most patients present multiple infections, although some display a specific predisposition to pneumococcal or mycobacterial diseases.[7] Almost all patients present infections caused by pyogenic bacteria, and only a few patients suffer from mycobacterial, fungal, and/or viral diseases. The most frequent pathogens observed include gram-positive (*Str. pneumoniae* and *Staph. aureus*) and gram-negative pyogenic bacteria (*P. aeruginosa* and *H. influenzae*). Patients bearing mutations in NEMO almost invariably have an impaired antibody response to glycans, including pneumococcal capsules in particular, as in half the IRAK-4- and MyD88-deficient patients explored for antibody responses to a subset of glycan antigens.[40] Thus, the bacterial diseases seen in NEMO-deficient patients are probably due in part to the impact of NEMO mutations on the TIR-signaling pathway. Conversely, the other infections seen in NEMO-deficient patients but not in IRAK-4-deficient and MyD88-deficient patients probably reflect the impairment of other signaling pathways.

The association of clinical disease caused by *Str. pneumoniae*, *Staph. aureus,* and *P. aeruginosa* is unique among primary immunodeficiencies other than IRAK-4, MyD88, NEMO, and IκBα deficiencies.[37] Primary immunodeficiencies affecting bacterial opsonization and splenic phagocytosis are associated with invasive pneumococcal disease. These conditions include most B- and T-cell defects, congenital asplenia, deficiencies of C3, the early component of the classical and alternative complement pathway.[39] These patients develop recurrent invasive pneumococcal disease due to *Str. pneumoniae*, but are less susceptible to *Staph. aureus* and *P. aeruginosa* infections.

Other primary immunodeficiencies, such as STAT3 and TYK2 deficiencies in HyperIgE syndromes, are associated with staphylococcal infections,[7] but patients with these primary immunodeficiencies do not suffer from invasive pneumococcal disease and *Pseudomonas* infection. Notably, two-thirds of the explored IRAK-4- and MyD88-deficient patients were found to have high levels of IgE, but these levels were modest with respect to the very high IgE levels described in STAT-3-deficient patients.

Finally, most primary immunodeficiencies involving phagocyte defects, including congenital neutropenia, leukocyte adhesion deficiency, and chronic granulomatous disease, are associated with severe infections caused by *P. aeruginosa* and *Staph. aureus,* but patients with these disorders are not particularly prone to invasive pneumococcal disease. [39] A diagnosis of IRAK-4 or MyD88 deficiency or of NEMO/IκBα-related defects should be considered even with only 1 or 2 of these 3 infections. Neonates, infants, and children with invasive pneumococcal disease, severe staphylococcal disease, or *Pseudomonas* lesions of the upper respiratory tract or peritoneum, particularly in cases of recurrence, should be tested for the NF-κB pathways, including the TIR pathway in particular.[2,9] This list is not exclusive, as systemic shigellosis was documented in 2 patients, and other infectious diseases associated with these primary immunodeficiencies may be revealed by the investigation of other patients in the future.

In IRAK-4- and MyD88-deficient patients, clinical and laboratory signs of inflammation develop slowly even in cases of severe infection. The current study confirms and expands previous work indicating that CRP concentration, total leukocyte counts, and neutrophil numbers are typically low, but may also rise to appropriately high levels during prolonged infections, whereas temperature frequently remains inappropriately low even in such infections.[18] Thus, weak signs of inflammation despite severe infection provide a further clue to possible defects in TIR signaling, although appropriately high levels of inflammatory signs do not rule out the diagnosis of TIR deficiency.[18] Impairment of the production of IL-6-inducible molecules, such as CRP, may be observed. IRAK-4- and MyD88-deficient cells produce small amounts of IL-6 and IL-8 in vitro upon activation with IL-1 and TLR

agonists.[25,38,49] As CRP contributes to the clearance of pyogenic bacteria including pneumococcus,[35,47] susceptibility to *Str. pneumoniae*, *Staph. aureus,* or *P. aeruginosa* may be increased by the slow rise in CRP levels. Similar delays in the development of signs of inflammation are observed in patients with NEMO and IκBα deficiencies, whose broader susceptibility to infections includes these pyogenic bacteria.[7]

Some IRAK-4-deficient patients (n = 10) had a delay in umbilical cord detachment and/or omphalitis. Other primary immunodeficiencies, such as leukocyte adhesion deficiency type 1 and Rac2 deficiency, have been associated with late loss of the umbilical cord and/or omphalitis, but extremely high levels of circulating neutrophils and a lack of pus formation in peripheral tissues are classically found in these disorders.[36] By contrast, in IRAK-4-and MyD88-deficient patients, impaired polymorphonuclear neutrophil mobilization and/or frank neutropenia occurs from the onset of infection, perhaps secondary to the lack of IL-8 production. Despite this neutropenia, pus formation is normal in IRAK-4- and MyD88-deficient patients. The precise mechanism of cord separation is unknown, but it does require MyD88- and IRAK-4-dependent signals, as well as CD18-expressing leukocytes. Conversely, unlike patients with various phagocyte defects, such as chronic granulomatous disease, none of the IRAK-4-and MyD88-deficient patients had inflammatory bowel disease.[36]

Despite conferring selective susceptibility to only a few bacteria, IRAK-4 and MyD88 deficiencies are nonetheless life-threatening in infancy and childhood, with a mortality rate of 38% in our series. Strikingly, however, although IRAK-4 and MyD88 appear to be vital in childhood, infections in patients lacking these proteins become rarer with age, with no death recorded in patients after the age of 8 years and no invasive infection after the age of 14 years, even in the absence of antibiotics or/and IgG prophylaxis in 7 patients over the age of 14 years. In total, this represents a cumulative time of 49 years without any InvBD for these patients. This dramatic improvement with age may be accounted for by adaptive antigen-specific T- and B-lymphocyte responses. Indeed, our patients displayed no detectable defect of protein antigen-specific T- and B-cell responses, although some patients were found to have weak antibody responses to a subset of glycan antigens.

Recent studies of neonatal bacterial sepsis in newborn mice suggest a reliance on innate immunity early in life, which progressively diminishes with age.[51] An alternative complementary hypothesis is that innate immune responses may also mature with age.[4,25] Other sensors, such as RIG-I-like helicases and NOD-like receptors, may progressively play a compensatory role. In any event, clinical improvement did not result solely from prophylaxis following diagnosis of the first infection or of the underlying deficit. The TIR pathway, including TLR responses in particular, remains dependent on IRAK-4/MyD88 with age, but the maturation of other pathways may gradually compensate for the lack of TIR signaling.

In this study, we show that the prognosis of IRAK-4 and MyD88 deficiencies is severe in infancy and early childhood, but improves substantially in adolescence. This finding is probably unique so far in the field of primary immunodeficiencies, which classically do not improve with age. This improvement with age is a hallmark of these conditions, not observed in other primary immunodeficiencies. A similar but less striking spontaneous improvement has been reported only in children with IL-12p40 and IL-12Rβ1 deficiencies. [10]

In conclusion, both IRAK-4 deficiency and MyD88 deficiency confer a predisposition to InvBD, mostly caused by *Str. pneumoniae*, *Staph. aureus*, and *P. aeruginosa*. In addition, both conditions confer a predisposition to NInvBD, often severe skin infections, mostly

caused by *Staph. aureus*, and severe forms of ear, nose, and throat infections caused by *P. aeruginosa*. Clinical status and outcome both improve with age. There seems to be a beneficial role of prophylaxis combining intensive vaccinations, oral antibiotics, and IgG injections.

The most important advice for the families and physicians of IRAK-4-deficient and MyD88-deficient patients is to initiate empiric parenteral antibiotic treatment as soon as infection is suspected or the patient develops a moderate fever, without taking inflammatory parameters into account, because patients may die from rapid invasive bacterial infection even if prophylactic measures are taken.

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Abbreviations

CRP	C-reactive protein
ELISA	enzyme-linked immunosorbent assay
IFN	interferon
IKBA	IκBα
IL	interleukin
IL-1R	interleukin-1 receptor
InvBD	invasive bacterial disease
IRAK	interleukin-1 receptor-associated kinase
MyD	myeloid differentiation factor
NEMO	nuclear factor-kappaB essential modulator
NInvBD	noninvasive bacterial disease
TIR	Toll/IL-1R
TLR	Toll-like receptor
TNF	tumor necrosis factor

References

1. Akira S, Takeda K. Toll-like receptor signalling. Nat Rev Immunol. 2004; 4:499–511. [PubMed: 15229469]
2. Alcais A, Abel L, Casanova JL. Human genetics of infectious diseases: between proof of principle and paradigm. J Clin Invest. 2009; 119:2506–2514. [PubMed: 19729848]

3. Arend WP, Palmer G, Gabay C. IL-1, IL-18, and IL-33 families of cytokines. Immunol Rev. 2008; 223:20–38. [PubMed: 18613828]
4. Belderbos ME, van Bleek GM, Levy O, Blanken MO, Houben ML, Schuijff L, Kimpen JL, Bont L. Skewed pattern of Toll-like receptor 4-mediated cytokine production in human neonatal blood: low LPS-induced IL-12p70 and high IL-10 persist throughout the first month of life. Clin Immunol. 2009; 133:228–237. [PubMed: 19648060]
5. Borgers H, Moens L, Picard C, Jeurissen A, Raes M, Sauer K, Proesmans M, De Boeck K, Casanova JL, Meyts I, Bossuyt X. Laboratory diagnosis of specific antibody deficiency to pneumococcal capsular polysaccharide antigens by multiplexed bead assay. Clin Immunol. 2010; 134:198–205. [PubMed: 19914139]
6. Bouma G, Doffinger R, Patel SY, Peskett E, Sinclair JC, Barcenas-Morales G, Cerron-Gutierrez L, Kumararatne DS, Davies EG, Thrasher AJ, Burns SO. Impaired neutrophil migration and phagocytosis in IRAK-4 deficiency. Br J Haematol. 2009; 147:153–156. [PubMed: 19663824]
7. Bustamante J, Boisson-Dupuis S, Jouanguy E, Picard C, Puel A, Abel L, Casanova JL. Novel primary immunodeficiencies revealed by the investigation of paediatric infectious diseases. Curr Opin Immunol. 2008; 20:39–48. [PubMed: 18083507]
8. Cardenes M, von Bernuth H, Garcia-Saavedra A, Santiago E, Puel A, Ku CL, Emile JF, Picard C, Casanova JL, Colino E, Bordes A, Garfia A, Rodriguez-Gallego C. Autosomal recessive interleukin-1 receptor-associated kinase 4 deficiency in fourth-degree relatives. J Pediatr. 2006; 148:549–551. [PubMed: 16647422]
9. Casanova JL, Abel L. Inborn errors of immunity to infection: the rule rather than the exception. J Exp Med. 2005; 202:197–201. [PubMed: 16027233]
10. Casanova JL, Abel L. Primary immunodeficiencies: a field in its infancy. Science. 2007; 317:617–619. [PubMed: 17673650]
11. Casrouge A, Zhang SY, Eidenschenk C, Jouanguy E, Puel A, Yang K, Alcais A, Picard C, Mahfoufi N, Nicolas N, Lorenzo L, Plancoulaine S, Senechal B, Geissmann F, Tabeta K, Hoebe K, Du X, Miller RL, Heron B, Mignot C, de Villemeur TB, Lebon P, Dulac O, Rozenberg F, Beutler B, Tardieu M, Abel L, Casanova JL. Herpes simplex virus encephalitis in human UNC-93B deficiency. Science. 2006; 314:308–312. [PubMed: 16973841]
12. Chapel H, Puel A, von Bernuth H, Picard C, Casanova JL. Shigella sonnei meningitis due to interleukin-1 receptor-associated kinase-4 deficiency: first association with a primary immune deficiency. Clin Infect Dis. 2005; 40:1227–1231. [PubMed: 15825022]
13. Courtois G, Smahi A, Reichenbach J, Doffinger R, Cancrini C, Bonnet M, Puel A, Chable-Bessia C, Yamaoka S, Feinberg J, Dupuis-Girod S, Bodemer C, Livadiotti S, Novelli F, Rossi P, Fischer A, Israel A, Munnich A, Le Deist F, Casanova JL. A hypermorphic IkappaBalpha mutation is associated with autosomal dominant anhidrotic ectodermal dysplasia and T cell immunodeficiency. J Clin Invest. 2003; 112:1108–1115. [PubMed: 14523047]
14. Davidson DJ, Currie AJ, Bowdish DM, Brown KL, Rosenberger CM, Ma RC, Bylund J, Campsall PA, Puel A, Picard C, Casanova JL, Turvey SE, Hancock RE, Devon RS, Speert DP. IRAK-4 mutation (Q293X): rapid detection and characterization of defective post-transcriptional TLR/IL-1R responses in human myeloid and non-myeloid cells. J Immunol. 2006; 177:8202–8211. [PubMed: 17114497]
15. Day N, Tangsinmankong N, Ochs H, Rucker R, Picard C, Casanova JL, Haraguchi S, Good R. Interleukin receptor-associated kinase (IRAK-4) deficiency associated with bacterial infections and failure to sustain antibody responses. J Pediatr. 2004; 144:524–526. [PubMed: 15069404]
16. de Beaucoudrey L, Puel A, Filipe-Santos O, Cobat A, Ghandil P, Chrabieh M, Feinberg J, von Bernuth H, Samarina A, Janniere L, Fieschi C, Stephan JL, Boileau C, Lyonnet S, Jondeau G, Cormier-Daire V, Le Merrer M, Hoarau C, Lebranchu Y, Lortholary O, Chandesris MO, Tron F, Gambineri E, Bianchi L, Rodriguez-Gallego C, Zitnik SE, Vasconcelos J, Guedes M, Vitor AB, Marodi L, Chapel H, Reid B, Roifman C, Nadal D, Reichenbach J, Caragol I, Garty BZ, Dogu F, Camcioglu Y, Gulle S, Sanal O, Fischer A, Abel L, Stockinger B, Picard C, Casanova JL. Mutations in STAT3 and IL12RB1 impair the development of human IL-17-producing T cells. J Exp Med. 2008; 205:1543–1550. [PubMed: 18591412]
17. Dinarello CA. Interleukin-1beta and the autoinflammatory diseases. N Engl J Med. 2009; 360:2467–2470. [PubMed: 19494224]

18. Enders A, Pannicke U, Berner R, Henneke P, Radlinger K, Schwarz K, Ehl S. Two siblings with lethal pneumococcal meningitis in a family with a mutation in Interleukin-1 receptor-associated kinase 4. J Pediatr. 2004; 145:698–700. [PubMed: 15520784]
19. Haraguchi S, Day NK, Nelson RP Jr, Emmanuel P, Duplantier JE, Christodoulou CS, Good RA. Interleukin 12 deficiency associated with recurrent infections. Proc Natl Acad Sci U S A. 1998; 95:13125–13129. [PubMed: 9789052]
20. Hoarau C, Gerard B, Lescanne E, Henry D, Francois S, Lacapere JJ, El Benna J, Dang PM, Grandchamp B, Lebranchu Y, Gougerot-Pocidalo MA, Elbim C. TLR9 activation induces normal neutrophil responses in a child with IRAK-4 deficiency: involvement of the direct PI3K pathway. J Immunol. 2007; 179:4754–4765. [PubMed: 17878374]
21. Janssen R, van Wengen A, Hoeve MA, ten Dam M, van der Burg M, van Dongen J, van de Vosse E, van Tol M, Bredius R, Ottenhoff TH, Weemaes C, van Dissel JT, Lankester A. The same IkappaBalpha mutation in two related individuals leads to completely different clinical syndromes. J Exp Med. 2004; 200:559–568. [PubMed: 15337789]
22. Jeurissen A, Moens L, Raes M, Wuyts G, Willebrords L, Sauer K, Proesmans M, Ceuppens JL, De Boeck K, Bossuyt X. Laboratory diagnosis of specific antibody deficiency to pneumococcal capsular polysaccharide antigens. Clin Chem. 2007; 53:505–510. [PubMed: 17259230]
23. Krause JC, Ghandil P, Chrabieh M, Casanova JL, Picard C, Puel A, Creech CB. Very late-onset group B Streptococcus meningitis, sepsis, and systemic shigellosis due to interleukin-1 receptor-associated kinase-4 deficiency. Clin Infect Dis. 2009; 49:1393–1396. [PubMed: 19814626]
24. Ku CL, Picard C, Erdos M, Jeurissen A, Bustamante J, Puel A, von Bernuth H, Filipe-Santos O, Chang HH, Lawrence T, Raes M, Marodi L, Bossuyt X, Casanova JL. IRAK4 and NEMO mutations in otherwise healthy children with recurrent invasive pneumococcal disease. J Med Genet. 2007; 44:16–23. [PubMed: 16950813]
25. Ku CL, von Bernuth H, Picard C, Zhang SY, Chang HH, Yang K, Chrabieh M, Issekutz AC, Cunningham CK, Gallin J, Holland SM, Roifman C, Ehl S, Smart J, Tang M, Barrat FJ, Levy O, McDonald D, Day-Good NK, Miller R, Takada H, Hara T, Al-Hajjar S, Al-Ghonaium A, Speert D, Sanlaville D, Li X, Geissmann F, Vivier E, Marodi L, Garty BZ, Chapel H, Rodriguez-Gallego C, Bossuyt X, Abel L, Puel A, Casanova JL. Selective predisposition to bacterial infections in IRAK-4-deficient children: IRAK-4-dependent TLRs are otherwise redundant in protective immunity. J Exp Med. 2007; 204:2407–2422. [PubMed: 17893200]
26. Kuhns DB, Long Priel DA, Gallin JI. Endotoxin and IL-1 hyporesponsiveness in a patient with recurrent bacterial infections. J Immunol. 1997; 158:3959–3964. [PubMed: 9103466]
27. Lavine E, Somech R, Zhang JY, Puel A, Bossuyt X, Picard C, Casanova JL, Roifman CM. Cellular and humoral aberrations in a kindred with IL-1 receptor-associated kinase 4 deficiency. J Allergy Clin Immunol. 2007; 120:948–950. [PubMed: 17544092]
28. Lopez-Granados E, Keenan JE, Kinney MC, Leo H, Jain N, Ma CA, Quinones R, Gelfand EW, Jain A. A novel mutation in NFKBIA/IKBA results in a degradation-resistant N-truncated protein and is associated with ectodermal dysplasia with immunodeficiency. Hum Mutat. 2008; 29:861–868. [PubMed: 18412279]
29. Manroe BL, Weinberg AG, Rosenfeld CR, Browne R. The neonatal blood count in health and disease. I. Reference values for neutrophilic cells. J Pediatr. 1979; 95:89–98. [PubMed: 480023]
30. McDonald DR, Brown D, Bonilla FA, Geha RS. Interleukin receptor-associated kinase-4 deficiency impairs Toll-like receptor-dependent innate antiviral immune responses. J Allergy Clin Immunol. 2006; 118:1357–1362. [PubMed: 17157666]
31. McDonald DR, Mooster JL, Reddy M, Bawle E, Secord E, Geha RS. Heterozygous N-terminal deletion of IkappaBalpha results in functional nuclear factor kappaB haploinsufficiency, ectodermal dysplasia, and immune deficiency. J Allergy Clin Immunol. 2007; 120:900–907. [PubMed: 17931563]
32. Medvedev AE, Lentschat A, Kuhns DB, Blanco JC, Salkowski C, Zhang S, Arditi M, Gallin JI, Vogel SN. Distinct mutations in IRAK-4 confer hyporesponsiveness to lipopolysaccharide and interleukin-1 in a patient with recurrent bacterial infections. J Exp Med. 2003; 198:521–531. [PubMed: 12925671]
33. Medzhitov R. Approaching the asymptote: 20 years later. Immunity. 2009; 30:766–775. [PubMed: 19538928]

34. Minegishi Y, Saito M, Tsuchiya S, Tsuge I, Takada H, Hara T, Kawamura N, Ariga T, Pasic S, Stojkovic O, Metin A, Karasuyama H. Dominant-negative mutations in the DNA-binding domain of STAT3 cause hyper-IgE syndrome. Nature. 2007; 448:1058–1062. [PubMed: 17676033]
35. Mold C, Du Clos TW. C-reactive protein increases cytokine responses to Streptococcus pneumoniae through interactions with Fc gamma receptors. J Immunol. 2006; 176:7598–7604. [PubMed: 16751406]
36. Ochs, H.; Edvard Smith, CI.; Puck, JM. Primary Immunodeficiency Diseases: A Molecular and Genetic Approach. 2. New York: Oxford University Press; 2007.
37. Picard C, Casanova JL, Abel L. Mendelian traits that confer predisposition or resistance to specific infections in humans. Curr Opin Immunol. 2006; 18:383–390. [PubMed: 16765581]
38. Picard C, Puel A, Bonnet M, Ku CL, Bustamante J, Yang K, Soudais C, Dupuis S, Feinberg J, Fieschi C, Elbim C, Hitchcock R, Lammas D, Davies G, Al-Ghonaium A, Al-Rayes H, Al-Jumaah S, Al-Hajjar S, Al-Mohsen IZ, Frayha HH, Rucker R, Hawn TR, Aderem A, Tufenkeji H, Haraguchi S, Day NK, Good RA, Gougerot-Pocidalo MA, Ozinsky A, Casanova JL. Pyogenic bacterial infections in humans with IRAK-4 deficiency. Science. 2003; 299:2076–2079. [PubMed: 12637671]
39. Picard C, Puel A, Bustamante J, Ku CL, Casanova JL. Primary immunodeficiencies associated with pneumococcal disease. Curr Opin Allergy Clin Immunol. 2003; 3:451–459. [PubMed: 14612669]
40. Puel A, Picard C, Ku CL, Smahi A, Casanova JL. Inherited disorders of NF-kappaB-mediated immunity in man. Curr Opin Immunol. 2004; 16:34–41. [PubMed: 14734108]
41. Qin J, Qian Y, Yao J, Grace C, Li X. SIGIRR inhibits interleukin-1 receptor- and toll-like receptor 4-mediated signaling through different mechanisms. J Biol Chem. 2005; 280:25233–25241. [PubMed: 15866876]
42. Suzuki N, Saito T. IRAK-4---a shared NF-kappaB activator in innate and acquired immunity. Trends Immunol. 2006; 27:566–572. [PubMed: 17046325]
43. Suzuki N, Suzuki S, Yeh WC. IRAK-4 as the central TIR signaling mediator in innate immunity. Trends Immunol. 2002; 23:503–506. [PubMed: 12297423]
44. Takada H, Yoshikawa H, Imaizumi M, Kitamura T, Takeyama J, Kumaki S, Nomura A, Hara T. Delayed separation of the umbilical cord in two siblings with Interleukin-1 receptor-associated kinase 4 deficiency: rapid screening by flow cytometer. J Pediatr. 2006; 148:546–548. [PubMed: 16647421]
45. Takeda K, Akira S. Toll-like receptors in innate immunity. Int Immunol. 2005; 17:1–14. [PubMed: 15585605]
46. van Bruggen R, Drewniak A, Tool AT, Jansen M, van Houdt M, Geissler J, van den Berg TK, Chapel H, Kuijpers TW. Toll-like receptor responses in IRAK-4-deficient neutrophils. J Innate Immun. 2010; 2:280–287. [PubMed: 20375545]
47. Volanakis JE. Human C-reactive protein: expression, structure, and function. Mol Immunol. 2001; 38:189–197. [PubMed: 11532280]
48. von Bernuth H, Ku CL, Rodriguez-Gallego C, Zhang S, Garty BZ, Marodi L, Chapel H, Chrabieh M, Miller RL, Picard C, Puel A, Casanova JL. A fast procedure for the detection of defects in Toll-like receptor signaling. Pediatrics. 2006; 118:2498–2503. [PubMed: 17142536]
49. von Bernuth H, Picard C, Jin Z, Pankla R, Xiao H, Ku CL, Chrabieh M, Mustapha IB, Ghandil P, Camcioglu Y, Vasconcelos J, Sirvent N, Guedes M, Vitor AB, Herrero-Mata MJ, Arostegui JI, Rodrigo C, Alsina L, Ruiz-Ortiz E, Juan M, Fortuny C, Yague J, Anton J, Pascal M, Chang HH, Janniere L, Rose Y, Garty BZ, Chapel H, Issekutz A, Marodi L, Rodriguez-Gallego C, Banchereau J, Abel L, Li X, Chaussabel D, Puel A, Casanova JL. Pyogenic bacterial infections in humans with MyD88 deficiency. Science. 2008; 321:691–696. [PubMed: 18669862]
50. Wernette CM, Frasch CE, Madore D, Carlone G, Goldblatt D, Plikaytis B, Benjamin W, Quataert SA, Hildreth S, Sikkema DJ, Kayhty H, Jonsdottir I, Nahm MH. Enzyme-linked immunosorbent assay for quantitation of human antibodies to pneumococcal polysaccharides. Clin Diagn Lab Immunol. 2003; 10:514–519. [PubMed: 12853378]

51. Wynn JL, Scumpia PO, Winfield RD, Delano MJ, Kelly-Scumpia K, Barker T, Ungaro R, Levy O, Moldawer LL. Defective innate immunity predisposes murine neonates to poor sepsis outcome but is reversed by TLR agonists. Blood. 2008; 112:1750–1758. [PubMed: 18591384]

52. Yang K, Puel A, Zhang S, Eidenschenk C, Ku CL, Casrouge A, Picard C, von Bernuth H, Senechal B, Plancoulaine S, Al-Hajjar S, Al-Ghonaium A, Marodi L, Davidson D, Speert D, Roifman C, Garty BZ, Ozinsky A, Barrat FJ, Coffman RL, Miller RL, Li X, Lebon P, Rodriguez-Gallego C, Chapel H, Geissmann F, Jouanguy E, Casanova JL. Human TLR-7-, -8-, and -9-mediated induction of IFN-alpha/beta and -lambda is IRAK-4 dependent and redundant for protective immunity to viruses. Immunity. 2005; 23:465–478. [PubMed: 16286015]

53. Zhang Q, Davis JC, Lamborn IT, Freeman AF, Jing H, Favreau AJ, Matthews HF, Davis J, Turner ML, Uzel G, Holland SM, Su HC. Combined immunodeficiency associated with DOCK8 mutations. N Engl J Med. 2009; 361:2046–2055. [PubMed: 19776401]

54. Zhang SY, Jouanguy E, Ugolini S, Smahi A, Elain G, Romero P, Segal D, Sancho-Shimizu V, Lorenzo L, Puel A, Picard C, Chapgier A, Plancoulaine S, Titeux M, Cognet C, von Bernuth H, Ku CL, Casrouge A, Zhang XX, Barreiro L, Leonard J, Hamilton C, Lebon P, Heron B, Vallee L, Quintana-Murci L, Hovnanian A, Rozenberg F, Vivier E, Geissmann F, Tardieu M, Abel L, Casanova JL. TLR3 deficiency in patients with herpes simplex encephalitis. Science. 2007; 317:1522–1527. [PubMed: 17872438]

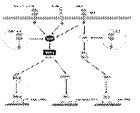

Figure 1.
Schematic representation of TIRs signaling pathway. MyD88 interacts with TLRs and IL-1Rs through a shared TIR domain. MyD88 is a key cytosolic adapter molecule, providing a bridge from TLRs and IL-1Rs to the 2 active kinases IRAK-4 and IRAK-1. IRAK-4 and IRAK-1 then activate at least the 2 signaling NF-kB and MAPK pathways. The MyD88- and IRAK-4-dependent TIR pathway leads among others to the synthesis of inflammatory cytokines, such as IL-1β, IL-6, IL-8, TNF-α, and to IFN-α/β and IFN-λ, at least for TLR7, TLR8 and TLR9. The MyD88- and IRAK-4-independent TIR pathway uses TRIF pathway after stimulation of TLR3 and TLR4. This pathway is important for IFN-α and IFN-β production.

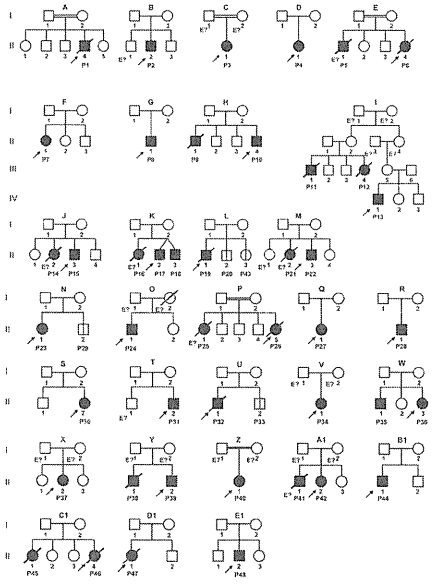

Figure 2.

Pedigrees of the 31 kindreds identified with IRAK-4 deficiency. Each kindred with IRAK-4 deficiency is designated by a capital letter (A-E1) each generation is designated by a Roman numeral (I–IV), and each individual is designated by an Arabic numeral (from left to right). Patients with a clinical phenotype are indicated by closed symbols. Patients with confirmed IRAK-4 deficiency but no clinical phenotype as yet are indicated by an open square divided by a black line. In each family, the proband is indicated by an arrow. Individuals whose genetic status could not be evaluated are indicated by "E?".

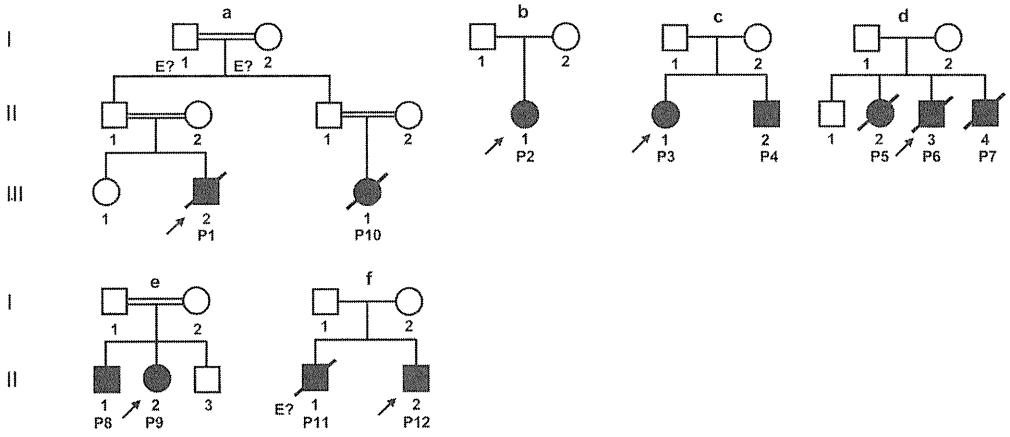

Figure 3.
Pedigrees of the 6 kindreds with MyD88 deficiency identified. Each kindred with MyD88 deficiency is designated by a lower case letter (a-f) ; each generation is designated by a Roman numeral (I–IV), and each individual is designated by an Arabic numeral (from left to right). Patients with a clinical phenotype are indicated by closed symbols. In each family, the proband is indicated by an arrow. Individuals whose genetic status could not be evaluated are indicated by "E?".

Figure 4.
Countries of origin of the 31 kindreds with IRAK-4 deficiency and the 6 kindreds with MyD88 deficiency identified. The number of patients identified in each country is indicated.

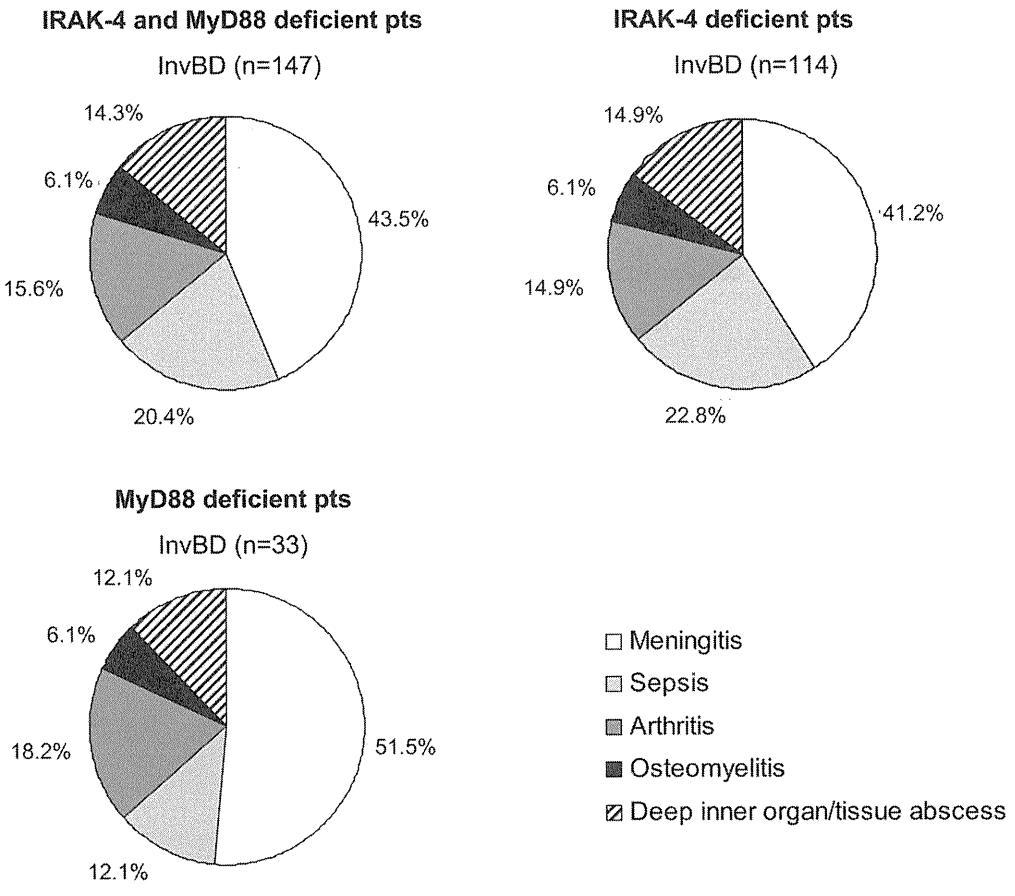

Figure 5.
Invasive bacterial infections (episodes): in all patients, in IRAK-4-deficient patients, and in MyD88-deficient patients.

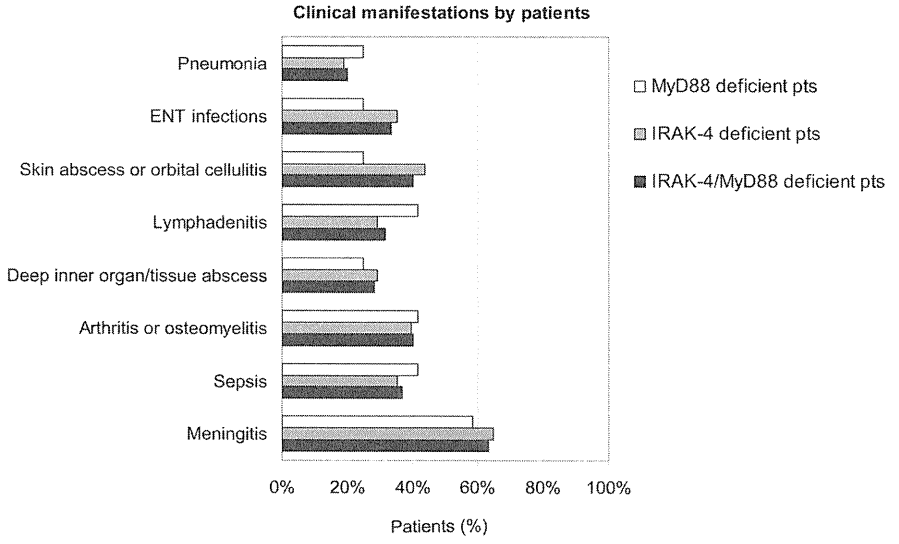

Figure 6.
Percentage of clinical manifestations found in each patient: in MyD88-deficient patients, in IRAK-4-deficient patients, and in all patients. (ENT = ear, nose, and throat.)

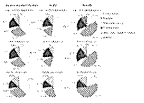

Figure 7.

Overview of pathogens isolated during bacterial infections of IRAK-4-deficient and MyD88-deficient patients. **Left column,** overview of all pathogens isolated (all documented infection). In IRAK-4-deficient patients: other *Streptococcus* species (*Str. agalactiae, Str. equis, Str. intermedius, Str. milleri, Str. pyogenes,* and *Str. parasanguis*), other gram-negative bacteria (*Shigella sonnei, Neisseria meningitidis, Serratia marcesens, Moraxella catarrhalis, Clostridium septicum, Haemophilus influenzae* type b, *Citrobacter freundii,* and *Escherichia coli*), and *Mycobacterium avium*. In MyD88-deficient patients: other *Streptococcus* species (β-hemolytic *Streptococci*) and other gram-negative bacteria (*Salmonella enteritidis, Haemophilus influnzae* type e, *Moraxella catarrhalis, Klebsiella pneumoniae,* and *E. coli*). **Center column,** pathogens isolated during invasive bacterial infections (InvBD) (meningitis, sepsis, arthritis, osteomyelitis, and deep abscesses). In IRAK-4-deficient patients: other *Streptococcus* species (*Str. agalactiae, Str. milleri, Str. pyogenes,* and *Str. parasanguis*) and other gram-negative bacteria (*Shigella sonnei, N. meningitidis, Serratia marcesens, H. influenzae* type b and *C. septicum*). In MyD88-deficient patients: other *Streptococcus* species (β-hemolytic *Streptococci*) and other gram-negative bacteria (*Salmonella enteritidis, H. influenzae* type e, and *Moraxella catarrhalis*). **Right column,** pathogens isolated during noninvasive bacterial infections (NinvBD). In IRAK-4-deficient patients: other *Streptococcus* species (*Str. equis, Str. intermedius, Str. pyogenes*) and other gram-negative bacteria (*Serratia marcesens, Moraxella catarrhalis, C. septicum, Citrobacter freundii,* and *E. coli*), and *M. avium.* In MyD88-deficient patients: other *Streptococcus* species (β-hemolytic *Streptococci*) and other gram-negative bacteria (*K. pneumoniae* and *E. coli*).

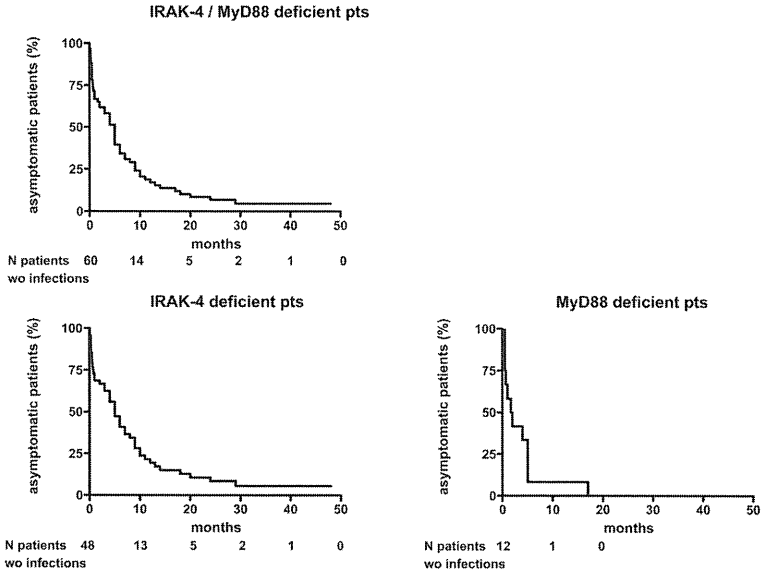

Figure 8.
Epidemiologic features of IRAK-4 and MyD88 deficiency. Incidence of first bacterial infection in IRAK-4-deficient and MyD88-deficient patients during the first 50 months of life. (wo = without, pts = patients.)

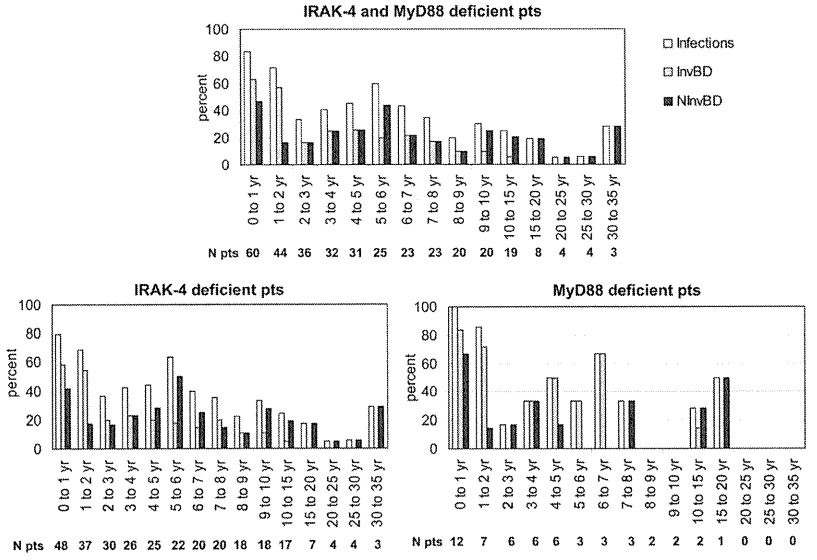

Figure 9.

Annual rate of bacterial infections per patient, as a percentage. P = patients presenting at least 1 infection over the course of a year. Percent = P over the total number of patients.

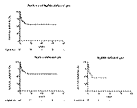

Figure 10.
Survival curve of IRAK-4-deficient and MyD88-deficient patients.

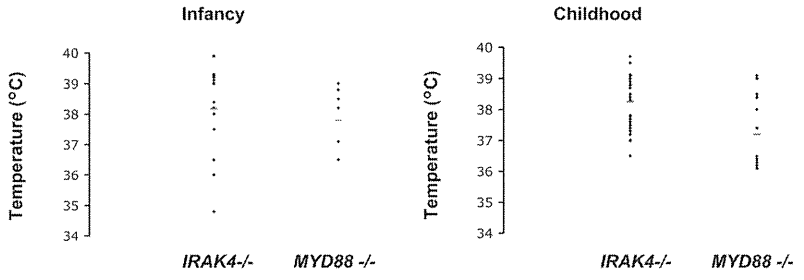

Figure 11.
The inflammatory phenotype of IRAK-4/MyD88-deficiency. Temperature during bacterial infection in infancy and childhood.

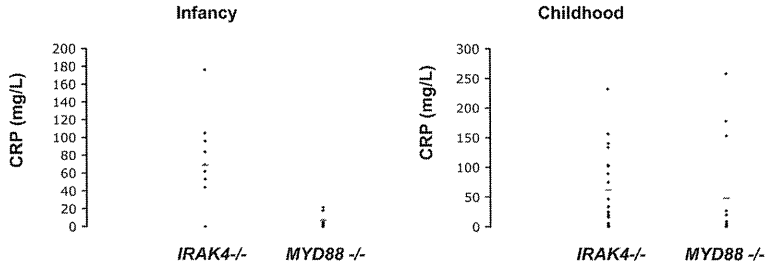

Figure 12.
CRP concentration during bacterial infection in infancy and childhood.

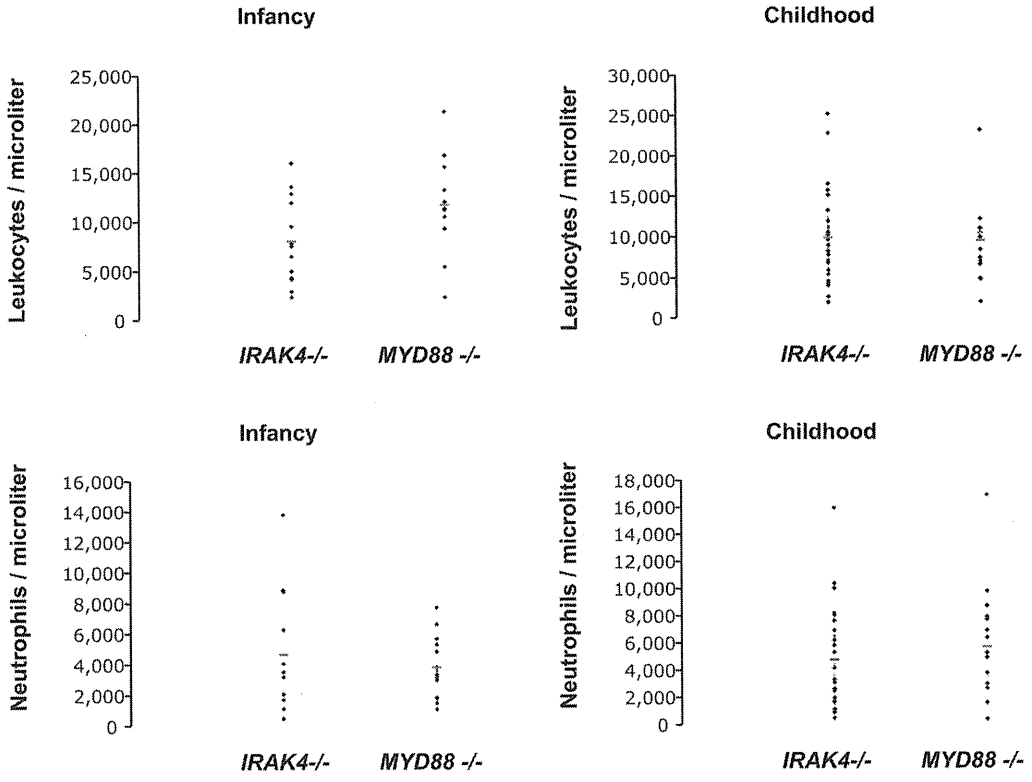

Figure 13.
Polymorphonuclear neutrophil counts during bacterial infection in infancy and childhood.