specific IgG) (PMID: 33877708). **Genetic testing** (WES/panels) is warranted when a monogenic IEI phenocopy is suspected — anti-polysaccharide IgG testing is recommended in the initial IEI work-up (PMID: 38933494).

Clinical criteria / differential. No universally accepted quantitative threshold; definition of an "adequate" response (magnitude, number of serotypes) remains controversial (PMID: 28588580; PMID: 32654695). **Differential diagnosis:** CVID, IgG subclass deficiency, selective IgA deficiency, XLA, Wiskott–Aldrich, DiGeorge, and secondary causes (splenectomy, HIV, malignancy) — all must be excluded (PMID: 8167745).

Screening. Immunoglobulin and vaccine-response testing should be part of the work-up of patients with recurrent sinopulmonary infection, chronic rhinosinusitis, or bronchiectasis of unclear cause; SAD/SPAD is under-diagnosed in these groups (PMID: 36285530).

Section 11 — Outcome / Prognosis

- **Overall prognosis:** generally **good**; deficiency may resolve, especially in children (PMID: 26454312):

> "Most patients have a good prognosis. The deficiency may resolve over time, especially in children." (PMID: 26454312)

- **Key complication: bronchiectasis**, driven by recurrent infection and **diagnostic delay** (122 vs 24 months with vs without bronchiectasis, p = 0.0042) (PMID: 40097777).
- **Treatment outcomes:** IgRT markedly reduces infection burden (mean antibiotic courses 7.9 → 0.7 per year, p < 0.001) (PMID: 40097777). Patients diagnosed after a single severe infection had **no relapse over median 85-month follow-up** (PMID: 40097777).
- **Morbidity / QoL:** significant HRQOL burden; caregiver burden in pediatric disease (PMID: 42447994; PMID: 42119234).
- **Prognostic factors:** infection history/severity, presence of bronchiectasis, and (for conjugate-vaccine protection) IgG subclass status and IgG2 at diagnosis (PMID: 34290713).

Section 12 — Treatment

Tiered management ladder: (1) prompt treatment of infections → (2) pneumococcal **conjugate vaccination** → (3) **antibiotic prophylaxis** → (4) **immunoglobulin replacement (IVIG/SCIG)** in refractory/severe cases (PMID: 32654695; PMID: 40097777).

> "Specific antibody deficiency is managed clinically with close follow-up and prompt treatment of infections, antibiotic prophylaxis, or immune globulin therapy." (PMID: 32654695)

Pneumococcal conjugate vaccine (PCV). Because conjugate vaccines present polysaccharide as a T-dependent protein-linked antigen, they bypass the TI-2 defect. In primary humoral immunodeficiency (n = 29) given PCV13, protection was **71.4%, 66.7%, and 56.0% at 1, 6, and 12 months**; IgG subclass deficiency, Ig replacement, and higher IgG2 at diagnosis predicted long-term protection (PMID: 34290713). Conjugate vaccination was favorable in **11/12** pediatric SAD patients (PMID: 27614984). Suggested NCIT: *Pneumococcal Conjugate Vaccine*.

> "71.4%, 66.7% and 56.0% of the patients were protected at one, six and twelve months respectively" (PMID: 34290713).

Immunoglobulin replacement therapy (IgRT). In adult SPAD, 40% received IgRT with a fall in mean antibiotic courses from 7.9 to 0.7 per year ($p < 0.001$) (PMID: 40097777). Route (IVIG vs SCIG) did not significantly affect pediatric QoL (PMID: 42119234). Suggested NCIT: *Intravenous Immunoglobulin Therapy*, *Subcutaneous Immunoglobulin*.

Antibiotic prophylaxis. Mainstay for reducing recurrent infection (PMID: 32654695).

Personalized strategy. Individualized because of the absence of a robust case definition and lack of controlled trials (PMID: 28588580). Gene/cell/RNA-based therapies are **not applicable** to primary SAD (relevant only to specific monogenic phenocopies).

Treatment tier	Intervention	Evidence / effect	NCIT-type term
1	Prompt antibiotic treatment of acute infection	Standard of care	Antibiotic Therapy
2	Pneumococcal conjugate vaccine (PCV13/15/20)	Bypasses TI-2 defect; 56–71% protected over 12 mo (PID)	Pneumococcal Conjugate Vaccine
3	Antibiotic prophylaxis	Reduces recurrent infection	Antibiotic Prophylaxis
4	IgRT (IVIG/SCIG)	Antibiotic courses 7.9 → 0.7/yr (p<0.001)	Immunoglobulin Replacement Therapy

Section 13 — Prevention

- **Primary prevention:** not applicable (intrinsic functional defect); focus is on infection prevention via **conjugate vaccination** and prophylactic antibiotics (PMID: 34290713; PMID: 32654695).
- **Secondary prevention:** early recognition and vaccine-challenge testing to prevent bronchiectasis (delay strongly linked to bronchiectasis) (PMID: 40097777); immunologic evaluation of at-risk groups (recurrent sinopulmonary infection, CRS, unexplained encapsulated-bacterial infection) (PMID: 36285530).
- **Tertiary prevention:** IgRT, airway clearance, and surveillance to prevent progression/ complications.
- **Immunization:** conjugate pneumococcal and Hib vaccines (T-dependent) are the cornerstone.
- **Counseling:** genetic counseling relevant only where a monogenic phenocopy is identified (PMID: 38933494).

Section 14 — Other Species / Natural Disease

- **Taxonomy of model species:** *Mus musculus* (NCBI:txid10090) is the principal experimental species.
- **Orthologous gene:** murine *Tnfrsf13b* (TACI) models the human TI-2 defect (PMID: 19605846).
- **Natural disease in other species / veterinary relevance / zoonosis:** No naturally occurring animal counterpart of isolated human SAD/SPAD is documented in the reviewed literature. Not zoonotic. Not applicable.
- **Comparative/evolutionary biology:** the TI-2 anti-capsular response and TACI–NF-κB signaling are conserved between mouse and human, enabling mechanistic modeling (PMID: 19605846).

Section 15 — Model Organisms

- **Model type:** mammalian (mouse).
- **Genetic model:** transgenic mice expressing the TACI **A144E** mutant (murine equivalent of human *TNFRSF13B* A181E) on a **TACI−/−** background (PMID: 19605846).
- **Phenotype recapitulation:** low serum IgA and **significantly impaired antibody responses to the TI-2 antigen TNP-Ficoll**, with impaired B-cell proliferation and IgG1/IgA secretion and impaired constitutive/ligand-induced NF-κB signaling (PMID: 19605846):

> "Transgenic mice expressing the A144E mutant on TACI(-/-) background had low serum IgA levels and significantly impaired antibody responses to the type II T-independent antigen TNP-Ficoll." (PMID: 19605846)

- **Additional mechanistic model:** neutrophil-depletion mouse studies show neutrophils are required for protective conjugate-vaccine antibody responses by restraining Tregs — relevant to why PCV works and how the response is regulated (PMID: 42565624).
- **Limitations:** these models capture the **TI-2 response defect** but not the full heterogeneity or idiopathic nature of primary human SAD; they primarily model CVID-associated TACI biology.

Mechanistic Model / Interpretation

SAD/SPAD is best understood as a **functional failure at one node of the humoral immune system — the thymus-independent type-2 response to bacterial capsular polysaccharides.** This response is intrinsically fragile: it matures late (inadequate < 2 years), forms no memory, and uses a narrow IgM/IgG2 repertoire (PMID: 8167745). When it fails, anti-capsular antibody is insufficient to opsonize *S. pneumoniae* and Hib, producing recurrent sinopulmonary infection. The two therapeutic levers both make sense in this framework: (1) **conjugate vaccines** re-route the antigen through T-dependent germinal-center help, restoring durable IgG (PMID: 34290713); and (2) **IgRT** supplies the missing antibody directly (PMID: 40097777).

The disease's "Mendelian" framing is misleading. Primary SAD has **no single causal gene** and is a diagnosis of exclusion (PMID: 28588580; PMID: 8167745). The genetic dimension enters in two ways: as **mechanistic insight** (TACI–NF-κB governs TI-2 responses; PMID: 19605846) and as **differential diagnosis** (monogenic IEI can phenocopy SAD and should be sought when clinically indicated; PMID: 38933494).

Evidence Base

PMID	Title (abbrev.)	Role
32654695	*Diagnosis and management of Specific Antibody Deficiency*	Definition + management ladder
28588580	*SAD: Controversies in Diagnosis and Management*	Normal Ig phenotype; lack of consensus
8167745	*Anti-capsular polysaccharide antibody deficiency states*	TI-2 immunobiology; secondary causes
9723664	*Influence of age on S. pneumoniae vaccine response*	1.3 µg/mL / 4-fold thresholds; age dependence
25498324	*SAD with normal Ig in children*	Age-adjusted pediatric criteria; impaired persistence
27614984	*SAD: PID associated to respiratory allergy*	Recurrent pneumonia 91.7%; asthma/ rhinitis; PCV benefit
36285530	*High frequency of SPAD in adults*	SPAD = 78.7% of PIDs; PID freq 39.8%
26454312	*Specific Antibody Deficiencies*	Good prognosis; may resolve
38933494	*Monogenic IEI with impaired polysaccharide IgG*	Phenocopies; test anti-PS IgG
19605846	*Murine A181E TACI mutation*	Mouse model; TACI–NF-κB; TNP-Ficoll
34290713	*PCV13 in primary humoral immunodeficiency*	Conjugate-vaccine protection over 12 mo
40097777	*55 adult SPAD patients*	Female 75%; delay/bronchiectasis; IgRT efficacy
39681261	*Functional testing in the Prevnar 20 era*	PPSV23 accuracy 81–84% in PCV era
40637813	*Multiplex ECL assay for SPAD*	Sens 95% / Spec 84% vs WHO ELISA
39836844	*Colombian IEI service*	PAD = largest IEI group (41.3%)
36605210	*J Project 30 countries*	PAD = 46.3% of 24,879 patients
42447994	*Shared decision-making / HRQOL in IEI*	QoL burden; PADQOL/CVID-QOL
42119234	*QoL and care burden SCIG/IVIG*	r = −0.710 child QoL vs caregiver burden

PMID	Title (abbrev.)	Role
42565624	*Neutrophils and PCV responses*	Neutrophil–Treg regulation of conjugate response
33877708	*IgM/IgA anti-PnPS assays*	Serotype-specific IgG remains the standard

Limitations and Knowledge Gaps

1. **No molecular case definition.** SAD is functionally defined, and thresholds for an "adequate" polysaccharide response (magnitude and number of serotypes) remain controversial and age-dependent (PMID: 28588580; PMID: 9723664).
2. **Uncertain incidence/prevalence.** No robust population-level SAD-specific rates exist; estimates are inferred from PAD-category registries and at-risk cohorts (PMID: 39836844; PMID: 36605210).
3. **PCV-era diagnostic erosion.** Universal conjugate vaccination reduces interpretable unique PPSV23 serotypes; although accuracy holds (81–84%), standardization is evolving (PMID: 39681261; PMID: 40637813).
4. **Small cohorts, few controlled trials.** Much clinical evidence rests on modest case series; treatment is individualized (PMID: 28588580).
5. **Genetic architecture underexplored.** The boundary between idiopathic SAD and monogenic phenocopies is not resolved; systematic genetic testing thresholds are undefined (PMID: 38933494).

Proposed Follow-up Experiments / Actions

1. **Harmonize the case definition:** multi-center consensus on age-adjusted, PCV-era serotype thresholds, ideally anchored to the validated 18-plex ECL assay against WHO ELISA (PMID: 40637813; PMID: 39681261).
2. **Prospective natural-history registry** to quantify SAD-specific incidence/prevalence, resolution rates in children, and bronchiectasis risk as a function of diagnostic delay (PMID: 40097777).

3. **Genetic yield study:** systematically apply WES/gene panels (including *TNFRSF13B*) to SAD-phenotype patients to define the proportion with identifiable monogenic phenocopies (PMID: 38933494; PMID: 19605846).
4. **Randomized/controlled comparison** of antibiotic prophylaxis vs IgRT vs conjugate-vaccine-only strategies stratified by infection severity and bronchiectasis status (PMID: 32654695).
5. **Mechanistic follow-up** on the allergy–SAD association and on neutrophil/Treg regulation of conjugate-vaccine responses to identify predictors of durable protection (PMID: 27614984; PMID: 42565624; PMID: 34290713).

Report compiled from 15 confirmed findings across 5 investigation iterations and 72 reviewed papers. Evidence types: predominantly human clinical (cohorts, case series, registries) plus one mouse mechanistic model (PMID: 19605846) and mouse/human conjugate-vaccine immunobiology (PMID: 42565624).
