Article

Changes in Invasive Pneumococcal Disease Caused by *Streptococcus pneumoniae* Serotype 1 following Introduction of PCV10 and PCV13: Findings from the PSERENADE Project

Julia C. Bennett [1,*], Marissa K. Hetrich [1], Maria Garcia Quesada [1], Jenna N. Sinkevitch [1], Maria Deloria Knoll [1,*], Daniel R. Feikin [2], Scott L. Zeger [1], Eunice W. Kagucia [3], Adam L. Cohen [4,†], Krow Ampofo [5], Maria-Cristina C. Brandileone [6], Dana Bruden [7], Romina Camilli [8], Jesús Castilla [9,10], Guanhao Chan [11], Heather Cook [12], Jennifer E. Cornick [13,14], Ron Dagan [15], Tine Dalby [16], Kostas Danis [17], Sara de Miguel [18], Philippe De Wals [19], Stefanie Desmet [20,21], Theano Georgakopoulou [22], Charlotte Gilkison [23], Marta Grgic-Vitek [24], Laura L. Hammitt [1,3], Markus Hilty [25], Pak-Leung Ho [26], Sanjay Jayasinghe [27], James D. Kellner [28], Jackie Kleynhans [29,30], Mirjam J. Knol [31], Jana Kozakova [32], Karl G. Kristinsson [33], Shamez N. Ladhani [34], Laura MacDonald [35], Grant A. Mackenzie [36,37,38], Lucia Mad'arová [39], Allison McGeer [40], Jolita Mereckiene [41], Eva Morfeldt [42], Tuya Mungun [43], Carmen Muñoz-Almagro [9,44,45], J. Pekka Nuorti [46,47], Metka Paragi [48], Tamara Pilishvili [49], Rodrigo Puentes [50], Samir K. Saha [51], Aalisha Sahu Khan [52], Larisa Savrasova [53,54], J. Anthony Scott [3], Anna Skoczyńska [55], Shigeru Suga [56], Mark van der Linden [57], Jennifer R. Verani [49,58], Anne von Gottberg [29,59], Brita A. Winje [60], Inci Yildirim [61], Khalid Zerouali [62,63], Kyla Hayford [1,‡] and the PSERENADE Team [§]

1   Johns Hopkins Bloomberg School of Public Health, Baltimore, MD 21205, USA; mhetric2@jhmi.edu (M.K.H.); mgarci64@jhmi.edu (M.G.Q.); jsinkev1@jhu.edu (J.N.S.); sz@jhu.edu (S.L.Z.); lhammitt@jhu.edu (L.L.H.); kylahayford@jhu.edu (K.H.)
2   Independent Consultant, 1296 Coppet, Switzerland; drf3217@gmail.com
3   KEMRI-Wellcome Trust Research Programme, Epidemiology and Demography Department, Centre for Geographic Medicine-Coast, P.O. Box 230-80108 Kilifi, Kenya; EKagucia@kemri-wellcome.org (E.W.K.); anthony.scott@lshtm.ac.uk (J.A.S.)
4   World Health Organization, 1202 Geneva, Switzerland; dvj1@cdc.gov
5   Division of Pediatric Infectious Diseases, Department of Pediatrics, University of Utah Health Sciences Center, Salt Lake City, UT 84132, USA; Krow.Ampofo@hsc.utah.edu
6   National Laboratory for Meningitis and Pneumococcal Infections, Center of Bacteriology, Institute Adolfo Lutz (IAL), São Paulo 01246-902, Brazil; maria.brandileone@ial.sp.gov.br
7   Arctic Investigations Program, Division of Preparedness and Emerging Infections, National Center for Emerging and Zoonotic Infectious Diseases, Centers for Disease Control and Prevention, Anchorage, AK 99508, USA; zkg9@cdc.gov
8   Department of Infectious Diseases, Italian National Institute of Health (Istituto Superiore di Sanità, ISS), 00161 Rome, Italy; romina.camilli@iss.it
9   CIBER Epidemiología y Salud Pública (CIBERESP), 28029 Madrid, Spain; jcastilc@navarra.es (J.C.); cma@sjdhospitalbarcelona.org (C.M.-A.)
10 Instituto de Salud Pública de Navarra—IdiSNA, 31003 Pamplona, Navarra, Spain
11 Singapore Ministry of Health, Communicable Diseases Division, Singapore 308442, Singapore; CHAN_Guanhao@moh.gov.sg
12 Centre for Disease Control, Department of Health and Community Services, Darwin, NT 8000, Australia; hcdarwin@gmail.com
13 Institute of Infection, Veterinary & Ecological Sciences, University of Liverpool, Liverpool CH64 7TE, UK; jcornick@mlw.mw
14 Malawi-Liverpool-Wellcome Trust Clinical Research Programme, Chichiri, P.O. Box 30096 Blantyre, Malawi
15 Faculty of Health Sciences, Ben-Gurion University of the Negev, 8410501 Beer-Sheva, Israel; rdagan@bgu.ac.il
16 Bacteria, Parasites and Fungi, Statens Serum Institut, DK-2300 Copenhagen, Denmark; TID@ssi.dk
17 Santé Publique France, the French National Public Health Agency, Saint Maurice CEDEX, 94415 Paris, France; Costas.DANIS@santepubliquefrance.fr
18 Epidemiology Department, Dirección General de Salud Pública, 28009 Madrid, Spain; sarade.miguel@salud.madrid.org
19 Department of Social and Preventive Medicine, Laval University, Québec, QC G1V 0A6, Canada; philippe.dewals@criucpq.ulaval.ca
20 Department of Microbiology, Immunology and Transplantation, KU Leuven, BE-3000 Leuven, Belgium; stefanie.desmet@uzleuven.be

21 National Reference Centre for Streptococcus Pneumoniae, University Hospitals Leuven,
3000 Leuven, Belgium

22 National Public Health Organisation, 15123 Athens, Greece; t.georgakopoulou@eody.gov.gr

23 Epidemiology Team, Institute of Environmental Science and Research, Porirua, Wellington 5240, New
Zealand; Charlotte.Gilkison@esr.cri.nz

24 Communicable Diseases Centre, National Institute of Public Health, 1000 Ljubljana, Slovenia;
Marta.Vitek@nijz.si

25 Swiss National Reference Centre for Invasive Pneumococci, Institute for Infectious Diseases,
University of Bern, 3012 Bern, Switzerland; Markus.Hilty@ifik.unibe.ch

26 Department of Microbiology and Carol Yu Centre for Infection, The University of Hong Kong,
Hong Kong, China; plho@hku.hk

27 National Centre for Immunisation Research and Surveillance and Discipline of Child and Adolescent Health,
Children's Hospital Westmead Clinical School, Faculty of Medicine and Health, University of Sydney,
Westmead, NSW 2145, Australia; sanjay.jayasinghe@health.nsw.gov.au

28 Department of Pediatrics, University of Calgary, and Alberta Health Services, Calgary, AB T3B 6A8, Canada;
kellner@ucalgary.ca

29 Centre for Respiratory Diseases and Meningitis, National Institute for Communicable Diseases of the
National Health Laboratory Service, Johannesburg 2192, South Africa; JackieL@nicd.ac.za (J.K.);
annev@nicd.ac.za (A.v.G.)

30 School of Public Health, Faculty of Health Sciences, University of the Witwatersrand,
Johannesburg 2000, South Africa

31 National Institute for Public Health and the Environment, 3721 MA Bilthoven, The Netherlands;
mirjam.knol@rivm.nl

32 National Institute of Public Health (NIPH), 100 42 Praha, Czech Republic; jana.kozakova@szu.cz

33 Department of Clinical Microbiology, Landspitali—The National University Hospital, Hringbraut,
101 Reykjavik, Iceland; karl@landspitali.is

34 Immunisation and Countermeasures Division, Public Health England, London NW9 5EQ, UK;
shamez.ladhani@phe.gov.uk

35 Public Health Scotland, Glasgow G2 6QE, UK; laura.macdonald4@phs.scot

36 Faculty of Infectious and Tropical Diseases, London School of Hygiene & Tropical Medicine, Keppel St,
London WC1E 7HT, UK; gmackenzie@mrc.gm

37 Medical Research Council Unit the Gambia at London School of Hygiene & Tropical Medicine,
P.O. Box 273 Banjul, The Gambia

38 New Vaccines Group, Murdoch Children's Research Institute, Parkville, Melbourne, VIC 3052, Australia

39 National Reference Centre for Pneumococcal and Haemophilus Diseases, Regional Authority of
Public Health, 975 56 Banská Bystrica, Slovakia; madarova@vzbb.sk

40 Toronto Invasive Bacterial Diseases Network, Laboratory Medicine and Pathobiology, University of Toronto,
Toronto, ON M5S 1A8, Canada; Allison.McGeer@sinaihealthsystem.ca

41 HSE Health Protection Surveillance Centre, Mountjoy, Dublin D01 A4A3, Ireland; jolita.mereckiene@hse.ie

42 Department of Microbiology, Public Health Agency of Sweden, 171 82 Solna, Sweden;
eva.morfeldt@folkhalsomyndigheten.se

43 National Center of Communicable Diseases (NCCD), Ministry of Health, Bayanzurkh District,
Ulaanbaatar 13336, Mongolia; tuya_mungun@yahoo.com

44 Medicine Department, Universitat Internacional de Catalunya, 08017 Barcelona, Spain

45 Molecular Microbiology Department, Hospital Sant Joan de Déu Research Institute,
08950 Esplugues de Llobregat, Barcelona, Spain

46 Department of Health Security, Finnish Institute for Health and Welfare, 00271 Helsinki, Finland;
pekka.nuorti@tuni.fi

47 Health Sciences Unit, Faculty of Social Sciences, University of Tampere, 33100 Tampere, Finland

48 Centre for Medical Microbiology, National Laboratory of Health, Environment and Food,
2000 Maribor, Slovenia; metka.paragi@nlzoh.si

49 National Center for Immunizations and Respiratory Diseases, Centers for Disease Control and Prevention,
Atlanta, GA 30333, USA; tpilishvili@cdc.gov (T.P.); qzr7@cdc.gov (J.R.V.)

50 Instituto de Salud Pública de Chile, Santiago 7780050, Santiago Metropolitan, Chile; rpuentes@ispch.cl

51 Child Health Research Foundation, Dhaka 1207, Bangladesh; samirk.sks@gmail.com

52 Ministry of Health and Medical Services, Suva, Fiji; aalisha@gmail.com

53 Centre for Disease Prevention and Control of Latvia, 1005 Riga, Latvia; larisa.savrasova@spkc.gov.lv

54 Doctoral Studies Department, Riga Stradinš University, 1007 Riga, Latvia

55 National Reference Centre for Bacterial Meningitis, National Medicines Institute, 00-725 Warsaw, Poland;
a.skoczynska@nil.gov.pl

56 Infectious Disease Center and Department of Clinical Research, National Hospital Organization Mie Hospital,
Tsu, Mie 514-0125, Japan; suga.shigeru.ke@mail.hosp.go.jp

57   National Reference Center for Streptococci, Department of Medical Microbiology, University Hospital
      RWTH Aachen, 52074 Aachen, Germany; mlinden@ukaachen.de
58   Centers for Disease Control and Prevention (CDC), Center for Global Health (CGH), Division of Global
      Health Protection (DGHP), P.O. Box 606-00621 Nairobi, Kenya
59   School of Pathology, Faculty of Health Sciences, University of the Witwatersrand, Braamfontein,
      Johannesburg 2000, South Africa
60   Department of Infection Control and Vaccine, Norwegian Institute of Public Health, 0456 Oslo, Norway;
      Brita.Askeland.Winje@fhi.no
61   Department of Pediatrics, Yale New Haven Children's Hospital, New Haven, CT 06504, USA;
      inci.yildirim@yale.edu
62   Bacteriology-Virology and Hospital Hygiene Laboratory, Ibn Rochd University Hospital Centre,
      Casablanca 20250, Morocco; khalid.zerouali2000@gmail.com
63   Department of Microbiology, Faculty of Medicine and Pharmacy, Hassan II University of Casablanca,
      Casablanca 20000, Morocco
*   Correspondence: jbenne63@jhu.edu (J.C.B.); mknoll2@jhu.edu (M.D.K.)
†   Present address: Centers for Disease Control and Prevention, Atlanta, GA, USA. Affiliation at the time this
      work was completed was World Health Organization.
‡   Present address: Pfizer, Inc. Collegeville, PA, USA. Affiliation at the time this work was completed was Johns
      Hopkins Bloomberg School of Public Health.
§   Members are listed in Appendix A Table A1.

Abstract: *Streptococcus pneumoniae* serotype 1 (ST1) was an important cause of invasive pneumococcal disease (IPD) globally before the introduction of pneumococcal conjugate vaccines (PCVs) containing ST1 antigen. The Pneumococcal Serotype Replacement and Distribution Estimation (PSERENADE) project gathered ST1 IPD surveillance data from sites globally and aimed to estimate PCV10/13 impact on ST1 IPD incidence. We estimated ST1 IPD incidence rate ratios (IRRs) comparing the pre-PCV10/13 period to each post-PCV10/13 year by site using a Bayesian multi-level, mixed-effects Poisson regression and all-site IRRs using a linear mixed-effects regression (N = 45 sites). Following PCV10/13 introduction, the incidence rate (IR) of ST1 IPD declined among all ages. After six years of PCV10/13 use, the all-site IRR was 0.05 (95% credibility interval 0.04–0.06) for all ages, 0.05 (0.04–0.05) for <5 years of age, 0.08 (0.06–0.09) for 5–17 years, 0.06 (0.05–0.08) for 18–49 years, 0.06 (0.05–0.07) for 50–64 years, and 0.05 (0.04–0.06) for ≥65 years. PCV10/13 use in infant immunization programs was followed by a 95% reduction in ST1 IPD in all ages after approximately 6 years. Limited data availability from the highest ST1 disease burden countries using a 3 + 0 schedule constrains generalizability and data from these settings are needed.

Keywords: invasive pneumococcal disease; pneumococcal conjugate vaccines; serotypes; vaccine impact

1. Introduction

Streptococcus pneumoniae is a major cause of pneumonia, meningitis, and pleural effusion in children and adults [1–4]. There are at least 100 known serotypes of pneumococci [5]. Before the introduction of pneumococcal conjugate vaccines (PCVs), serotype 1 (ST1) was one the most common causes of invasive pneumococcal disease (IPD), especially in Asia and Africa, and globally was responsible for approximately 9% of IPD among children <5 years of age [6]. ST1 is distinct from other serotypes in that it has a high invasiveness potential, is not commonly carried in the nasopharynx [7,8], and in some settings occurs in a cyclical pattern, approximately every 3–9 years [9–11]. Additionally, ST1 can cause large pneumococcal outbreaks among all ages, including older children and young adults, in the African meningitis belt and other outbreak-prone settings with up to 10–30-fold increases in ST1 cases compared to pre-outbreak baselines [12–15].

The first PCV licensed for use in infants, seven-valent PCV (Prevenar/Prevnar, Pfizer), did not include ST1 antigen. Since then, the introduction of PCVs containing ST1 antigen (PCV10 [Synflorix, GlaxoSmithKline], PCV13 [Prevenar13/Prevnar13, Pfizer]) into many national infant immunization programs since 2009 has been shown to substantially reduce

ST1 IPD and end pneumococcal outbreaks caused by ST1. These effects have been demonstrated among directly immunized children and also unvaccinated older children and adults, through indirect effects, in both high and low IPD burden settings [9,10,12,16–20]. However, in some PCV10/13 using settings ST1 outbreaks continued to occur or ST1 IPD incidence rates did not substantially decline in the early years immediately following PCV10/13 introduction [21–24].

Evaluating the impact of PCV10/13 vaccination on ST1 IPD is challenging in a single surveillance site. In many settings, annual ST1 incidence rates are unstable because case counts are small, particularly after vaccine introduction. Many sites are also limited by short pre- and post-vaccine introduction surveillance periods, further limiting inferences that can be drawn from a single site. Assessing vaccine impact is also confounded by the cyclic nature of ST1 in which it is common to observe multiple years of zero ST1 cases prior to vaccine use. Quantifying the impact of PCV10/13 on ST1, which has several unique characteristics compared to other vaccine-type serotypes included in currently licensed PCVs, is important for policymakers seeking to reduce the burden of ST1 IPD through immunization. The Pneumococcal Serotype Replacement and Distribution Estimation (PSERENADE) project evaluated all available published and unpublished serotype-specific IPD data to estimate the impact of PCV10/PCV13 on ST1 IPD incidence at the global scale.

2. Materials and Methods

2.1. Data Collection and Eligibility Criteria

IPD surveillance sites with eligible data contributed annual serotype-specific IPD case data and population denominators to the project. A systematic approach to identify eligible sites and request data is described in detail elsewhere [25]. ST1 IPD was defined as the isolation of *Streptococcus pneumoniae* from a normally sterile site or detection of pneumococcus in cerebrospinal fluid (CSF) or pleural fluid using *lytA*-based polymerase chain reaction (PCR), or antigen testing confirmed as ST1. Sites with ST1 IPD case counts and population denominators that met eligibility criteria were included in the analysis (Box 1, Table 1, Table S1).

Box 1. Inclusion criteria.

---

1. Site reports annual ST1 IPD incidence data:
    -   ST1 case counts by age group, and
    -   Population-based denominators by age group.
2. At least 50% of isolates serotyped for included years by age group.
3. At least one complete year of data post-PCV10/13 introduction, excluding the year of introduction.
4. At least 50% uptake for primary PCV series at 12 months of age in at least one year post-PCV10/13 introduction.
5. PCV10 or PCV13 is universally recommended for all infants in the national infant immunization schedule.
6. No major changes or biases in surveillance that would affect estimates of ST1 incidence rates.

Two PSERENADE coordinators conducted a standard data quality review for each site to evaluate if surveillance system changes or other factors besides PCV introductions influenced incidence rates (IR) of IPD over available years of surveillance data [25]. After review and discussion with site investigators, certain site-year-age group data were excluded if determined to fall within periods of differential surveillance capture or if the impact of changes in surveillance protocols on IPD IRs could not be accounted for in the analysis. For all sites, we defined the year of PCV introduction as the year PCV10/13 was universally introduced if PCV was introduced in the first three quarters of the year, or as the following calendar year if otherwise. For data submitted in epidemiologic years rather than calendar years, the introduction year was defined accordingly. For all sites, the year of PCV10/13 introduction was defined as 'year 0' for the analyses.

Table 1. Description of infant pneumococcal conjugate vaccine program and surveillance data for included sites. Ordered by vaccine product and schedule.

Site	PCV10 Period	PCV13 Period	PCV10/13 Schedule	PCV7 Use	PCV10/13 Catch-Up	Mean PCV10/13 Uptake (%)		Included in ST1 Analysis		ST1 Cases Included in Analysis (n)	Surveillance Years Pre- and Post-PCV10/13 (n)	Proportion ST1 IPD Cases from CSF (%)
						Primary Series *	WUENIC PCV3 ***	0–17 Years	≥18 Years			
Finland	2010–	–	2 + 1	N	N	95	90	Y	Y	46	Pre: 6 Post: 8	4.3
Iceland	2011–	–	2 + 1	N	N	97	89	Y	Y	22	Pre: 16 Post: 8	0.0
Latvia	2012–	–	2 + 1	Y	N	91	83	N [b]	Y; ≥50y	5	Pre: 0 Post: 7	20.0
Slovenia	2015–2019	2019–	2 + 1	N	N	55	55	Y	Y	259	Pre: 6 Post: 4	0.0
Netherlands	2011–	–	3 + 1/2 + 1	Y	N	95	94	Y	Y	642	Pre: 7 Post: 8	2.2
Asembo, Kenya	2011–	–	3 + 0	N	Y	86	78	Y	Y; 18–49y	43	Pre: 1 Post: 8	NA
Kilifi, Kenya	2011–	–	3 + 0	N	Y	82	78	Y	Y; 18–64y	204	Pre: 11 Post: 6	19.6
Japan	–	2013–	3 + 1	Y	N	94 **	98	Y	Y; ≥65y	11	Pre: 4 Post: 5	0.0
ABCs, USA	–	2010–	3 + 1	Y	Y	88	93	Y	Y	664	Pre: 12 Post: 8	0.6
Alaska, USA	–	2010–	3 + 1	Y	Y	83	93	Y	Y	92	Pre: 19 Post: 8	0.0
Massachusetts, USA	–	2010–	3 + 1	Y	Y	94	93	Y; <5y	NA	1	Pre: 8 Post: 8	0.0
Southwest, USA (Indigenous)	–	2010–	3 + 1	Y	Y	82	93	Y	Y	180	Pre: 15 Post: 9	2.2
Alberta, Canada	–	2010–	2 + 1	Y	N	88 **	77	Y; <5y	Y	16	Pre: 10 Post: 8	0.0
Denmark	–	2010–	2 + 1	Y	N	91 **	93	Y	Y	2089	Pre: 10 Post: 9	2.2
France	–	2010–	2 + 1	Y	N	93	91	Y	Y	1346	Pre: 9 Post: 9	5.9
Ireland	–	2010–	2 + 1	Y	N	91	91	Y	Y	58	Pre: 3 Post: 8	0.0
Israel	–	2010–	2 + 1	Y	N	95	93	Y	Y	677	Pre: 8 Post: 8	3.4
Italy	–	2010–	2 + 1	Y	N	86 **	87	Y	Y	193	Pre: 0 Post: 9	6.7

Table 1. *Cont.*

Site	PCV10 Period	PCV13 Period	PCV10/13 Schedule	PCV7 Use	PCV10/13 Catch-Up	Mean PCV10/13 Uptake (%)		Included in ST1 Analysis			Surveillance Years Pre- and Post-PCV10/13 (n)	Proportion ST1 IPD Cases from CSF (%)
						Primary Series *	WUENIC PCV3 ***	0–17 Years	≥18 Years	ST1 Cases Included in Analysis (n)		
Norway	–	2011–	2 + 1	Y	N	93	93	Y	Y	637	Pre: 7 Post: 7	1.4
Singapore	–	2011–	2 + 1	Y	Y	84	74	N [d]	Y; ≥50y	8	Pre: 2 Post: 8	0.0
South Africa	–	2011–	2 + 1	Y	Y	77 **	77	Y	Y	3292	Pre: 6 Post: 8	38.2
Madrid, Spain	–	2010–	2 + 1	Y	N	98	93	Y	Y	479	Pre: 3 Post: 9	0.8
Switzerland	–	2010–	2 + 1	Y	Y	79 **	77	Y	Y	436	Pre: 8 Post: 7	0.5
England, UK	–	2010–	2 + 1	Y	N	94	92	Y	Y	4214	Pre: 10 Post: 10	1.5
Scotland, UK	–	2010–	2 + 1	Y	N	97	92	Y	Y	578	Pre: 10 Post: 9	NA
Germany	–	2009–	3 + 1/2 + 1	Y	N	85	93	Y	Y	760	Pre: 5 Post: 9	4.1
Catalonia, Spain	–	2010–2015 [a] 2016–	3 + 1/2 + 1	Y [a]	N	70	93	Y	Y	1111	Pre: 4 Post: 8	1.5
Navarra, Spain	–	2010–2015 [a] 2016–	3 + 1/2 + 1	Y [a]	N	71	93	Y	Y	93	Pre: 9 Post: 9	0.0
Australia (Non-Indigenous)	–	2011–	3 + 0	Y	Y	92	92	Y	Y	371	Pre: 9 Post: 7	0.8
Basse, The Gambia	–	2011–	3 + 0	Y	N	77	95	Y	N [b]	71	Pre: 2 Post: 7	1.4
Blantyre District, Malawi	–	2011–	3 + 0	N	Y	92	88	Y	Y	229	Pre: 5 Post: 7	55.5
Northern Territory, Australia	2009–2011	2011–	3 + 1	Y	Y	88	92	Y	Y	97	Pre: 16 Post: 8	1.0
Quebec-Nunavik, Canada	2009–2010	2011–	3 + 1	Y	N	97	75	Y; <5y	N [c]	1	Pre: 9 Post: 10	0.0
Hong Kong	2010–2011	2011-	3 + 1	Y	N	98	–	N [d]	Y; 18–49y	1	Pre: 0 Post: 5	0.0
New Zealand	2011–2014 2017–	2014–2017	3 + 1	Y	N	93	93	Y	Y	334	Pre: 9 Post: 8	0.6
Belgium	2015–2019	2011–2015 2019–	2 + 1	Y	N	95 **	94	Y	NA	872	Pre: 5 Post: 8	1.3

Table 1. *Cont.*

Site	PCV10 Period	PCV13 Period	PCV10/13 Schedule	PCV7 Use	PCV10/13 Catch-Up	Mean PCV10/13 Uptake (%)		Included in ST1 Analysis		ST1 Cases Included in Analysis (n)	Surveillance Years Pre- and Post-PCV10/13 (n)	Proportion ST1 IPD Cases from CSF (%)
						Primary Series *	WUENIC PCV3 ***	0–17 Years	≥18 Years			
Poland	2017–	2017– [e]	2 + 1	N	N	94	60	Y	N [b]	69	Pre: 9 Post: 2	4.3
Quebec (excluding Nunavik), Canada	2009–2010 2018–	2011–2018	2 + 1	Y	N	97	75	Y	Y	43	Pre: 8 Post: 10	0.0
Metropolitan Region, Chile	2011–2015	2016–	2 + 1	Y	N	97	88	Y	Y	437	Pre: 9 Post: 8	2.7
Non-Metropolitan Regions, Chile	2011–2017	2017–	2 + 1	N	N	97	89	Y	Y	69	Pre: 0 Post: 7	0.0
Grand Casablanca, Morocco	2012–	2010–2012	2 + 1	N	N	91	90	Y	Y; 18–49y	29	Pre: 4 Post: 7	37.9
Slovakia	2011–	2011–	2 + 1	Y	Y	97	97	Y	Y	20	Pre: 0 Post: 7	5.0
Sweden	2010–	2010–2019	2 + 1	Y	N	97 **	97	Y	Y	84	Pre: 1 Post: 5	NA
Ontario, Canada	2009–2010	2010–	3 + 1/2 + 1	Y	Y	72 **	79	N [d]	Y	9	Pre: 3 Post: 9	0.00
Czech Republic	2010–	2010–	3 + 1/2 + 1	N	N	74 **	–	Y	Y	227	Pre: 2 Post: 8	2.2

PCV: Pneumococcal conjugate vaccines. ST1: Serotype 1. CSF: Cerebrospinal fluid. – Not universally used. Y: Yes; N: No; NA: Not applicable. [a] Recommended for high-risk populations only but had substantial (≥50% annually) private market uptake among the general population. [b] Biases in surveillance system over time that could not be accounted for. [c] Low proportion of cases serotyped. [d] Zero ST1 cases in all years. [e] Private market uptake of approximately 30% annually. * Annual PCV uptake estimates provided by the surveillance site for the primary series of PCV by 12 months of age (if available, for some sites up to 15 months of age), excluding year of vaccine rollout. ** Annual PCV uptake estimates provided by the surveillance site for the primary series plus the booster dose by 23 months of age, excluding year of vaccine rollout. *** WHO and UNICEF Estimates of National Immunization Coverage (WUENIC) PCV3 uptake, excluding the year of vaccine rollout (PCV3 represents the third dose whether given before 12 months or at or after 12 months, but in some cases uptake estimates may reflect the percentage of surviving infants who received two doses of PCV prior to the first birthday).

2.2. Data Analysis

2.2.1. Adjustments for Missing Data

Adjustments for missing serotype data assume that missing serotype data are missing completely at random, that is the serotype distribution of serotyped cases is not biased or different from the serotype distribution of cases that were not serotyped or not fully serotyped. Site-year-age group strata that violated this assumption or reported serotypes for less than 50% of cases were excluded from the ST1 analysis for that stratum. For cases that were reported as not serotyped (serotyping was not attempted for any reason), the population denominators were adjusted by the proportion of cases that were serotyped (i.e., annual denominator * percent of cases that were serotyped in that year) for each site by year and age group. Because the proportion of cases serotyped varies across sites, population denominators were adjusted rather than reapportioning serotypes to unknown serotype cases in order to give appropriate weight to sites in the model based on serotype data reported. If ST1 and a second serotype was reported for a case, it was included as an ST1 case. Cases reported as a serotype pool which includes ST1 (e.g., pool A) were excluded. For cases with unknown age, the population denominators were adjusted by the proportion of cases with known age (i.e., annual denominator * percent of cases with known age in that year) for each year and age group. Minor changes were made to the cut-offs for age groups when standard age categories used for analyses were not available from the site.

2.2.2. Statistical Analysis

Annual ST1 IPD incidence rate ratios (IRRs) comparing the pre-PCV10/13 period to each post-PCV10/13 year were estimated by age group and for all ages in a three-step process. First, ST1 IR curves were estimated over years of available data for each site using a Bayesian multi-level, mixed-effects Poisson regression using the MCMCglmm package in R [26]. The model included data from all sites (using either PCV10 or PCV13) with an offset for population denominator and random effects for all of the site-specific regression coefficients, which allows for heterogeneity among sites in the shapes of their incidence curves. Sites using PCV10 and PCV13 were modeled together to increase sample size and as no difference in impact on ST1 IPD was observed by product (Figure S3). The regression identified commonalities within and across sites in the direction of change over time and smoothed out observed annual variability. Data points from the same site were treated as repeated measures over time and sites with small case counts or few years of data had less influence than sites with larger case counts and many years of data.

ST1 outbreaks tended to occur in a cyclical pattern prior to the introduction of PCV10/13. The model did not account for outbreaks occurring in a cyclical pattern. Therefore, in order to generate an expected baseline ST1 IPD IR in any given year, the regression modeled pre-PCV10/13 IRs as a single mean rate with a slope of zero to capture an 'average' pre-PCV10/13 ST1 IR. PCV7 years of use were included in the pre-PCV10/13 period as no consistent impact of PCV7 on ST1 IRs, either increases (i.e., serotype replacement) or decreases, were observed across sites, as expected given pre-PCV10/13 ST1 carriage patterns [7]. This increased the number of pre-PCV10/13 years included in the analysis and better captured the baseline ST1 IR. For each site, a non-linear break (allowing an abrupt hinge in the curve) was included in the model one year prior to PCV10/13 introduction to capture the change from the pre-PCV10/13 period to the year of PCV10/13 introduction and cubic splines knots (allowing a smooth change in the slope) were included for each site at years +1 and +3 (the second and fourth year of PCV10/13 use) to allow for flexibility in the IR of ST1 over time for each site following PCV10/13 introduction. Site-specific modeled ST1 IR curves were visually inspected for model fit and approved by site investigators with expertise in IPD surveillance at each site.

Second, the pre-PCV10/13 ST1 IR was used as a counterfactual ST1 IR (i.e., an expected ST1 IR in any given post-PCV10/13 year in the absence of PCV10/13 introduction) for sites with both pre- and post-PCV10/13 data. The site-specific modeled ST1 IR and

counterfactual IR were used to estimate site-specific annual IRRs in each post-PCV10/13 year (reported as the mean of the posterior distribution of rate ratios) for each site. Site-specific IRRs were not generated for sites without pre-PCV10/13 years of data. Credibility intervals (CIs, Bayesian confidence interval analog) were estimated using the 2.5 and 97.5 percentiles of the posterior distribution of the IRs (Figure S1).

Finally, modeled site-specific IRRs were used to estimate all-site weighted average IRRs in each post-PCV10/13 year using a linear mixed-effects regression where site-specific IRRs were regressed on time since PCV10/13 introduction and weighted to give more influence to sites whose IRR standard errors were smaller. In sensitivity analyses, the all-site weighted average IRRs were estimated restricting to sites with data in all age groups and after adjusting the counterfactual IR by all-serotype IPD pre-PCV trends. All analyses were conducted in R (R Core Team, 2019).

3. Results

3.1. Description of Sites and Included Data

Of the 52 sites that met data collection eligibility criteria and contributed data to the PSERENADE project, 45 were included in the serotype 1 analysis (41 for children <5 years of age, 38 for 5–17 years of age, 37 for 18–49 years of age, 36 for 50–64 years of age, and 36 for ≥65 years of age). Two sites were excluded due to their population-based surveillance being restricted to pneumococcal meningitis, four sites were excluded due to a combination of biases in the surveillance system over time, such as changed to surveillance protocols, that could not be accounted for in the analysis and/or less than 50% of cases being serotyped, and one site was excluded due to zero ST1 cases being reported in all years of available data. Additionally, several age groups from included sites did not meet eligibility criteria and were excluded (Table S1).

Seven sites (16%) included in the analysis used PCV10, 24 (53%) used PCV13, and 14 (31%) used a combination of PCV10 and PCV13 in the infant PCV program. Only 14 (31%) sites introduced PCV10 or PCV13 into the routine immunization schedule with a catch-up campaign. The majority of sites used a PCV schedule including a booster dose (40, 89% used a 2 + 1 or 3 + 1 schedule and 5, 11% used a 3 + 0 schedule). Nearly half were from Europe (22 (49%)), 8 (18%) were from North America, 5 (11%) from Sub-Saharan Africa, 3 (7%) from Oceania, 3 (7%) from Asia, 2 (4%) from Latin America and the Caribbean and 2 (4%) from Northern Africa and Western Asia. The median PCV10/13 uptake for all years of available data after PCV10/13 introduction was 92% (range: 55–98%) (Table 1).

Of included sites with available data on specimen type, the median proportion of all ST1 IPD cases from CSF was 1.4% (range: 0–55.5%). Annual site-specific ST1 IRRs were estimated for 40 (89%) sites with both pre- and post-PCV10/13 ST1 surveillance data. The median number of surveillance years included in the analysis was 7 (range: 0–19) prior to the introduction of PCV10/13 and 8 (range: 2–10) after the introduction of PCV10/13 (including the year of PCV10/13 introduction). The median proportion of cases serotyped annually was 94% (range: 50–100%). The median number of ST1 cases included in the analysis per site was 29 (range: 1–499) for children <5 years of age, 46 (range: 2–768) for 5–17 years of age, 51 (range: 1–1776) for 18–49 years of age, 25 (range: 1–753) for 50–64 years of age, and 26 (range: 1–748) for ≥65 years of age (Table 1, Figure 1).
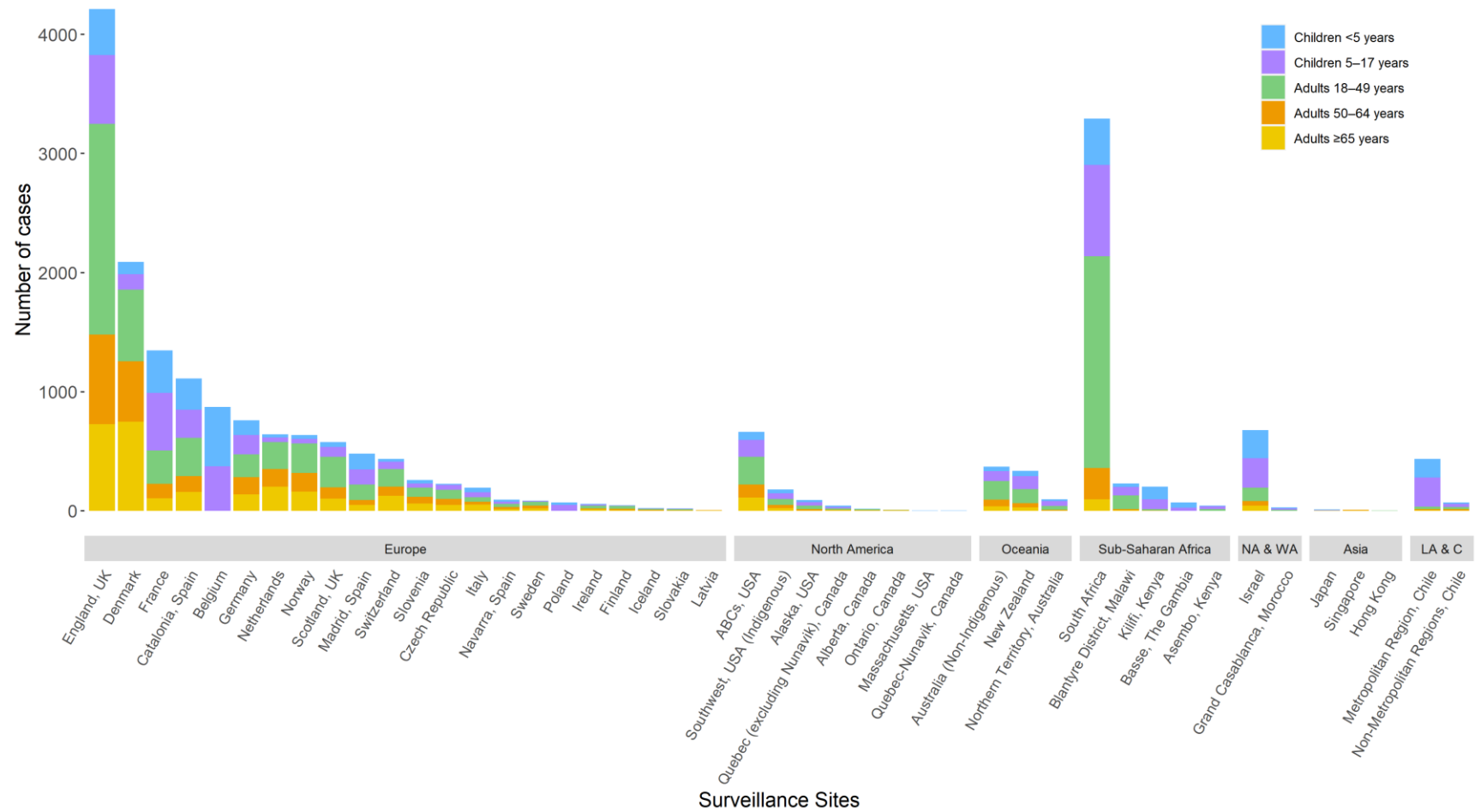
Figure 1. Number of serotype 1 cases per site included in the analysis by region and age group. NA & WA–Northern Africa and Western Asia; LA & C–Latin America and the Caribbean. Not all age groups were included for all sites (Table S1). Analyses were done with minor changes to age groups for certain sites to align with availability of population denominators and age groups provided by sites in aggregate: the <5 years age group includes 0–5 years from Morocco; the 5–17 years age group included 5–14 years from Japan and Kilifi, Kenya, 5–15 years from Germany, 6–14 years from Morocco, and 5–19 years from Australia and Malawi; and the 18–49 years age group includes 15–49 years from Japan and Kilifi, Kenya, 15–59 years from Morocco, 16–49 years from Germany, and 20–49 years from Australia and Malawi.

3.2. Impact of PCV10/13 on ST1 Incidence

All-site weighted average ST1 IPD IRRs comparing the pre-PCV10/13 period to each post-PCV10/13 year are shown in Table 2 and Figure 2. The all-site weighted average IRRs in the year of PCV10/13 introduction by age group ranged from 0.82 to 1.09 and was 1.09 (95% CI: 0.92–1.29) for children <5 years of age, 1.06 (0.88–1.28) for 5–17 years of age, 0.94 (0.73–1.22) for 18–49 years of age, 0.85 (0.70–1.04) for 50–64 years of age, and 0.82 (0.68–0.99) for ≥65 years of age. The ST1 IRR declined for every age group in each subsequent post-PCV10/13 year. By the sixth year of PCV10/13 use (year +5 post-PCV10/13 introduction), the all-site weighted average IRR compared to the pre-PCV10/13 period was 0.05 (0.04–0.06) for all ages, or a 95% relative reduction in ST1 IPD compared to the pre-PCV10/13 period. The reduction in ST1 IPD for each age group ranged from 92% to 95% in the sixth year of PCV10/13 use: IRR 0.05 (0.04–0.05) for children <5 years of age, 0.08 (0.06–0.09) for 5–17 years of age, 0.06 (0.05–0.08) for 18–49 years of age, 0.06 (0.05–0.07) for 50–64 years of age, and 0.05 (0.04–0.06) for ≥65 years of age.

In the early years of PCV10/13 use, site-specific IRRs were heterogeneous. Some sites reported outbreaks or had elevated levels of ST1 IPD around the time of PCV10/13 introduction, including two sites with very small sample sizes and large proportion increases in ST1 IRs. Other sites had little to no ST1 disease at the time of PCV10/13 introduction compared to the pre-PCV10/13 ST1 IRs. After five years of PCV10/13 use (year +4 post-PCV10/13), the impact of PCV10/13 on ST1 IPD was homogeneous across all included sites and age groups. No ST1 outbreaks were observed after five or more years of PCV10/13 use in any site (Figure 3). Results were similar when analyses were restricted to sites with data in all age groups (results not shown), when sites with very small sample size were excluded (results not shown), and after adjusting the counterfactual IR by all-serotype IPD pre-PCV trends (Figure S2). No differences in ST1 impact were observed by visual inspection among the included sites by PCV product, region, infant PCV schedule, or adult pneumococcal polysaccharide vaccine recommendation (Figures S3–S6). One site, which was excluded from the analytic model because the dataset was limited to meningitis cases, observed declines in ST1 pneumococcal meningitis IRs after PCV10 introduction that were consistent with declines seen in ST1 IPD in the other sites (Figure S7).

Table 2. Serotype 1 invasive pneumococcal disease all-site weighted average incidence rate ratios comparing the annual post-PCV10/13 incidence rate to the average pre-PCV10/13 incidence rate by age group.

	Year Post-PCV10/13 Introduction									
	0 *	1	2	3	4	5	6	7	8	9
Children <5 Years										
Nnumber of Sites [a]	37	37	36	36	35	34	33	27	10	3
IRR (95% CI)	1.09 (0.92–1.29)	0.57 (0.48–0.67)	0.29 (0.25–0.35)	0.15 (0.13–0.18)	0.08 (0.07–0.09)	0.05 (0.04–0.05)	0.03 (0.02–0.03)	0.02 (0.02–0.02)	0.01 (0.01–0.02)	0.01 (0.01–0.01)
Children 5–17 Years										
Number of Sites [a]	34	34	33	33	32	31	30	24	9	2
IRR (95% CI)	1.06 (0.88–1.28)	0.67 (0.55–0.80)	0.41 (0.34–0.49)	0.24 (0.20–0.29)	0.14 (0.11–0.16)	0.08 (0.06–0.09)	0.04 (0.04–0.05)	0.03 (0.02–0.03)	0.01 (0.01–0.02)	0.01 (0.01–0.01)
Adults 18–49 Years										
Numbers of Sites [a]	29	29	29	29	28	28	27	22	9	2
IRR (95% CI)	0.94 (0.73–1.22)	0.57 (0.44–0.74)	0.34 (0.26–0.44)	0.20 (0.15–0.25)	0.11 (0.09–0.14)	0.06 (0.05–0.08)	0.03 (0.03–0.04)	0.02 (0.01–0.02)	0.01 (0.01–0.01)	0.01 (0.00–0.01)
Adults 50–64 Years										
Number of Sites [a]	29	29	29	29	27	27	27	22	9	2
IRR (95% CI)	0.85 (0.70–1.04)	0.54 (0.44–0.65)	0.33 (0.27–0.40)	0.19 (0.15–0.23)	0.10 (0.08–0.12)	0.06 (0.05–0.07)	0.03 (0.03–0.04)	0.02 (0.02–0.02)	0.01 (0.01–0.01)	0.01 (0.01–0.01)
Adults ≥65 Years										
Number of Sites [a]	28	28	28	28	27	27	27	22	9	2
IRR (95% CI)	0.82 (0.68–0.99)	0.56 (0.46–0.67)	0.36 (0.30–0.43)	0.20 (0.17–0.24)	0.10 (0.08–0.12)	0.05 (0.04–0.06)	0.03 (0.02–0.03)	0.02 (0.01–0.02)	0.01 (0.01–0.01)	0.01 (0.00–0.01)
All ages										
Number of Sites [a]	39	39	38	38	37	36	35	29	11	3
IRR (95% CI)	0.98 (0.79–1.21)	0.57 (0.47–0.71)	0.33 (0.27–0.40)	0.18 (0.15–0.22)	0.10 (0.08–0.12)	0.05 (0.04–0.06)	0.03 (0.02–0.04)	0.02 (0.01–0.02)	0.01 (0.01–0.01)	0.01 (0.01–0.01)

PCV: Pneumococcal conjugate vaccine. * Year of PCV10/13 introduction. [a] Number of sites with both pre- and post-PCV10/13 data in each post-PCV10/13 year. All-site weighted average IRRs estimated by post-PCV10/13 year and age group using linear mixed-effects regression.
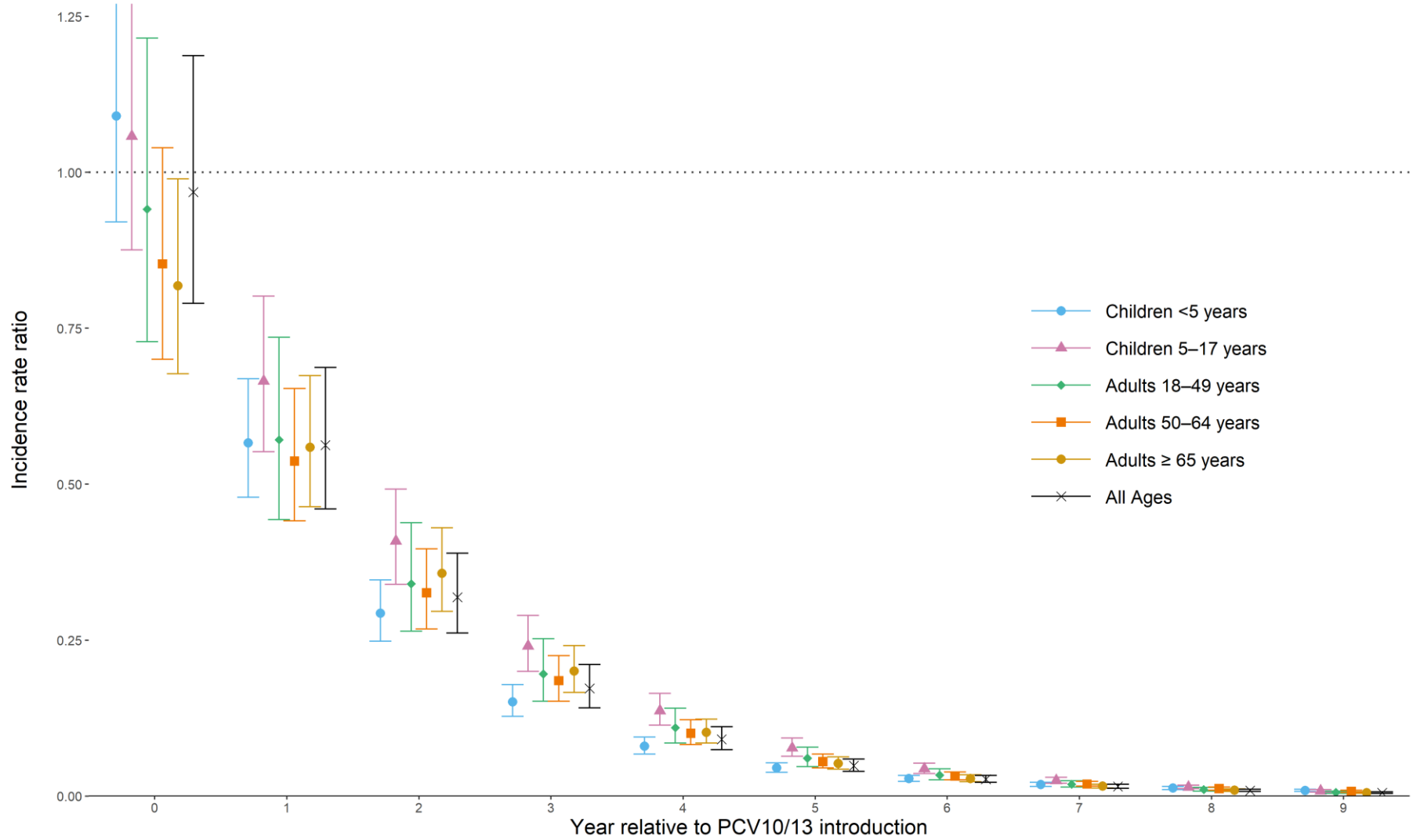
Figure 2. All-site weighted average incidence rate ratios for serotype 1 invasive pneumococcal disease for all ages and by age group. All ages' analysis (in black) is not an average of each age-specific estimate in each year but rather a re-analysis of the total cases from all ages reporting at each site.
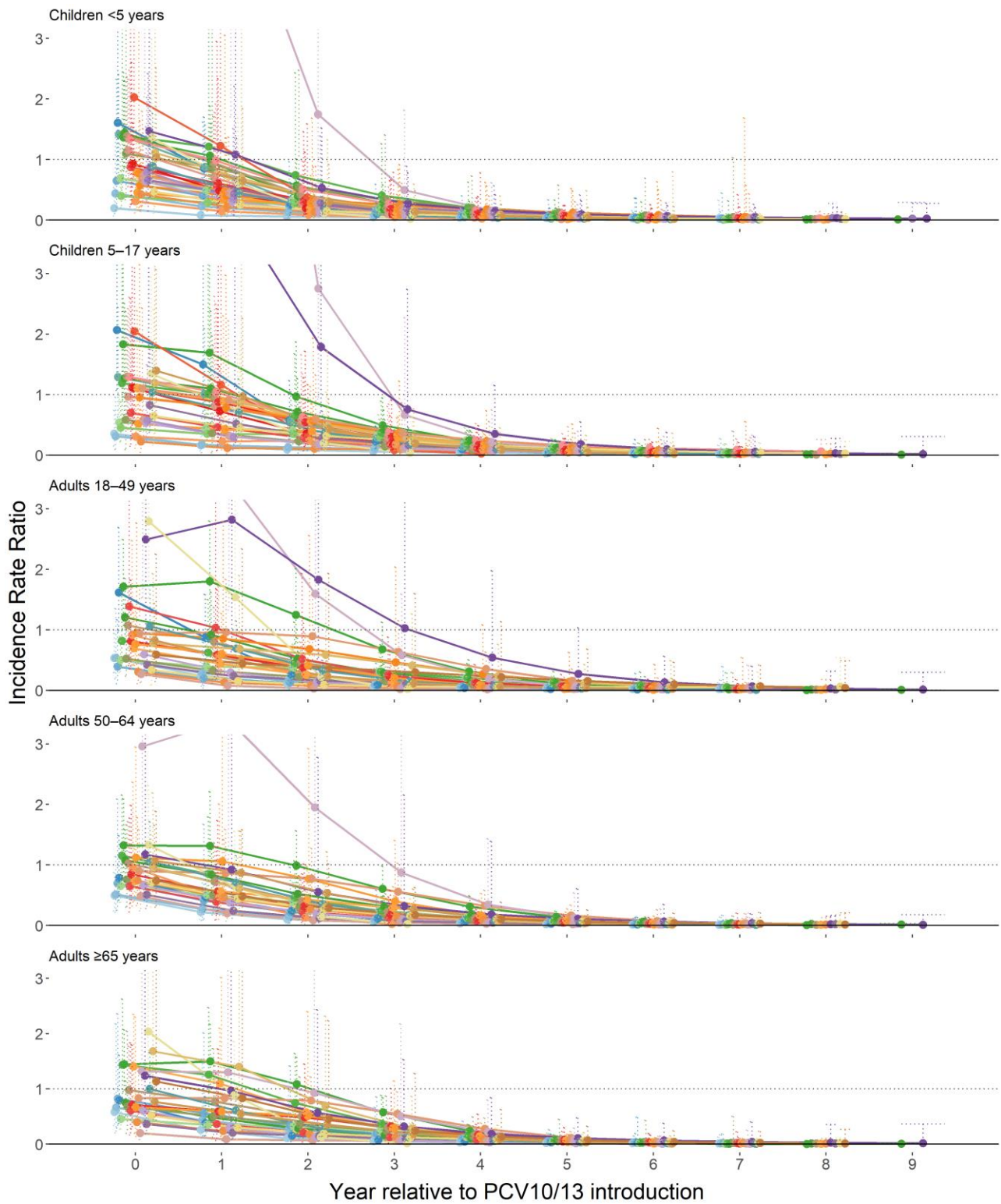
Figure 3. Site-specific modeled serotype 1 invasive pneumococcal disease incidence rate ratios comparing each post-PCV10/13 year to pre-PCV10/13 average, by age group.

4. Discussion

Our analysis demonstrates that there have been large and sustained decreases in ST1 IPD among both children targeted for immunization and among unvaccinated older children and adults through indirect effects. We used a standardized approach to analyze data from 45 surveillance sites and analytic methods that strengthened predictions from sites with few years of data and small sample sizes by borrowing strength from the overall trends observed across all sites. This allowed sites with few years of data and small sample sizes to still contribute proportionately to the analysis where data were available. As a result, this analysis is the most comprehensive assessment of changes in ST1 IPD after PCV10/13 introduction and demonstrates homogeneity in long-term impact of PCV10/13 on ST1 IPD across sites. These results were used to inform global vaccine policy recommendations around the use of pneumococcal vaccines in community outbreak settings [27].

The all-site weighted average IRRs are consistent with findings from individual surveillance sites on the long-term impact of PCV10/13 on ST1 IPD [9,10,12,16–20]. In the first several years of PCV10/13 use, the observed impact of PCV10/13 on ST1 IPD was heterogeneous, in part, due to the cyclic and outbreak nature of ST1 IPD and likely reflects heterogeneity in pre-PCV10/13 temporal trends with respect to the timing of PCV10/13 introduction. In some sites, ST1 IPD rates in the early years were greater than the pre-PCV10/13 average (because cyclical increases or outbreaks occurred at the time of or immediately following PCV10/13 introduction or because of noise in small datasets) and in other sites ST1 IPD rates were lower than the pre-PCV10/13 average immediately following PCV10/13 introduction. However, further into the PCV10/13 period, every site had sustained reductions in ST1 IPD below the pre-PCV10/13 rate. Prior to PCV10/13 introduction ST1 was known to cause severe disease to a greater degree in older children and younger adults compared to other serotypes [3,13,28] and importantly, we observed substantial reductions in ST1 IPD for all age groups. There was concern prior to the widespread introduction of PCV10/13 regarding the immunogenicity of PCV10/13 when used without a booster dose against ST1 [29]. Although only five sites using a 3 + 0 schedule were included in the analysis, the direct and indirect effects for ST1 IPD after several years of PCV10/13 use in these sites were consistent with patterns observed in sites using a booster dose schedule.

Although not observed in all sites and CIs overlap, our results showed slightly smaller declines in ST1 IPD for children <18 years compared to adults ≥18 years in the year of PCV10/13 introduction, which is contradictory to expected patterns of indirect effects among non-immunized adults following introduction of an infant vaccine [30]. This may reflect secular trends unrelated to vaccine introduction or differences in the hospital and surveillance systems between adults and pediatrics and an increased focus on pediatric surveillance around the time of pediatric vaccine introduction leading to greater detection of pediatric cases compared to adults. Ninety-two percent of sites with adult ST1 data included in the analysis have an adult pneumococcal polysaccharide vaccine recommendation. Although this may have reduced the burden of ST1 IPD among vaccinated adults prior to infant PCV10/13 programs, this does not explain observed patterns in the year of PCV10/13 introduction. The majority of adult polysaccharide vaccine programs began many years prior to the introduction of PCV10/13, recommendations vary by site for adult pneumococcal vaccine use, and data on vaccine uptake among adults was limited. We were not able to detect differences by adult pneumococcal vaccine program recommendation. Despite this, we see substantial and sustained declines in ST1 IPD for all age groups in the following years of PCV10/13 use.

To understand the impact of PCV10/13 introduction, data were restricted to sites with at least 50% uptake for the primary PCV series at 12 months of age in at least one-year post-PCV10/13 introduction and majority of included sites had high PCV uptake. This resulted in most data coming from high-income countries and limited inferences can be made to other regions or areas with lower vaccine uptake. Further, the majority of the data are from

sites that used a booster dose. Among the five sites with a 3 + 0 schedule, four introduced PCV10/13 with a catch-up program. Therefore, any added effects of a booster dose and catch-up programs could not be assessed, and results may not be reflective of other settings. In particular, data were limited from areas prone to pneumococcal meningitis outbreaks, such as the African meningitis belt. Only one site from the African meningitis belt, The Gambia, was included in the analysis where a 3 + 0 schedule of PCV13 was introduced without a catch-up program. Although there were few ST1 cases (*n* = 71), ST1 trends for children <18 years of age were consistent with other non-meningitis belt countries in Africa and other regions. In the 4 other sites that used a 3 + 0 schedule (all of which introduced PCV10/13 with a catch-up campaign), ST1 trends were also similar to those observed in sites using a 2 + 1 or 3 + 1 schedule among both children and adults. Two meningitis belt countries with documented pneumococcal outbreaks after PCV13 introduction with a 3 + 0 schedule, Ghana and Burkina Faso, did not contribute data to the PSERENADE project. As in The Gambia, the proportion of ST1 cases occurring among children <5 years of age decreased compared to the pre-PCV13 period in Ghana and Burkina Faso [22–24]. However, pneumococcal meningitis outbreaks in persons >5 years of age were documented four years after PCV13 introduction in the Brong-Ahafo region of Ghana (outside of the traditional meningitis belt) [22] and five years after introduction in the Upper West and Northern regions of Ghana (within the traditional meningitis belt) [23]. In both of these outbreaks a large proportion of cases were due to ST1 (between 62–80%) [22,23]. PCV13 uptake in these specific communities was undocumented and national PCV13 uptake in the first two years of use was low in Ghana (41–68%) [22]. In Burkina Faso after 3 years of PCV13 use, ST1 meningitis rates declined by 59% for children <1 year of age, by 25% for children 1–4 years of age, and by 8–17% for individuals ≥5 years of age. Slightly larger declines were observed for all PCV13 serotype meningitis (76% decline for children <1 year, 58% decline for children 1–4 years, and 14–20% decline for individuals ≥5 years of age) [24]. The remaining PCV13 serotype meningitis among individuals ≥1 year of age indicates that indirect effects have not been fully achieved for all vaccine serotypes, including but not limited to ST1, and the 59% decline in ST1 disease among children <1 year of age suggests that after 3 years of use the PCV program has not yet sufficiently protected children targeted for immunization. Although the association between PCV uptake and indirect effects are not well understood, this may indicate low vaccine uptake. The persistence of ST1 IPD in unvaccinated persons in the first five years of PCV10/13 use is consistent with our results, as ST1 outbreaks were still observed in some sites during the first five years of PCV10/13 use and significant declines in ST1 IPD were not observed for some sites until after 5 years of PCV10/13 use (Figure 3). As recommended by WHO, continuation of comprehensive, high-quality serotype-specific IPD surveillance and vaccine uptake monitoring in the African meningitis belt sites still experiencing ST1 outbreaks in the post-PCV period and in countries with suboptimal PCV10/13 uptake could improve understanding of ST1 in these settings with schedules lacking a booster dose or with low PCV10/13 uptake [31].

This analysis was also limited in its ability to model the counterfactual ST1 IR in the absence of PCV10/13. An ideal ST1 counterfactual IR would have modeled the cyclical pattern of ST1 IPD in the absence of PCV10/13 introduction as a baseline comparison for each post-PCV10/13 year, as has been done for single site analyses, but is challenging without monthly data [11]. Due to the number of available years of pre-PCV data and small ST1 sample size, this was not possible for the majority of sites and instead an average pre-PCV10/13 ST1 IR was used as the counterfactual ST1 IR. Using the average pre-PCV10/13 ST1 IR would most likely lead to less valid effect estimates in the early years of PCV10/13 use and may contribute to unexplained differences in IRRs between age groups in the year of PCV10/13 introduction. However, this would have limited impact on the estimates in later post-PCV10/13 later years. Although a high proportion of the cases from included sites were fully serotyped, another limitation of this analysis, which cannot be tested, is the assumption that the prevalence of ST1 among cases that were serotyped is not

biased from the prevalence of ST1 cases among cases that were not serotyped or not fully serotyped. Finally, the number of sites with post-PCV10/13 data declined over time and sites with longer follow-up periods tend to be from high-income countries that generally introduced PCV10/13 earlier than low- and middle-income countries. Eleven sites had data through the ninth year of PCV10/13 use and only three sites had data in the tenth year of PCV10/13 use.

These results can provide important context for evaluating the impact of PCV10/13 on other individual serotypes. ST1 is unique from other vaccine-serotypes in its invasiveness potential, carriage patterns, ability to cause large outbreaks among all ages, and association with meningitis [7,8,12–15]. Future analyses using the PSERENADE dataset will evaluate the impact of PCV10/13 on other individual vaccine and non-vaccine serotypes.

5. Conclusions

The introduction of PCV10/13 into infant immunization programs has been associated with the near elimination of ST1 IPD in all ages after approximately 6 years of use, including in settings without a booster dose schedule but with high PCV10/13 uptake, where data are available. Improved population-level serotype-specific IPD surveillance for all ages, including for meningitis, is needed from settings using a 3 + 0 schedule with a history of ongoing ST1 outbreaks in the post-PCV10/13 period, particularly the African meningitis belt, and in countries with suboptimal PCV10/13 uptake. This would allow for a more comprehensive evaluation of the indirect effects of PCV10/13 in older children and adults living in high burden settings using a 3 + 0 schedule or with low PCV10/13 uptake.

Supplementary Materials: The following are available online at https://www.mdpi.com/article/10.3390/microorganisms9040696/s1, Figure S1: Method for estimating annual ST1 IPD IRRs comparing the pre-PCV10/13 period to each post-PCV10/13 year for each included site with pre- and post-PCV10/13 data: example for children <5 years from one site, Figure S2: All-site weighted average IRRs for ST1 IPD for all ages and by age group adjusted for pre-PCV trends in all-serotype IPD (*n* = 30 sites), Figure S3: Site-specific modeled ST1 IPD IRRs by PCV product and age group, Figure S4: Site-specific modeled ST1 IPD IRRs by region and age group, Figure S5: Site-specific modeled ST1 IPD IRRs by infant PCV10/13 schedule and age group, Figure S6: Site-specific modeled ST1 IPD IRRs for adults $\geq$ 65 years by adult pneumococcal polysaccharide vaccine recommendation, Figure S7: Incidence rate of ST1 meningitis cases from cerebrospinal fluid (CSF) in Brazil by age group and year relative to PCV10 introduction (*n* = 51 cases), Table S1: Sites included in PSERENADE evaluated for the serotype 1 analysis by age group.

Author Contributions: Conceptualization, J.C.B., K.H., D.R.F., M.D.K.; methodology, J.C.B., S.L.Z., K.H., M.D.K., E.W.K.; software and analysis, J.C.B., S.L.Z.; writing—original draft preparation, J.C.B., K.H., M.K.H., J.N.S.; writing—review and editing, D.R.F., M.D.K., S.L.Z., M.G.Q., E.W.K., K.A., M.-C.C.B., D.B., R.C., J.C., G.C., H.C., J.E.C., R.D., T.D., K.D., S.d.M., P.D.W., S.D., T.G., C.G., M.G.-V., L.L.H., M.H., P.-L.H., S.J., J.D.K., J.K. (Jackie Kleynhans), M.J.K., J.K. (Jana Kozakova), K.G.K., S.N.L., L.M. (Laura MacDonald), G.A.M., L.M. (Lucia MadaarovA), A.M., J.M., E.M., T.M., C.M.-A., J.P.N., M.P., T.P., R.P., S.K.S., A.S.K., L.S., J.A.S., A.S., S.S., M.v.d.L., J.R.V., A.v.G., B.A.W., I.Y., K.Z.; visualization, J.C.B., M.K.H.; supervision, K.H., M.D.K., A.L.C.; project administration, J.C.B., M.G.Q.; funding acquisition, A.L.C., M.D.K., K.H.; data curation, E.W.K., K.A., M.-C.C.B., D.B., R.C., J.C., G.C., H.C., J.E.C., R.D., T.D., K.D., S.d.M., P.D.W., S.D., T.G., C.G., M.G.-V., L.L.H., M.H., P.-L.H., S.J., J.D.K., J.K. (Jackie Kleynhans), M.J.K., J.K. (Jana Kozakova), K.G.K., S.N.L., L.M. (Laura MacDonald), G.A.M., L.M. (Lucia MadaarovA), A.M., J.M., E.M., T.M., C.M.-A., J.P.N., M.P., T.P., R.P., S.K.S., A.S.K., L.S., J.A.S., A.S., S.S., M.v.d.L., J.R.V., A.v.G., B.A.W., I.Y., K.Z. All authors provided input for the analytic methodology and critically reviewed results. All authors have read and agreed to the published version of the manuscript.

Institutional Review Board Statement: This study was determined to not quality as human subjects research as defined by DHHS regulations 45 CFR 46.102 by the Johns Hopkins Bloomberg School of

Public Health Institutional Review Board, due to the use of existing, de-identified data. Therefore, Institutional Review Board oversight was not required, and ethical review and approval were waived for this study.

Informed Consent Statement: Not applicable.

Data Availability Statement: Restrictions apply to the availability of these data. Data were obtained under data sharing agreements from contributing surveillance sites and can only be shared by contributing organizations with their permission.

Disclaimer: The findings and conclusions in this report are those of the authors and do not necessarily represent the official position of the Centers for Disease Control and Prevention or the World Health Organization (WHO).

Appendix A

Table A1. PSERENADE Team.

Name	Affiliation
Pedro Alarcon	Instituto de Salud Pública de Chile, 7780050 Santiago, Santiago Metropolitan, Chile
Samanta C. G. Almeida	National Laboratory for Meningitis and Pneumococcal Infections, Center of Bacteriology, Institute Adolfo Lutz (IAL), São Paulo 01246-902, Brazil
Zahin Amin-Chowdhury	Immunisation and Countermeasures Division, Public Health England, NW9 5EQ, London, United Kingdom
Michelle Ang	National Public Health Laboratory, National Centre for Infectious Diseases, 308442, Singapore
Mária Avdicová	National Reference Centre for Pneumococcal and Haemophilus Diseases, Regional Authority of Public Health, 975 56 Banská Bystrica, Slovak Republic
Naor Bar-Zeev	Malawi-Liverpool-Wellcome Trust Clinical Research Programme, P.O. Box 30096, Chichiri, Blantyre 3, Malawi; Johns Hopkins Bloomberg School of Public Health, Baltimore, MD 21205, United States
Godfrey Bigogo	Centre for Global Health Research, Kenya Medical Research Institute, P.O. Box: 1578-40100, Kisumu, Kenya
Rita Born	Federal Office of Public Health, 3097 Liebefeld, Switzerland
Michael G. Bruce	Arctic Investigations Program, Division of Preparedness and Emerging Infections, National Center for Emerging and Zoonotic Infectious Diseases, Centers for Disease Control and Prevention, Anchorage, AK 99508, United States
Carrie L. Byington	University of Utah Department of Pediatrics (emeritus), Salt Lake City, UT 84108, United States; University of California Health System, Oakland, CA 94607, United States
Kin-Hung Chow	Department of Microbiology and Carol Yu Centre for Infection, The University of Hong Kong, Hong Kong SAR, China
Urtnasan Chuluunbat	National Center of Communicable Diseases (NCCD), Ministry of Health, Bayanzurkh district, 13336 Ulaanbaatar, Mongolia
Pilar Ciruela	Surveillance and Public Health Emergency Response, Public Health Agency of Catalonia, 08005 Barcelona, Spain; CIBER Epidemiología y Salud Pública, (CIBERESP), 28029 Madrid, Spain
Cheryl Cohen	Centre for Respiratory Diseases and Meningitis, National Institute for Communicable Diseases of the National Health Laboratory Service, Sandringham, 2192 Johannesburg, South Africa; School of Public Health, Faculty of Health Sciences, University of the Witwatersrand, Johannesburg, South Africa
Mary Corcoran	Irish Meningitis and Sepsis Reference Laboratory, Children's Health Ireland at Temple Street, Rotunda, Dublin 1, D01 XD99, Ireland
Geneviève Deceuninck	Quebec University Hospital Research Centre, Québec, QC G1V 4G2, Canada
Martina Del Manso	Department of Infectious Diseases, Italian National Institute of Health (Istituto Superiore di Sanità, ISS), 00161 Rome, Italy
Idrissa Diawara	Faculty of Sciences and Health Techniques, Mohammed VI University of Health Sciences (UM6SS) of Casablanca, Casablanca, Morocco; National Reference Laboratory, Mohammed VI University of Health Sciences (UM6SS), 82403 Casablanca, Morocco

Table A1. *Cont.*

Name	Affiliation
Janepsy Díaz	Instituto de Salud Pública de Chile, 7780050 Santiago, Santiago Metropolitan, Chile
Elina Dimina	Centre for disease prevention and control of Latvia, Riga, 1005, Latvia
Mignon du Plessis	Centre for Respiratory Diseases and Meningitis, National Institute for Communicable Diseases of the National Health Laboratory Service, Sandringham, 2192 Johannesburg, South Africa
Helga Erlendsdottir	Department of Clinical Microbiology, Landspitali—The National University Hospital, Hringbraut, 101 Reykjavik, Iceland
Yvonne Galloway	Epidemiology Team, Institute of Environmental Science and Research, Porirua, 5240 Wellington, New Zealand
Ryan Gierke	National Center for Immunizations and Respiratory Diseases, Centers for Disease Control and Prevention, Atlanta, GA 30333, United States
Noga Givon-Lavi	Pediatric Infectious Disease Unit and Clinical Microbiology Laboratory, Soroka University Medical Center, Ben-Gurion University of the Negev, Beer-Sheva, 8410501, Israel
Marcela Guevara	Instituto de Salud Pública de Navarra—IdiSNA, 31003 Pamplona, Navarra, Spain; CIBER Epidemiología y Salud Pública, (CIBERESP), 28029 Madrid, Spain
Ilias Hossain	Medical Research Council, The Gambia Unit, Fajara, The Gambia
Vicki Krause	Centre for Disease Control, Department of Health and Community Services, Darwin City NT 8000, Australia
Pavla Krizova	National Institute of Public Health (NIPH), 100 42, Praha 10, Czech Republic
Alicja Kuch	National Reference Centre for Bacterial Meningitis, National Medicines Institute, 00-725 Warsaw, Poland
Brigitte Lefebvre	Laboratoire de Santé Publique du Québec, Sainte-Anne-de-Bellevue, Quebec H9X 3R5, Canada
Tiia Lepp	Department of Communicable Disease and Control and Health Protection, Public Health Agency of Sweden, 171 82 Solna, Sweden
Ioanna Magaziotou	National Public Health Organisation, 15123 Athens, Greece
Kazunori Oishi	Toyama Institute of Health, Imizu, 939-0363 Toyama, Japan
Stephen I. Pelton	Boston University Schools of Medicine and Public Health, Boston, MA 02118, United States
Kate Pennington	Communicable Disease Epidemiology and Surveillance Section, Office of Health Protection, Australian Government Department of Health, 2606 Canberra ACT, Australia
Marie-Cecile Ploy	University Hospital Centre Limoges, Regional Observatories for Pneumococci, 87000 Limoges, France
Hafizur Rahman	Child Health Research Foundation, Dhaka 1207, Bangladesh
Rita Reyburn	Murdoch Children's Research Institute, Parkville VIC 3052, Australia
Leah J. Ricketson	Department of Pediatrics, University of Calgary, and Alberta Health Services, Calgary Alberta T3B 6A8, Canada
Juan Carlos Sanz	Laboratorio Regional de Salud Pública, Dirección General de Salud Pública, Comunidad de Madrid, 28053 Madrid, Spain
Kevin Scott	Bacterial Respiratory Infection Service, Scottish Microbiology Reference Laboratory, NHS GG&C, G31 2ER Glasgow, United Kingdom
Catherine G. Sutcliffe	Johns Hopkins Bloomberg School of Public Health, Baltimore, MD 21205, United States
Koh Cheng Thoon	KK Women's and Children's Hospital, 229899, Singapore
Maija Toropainen	Department of Health Security, Finnish Institute for Health and Welfare, 00271 Helsinki, Finland
Georgina Tzanakaki	National Meningitis Reference Laboratory, National School of Public Health Athens, Athens, Greece
Palle Valentiner-Branth	Infectious Disease Epidemiology and Prevention, Statens Serum Institut, DK-2300 Copenhagen S, Denmark
Nina M. van Sorge	Medical Microbiology and Infection Prevention, Netherlands Reference Laboratory for Bacterial Meningitis, Amsterdam University Medical Centers, location AMC, University of Amsterdam, 1105 AZ Amsterdam, The Netherlands

Table A1. *Cont.*

Name	Affiliation
Emmanuelle Varon	National Reference Centre for Pneumococci, Centre Hospitalier Intercommunal de Créteil, 94000 Créteil, France
Didrik F. Vestrheim	Department of Infection Control and Vaccine, Norwegian Institute of Public Health, 0456 Oslo, Norway
Toronto Invasive Bacterial Diseases Network	

Table A2. Acknowledgement List.

PSERENADE Technical Advisory Group
Thomas Cherian
William P. Hausdorff
Marc Lipsitch
Shabir A. Madhi
Elizabeth Miller
Catherine Satzke
Cynthia G. Whitney
World Health Organization
Katherine L. O'Brien
Jenny A. Walldorf
Johns Hopkins University
Yunfeng Cao
Peggy Gross
Donna Hesson
Ananya Kumar
Kate Perepezko
Meagan E. Peterson
Francesca Schiaffino Salazar
Daniel Stephens
Yangyupei Yang
EpiConcept
Camelia Savulescu
European Centre for Disease Prevention and Control
Edoardo Colzani
Pan American Health Organization
Lúcia Helena de Oliveira
Dirección General de Salud Pública, Comunidad de Madrid, Spain
Luis García Comas
Maria Ordobás Gavín
Department of Infectious Diseases, Italian National Institute of Health (Istituto Superiore di Sanità, ISS), Rome, Italy
Flavia Riccardo

Table A2. *Cont.*

Department of Microbiology, Faculty of Medicine and Pharmacy, Hassan II University of Casablanca, Casablanca, Morocco; Bacteriology-Virology and Hospital Hygiene Laboratory, Ibn Rochd University Hospital Centre, Casablanca, Morocco
Néhémie Nzoyikorera
Surveillance and Public Health Emergency Response, Public Health Agency of Catalonia, Barcelona, Spain
Sonia Broner
Conchita Izquierdo
Australian National Notifiable Diseases Surveillance data were provided by the Office of Health Protection, Australian Government Department of Health, on behalf of the Communicable Diseases Network Australia and the Enhanced Invasive Pneumococcal Disease Surveillance Working Group.

References

1. Wahl, B.; O'Brien, K.L.; Greenbaum, A.; Majumder, A.; Liu, L.; Chu, Y.; Lukšić, I.; Nair, H.; McAllister, D.A.; Campbell, H.; et al. Burden of Streptococcus Pneumoniae and Haemophilus Influenzae Type b Disease in Children in the Era of Conjugate Vaccines: Global, Regional, and National Estimates for 2000–15. *Lancet Glob. Health* **2018**, *6*, e744–e757. [CrossRef]
2. Troeger, C.; Blacker, B.; Khalil, I.A.; Rao, P.C.; Cao, J.; Zimsen, S.R.M.; Albertson, S.B.; Deshpande, A.; Farag, T.; Abebe, Z.; et al. Estimates of the Global, Regional, and National Morbidity, Mortality, and Aetiologies of Lower Respiratory Infections in 195 Countries, 1990–2016: A Systematic Analysis for the Global Burden of Disease Study 2016. *Lancet Infect. Dis.* **2018**, *18*, 1191–1210. [CrossRef]
3. Hausdorff, W.P.; Feikin, D.R.; Klugman, K.P. Epidemiological Differences among Pneumococcal Serotypes. *Lancet Infect. Dis.* **2005**, *5*, 83–93. [CrossRef]
4. Ritchie, N.D.; Mitchell, T.J.; Evans, T.J. What Is Different about Serotype 1 Pneumococci? *Future Microbiol.* **2011**, *7*, 33–46. [CrossRef] [PubMed]
5. Ganaie, F.; Saad, J.S.; McGee, L.; van Tonder, A.J.; Bentley, S.D.; Lo, S.W.; Gladstone, R.A.; Turner, P.; Keenan, J.D.; Breiman, R.F.; et al. A New Pneumococcal Capsule Type, 10D, Is the 100th Serotype and Has a Large Cps Fragment from an Oral Streptococcus. *mBio* **2020**, *11*. [CrossRef]
6. Johnson, H.L.; Deloria-Knoll, M.; Levine, O.S.; Stoszek, S.K.; Hance, L.F.; Reithinger, R.; Muenz, L.R.; O'Brien, K.L. Systematic Evaluation of Serotypes Causing Invasive Pneumococcal Disease among Children Under Five: The Pneumococcal Global Serotype Project. *PLoS Med.* **2010**, *7*, e1000348. [CrossRef] [PubMed]
7. Brueggemann, A.B.; Peto, T.E.A.; Crook, D.W.; Butler, J.C.; Kristinsson, K.G.; Spratt, B.G. Temporal and Geographic Stability of the Serogroup-Specific Invasive Disease Potential of Streptococcus Pneumoniae in Children. *J. Infect. Dis.* **2004**, *190*, 1203–1211. [CrossRef] [PubMed]
8. Bricio-Moreno, L.; Chaguza, C.; Yahya, R.; Shears, R.K.; Cornick, J.E.; Hokamp, K.; Yang, M.; Neill, D.R.; French, N.; Hinton, J.C.D.; et al. Lower Density and Shorter Duration of Nasopharyngeal Carriage by Pneumococcal Serotype 1 (ST217) May Explain Its Increased Invasiveness over Other Serotypes. *mBio* **2020**, *11*. [CrossRef]
9. Ladhani, S.N.; Collins, S.; Djennad, A.; Sheppard, C.L.; Borrow, R.; Fry, N.K.; Andrews, N.J.; Miller, E.; Ramsay, M.E. Rapid Increase in Non-Vaccine Serotypes Causing Invasive Pneumococcal Disease in England and Wales, 2000-17: A Prospective National Observational Cohort Study. *Lancet Infect. Dis.* **2018**, *18*, 441–451. [CrossRef]
10. Hammitt, L.L.; Etyang, A.O.; Morpeth, S.C.; Ojal, J.; Mutuku, A.; Mturi, N.; Moisi, J.C.; Adetifa, I.M.; Karani, A.; Akech, D.O.; et al. Effect of Ten-Valent Pneumococcal Conjugate Vaccine on Invasive Pneumococcal Disease and Nasopharyngeal Carriage in Kenya: A Longitudinal Surveillance Study. *Lancet Lond. Engl.* **2019**, *393*, 2146–2154. [CrossRef]
11. Harboe, Z.B.; Dalby, T.; Weinberger, D.M.; Benfield, T.; Mølbak, K.; Slotved, H.-C.; Suppli, C.H.; Konradsen, H.B.; Valentiner-Branth, P. Impact of 13-Valent Pneumococcal Conjugate Vaccination in Invasive Pneumococcal Disease Incidence and Mortality. *Clin. Infect. Dis.* **2014**, *59*, 1066–1073. [CrossRef]
12. Cook, H.M.; Giele, C.M.; Jayasinghe, S.H.; Wakefield, A.; Krause, V.L. An Outbreak of Serotype-1 Sequence Type 306 Invasive Pneumococcal Disease in an Australian Indigenous Population. *Commun. Dis. Intell.* **2020**, *44*. [CrossRef] [PubMed]
13. Leimkugel, J.; Adams Forgor, A.; Gagneux, S.; Pflüger, V.; Flierl, C.; Awine, E.; Naegeli, M.; Dangy, J.; Smith, T.; Hodgson, A.; et al. An Outbreak of Serotype 1 *Streptococcus Pneumoniae* Meningitis in Northern Ghana with Features That Are Characteristic of *Neisseria Meningitidis* Meningitis Epidemics. *J. Infect. Dis.* **2005**, *192*, 192–199. [CrossRef]
14. Yaro, S.; Lourd, M.; Traoré, Y.; Njanpop-Lafourcade, B.-M.; Sawadogo, A.; Sangare, L.; Hien, A.; Ouedraogo, M.S.; Sanou, O.; Parent du Châtelet, I.; et al. Epidemiological and Molecular Characteristics of a Highly Lethal Pneumococcal Meningitis Epidemic in Burkina Faso. *Clin. Infect. Dis. Off. Publ. Infect. Dis. Soc. Am.* **2006**, *43*, 693–700. [CrossRef]
15. Proulx, J.; Déry, S.; Jetté, L.; Ismaël, J.; Libman, M.; De Wals, P. Pneumonia Epidemic Caused by a Virulent Strain of Streptococcus Pneumoniae Serotype 1 in Nunavik, Quebec. *Can. Commun. Dis. Rep.* **2002**, *28*, 129–131. [PubMed]

16. Von Gottberg, A.; de Gouveia, L.; Tempia, S.; Quan, V.; Meiring, S.; von Mollendorf, C.; Madhi, S.A.; Zell, E.R.; Verani, J.R.; O'Brien, K.L.; et al. Effects of Vaccination on Invasive Pneumococcal Disease in South Africa. *N. Engl. J. Med.* **2014**, *371*, 1889–1899. [CrossRef] [PubMed]

17. Angoulvant, F.; Levy, C.; Grimprel, E.; Varon, E.; Lorrot, M.; Biscardi, S.; Minodier, P.; Dommergues, M.A.; Hees, L.; Gillet, Y.; et al. Early Impact of 13-Valent Pneumococcal Conjugate Vaccine on Community-Acquired Pneumonia in Children. *Clin. Infect. Dis.* **2014**, *58*, 918–924. [CrossRef]

18. Camilli, R.; D'Ambrosio, F.; Del Grosso, M.; Pimentel de Araujo, F.; Caporali, M.G.; Del Manso, M.; Gherardi, G.; D'Ancona, F.; Pantosti, A. Impact of Pneumococcal Conjugate Vaccine (PCV7 and PCV13) on Pneumococcal Invasive Diseases in Italian Children and Insight into Evolution of Pneumococcal Population Structure. *Vaccine* **2017**, *35*, 4587–4593. [CrossRef] [PubMed]

19. Ciruela, P.; Izquierdo, C.; Broner, S.; Muñoz-Almagro, C.; Hernández, S.; Ardanuy, C.; Pallarés, R.; Domínguez, A.; Jané, M.; Esteva, C.; et al. The Changing Epidemiology of Invasive Pneumococcal Disease after PCV13 Vaccination in a Country with Intermediate Vaccination Coverage. *Vaccine* **2018**, *36*, 7744–7752. [CrossRef]

20. Andrews, N.J.; Waight, P.A.; Burbidge, P.; Pearce, E.; Roalfe, L.; Zancolli, M.; Slack, M.; Ladhani, S.N.; Miller, E.; Goldblatt, D. Serotype-Specific Effectiveness and Correlates of Protection for the 13-Valent Pneumococcal Conjugate Vaccine: A Postlicensure Indirect Cohort Study. *Lancet Infect. Dis.* **2014**, *14*, 839–846. [CrossRef]

21. Mackenzie, G.A.; Hill, P.C.; Jeffries, D.J.; Hossain, I.; Uchendu, U.; Ameh, D.; Ndiaye, M.; Adeyemi, O.; Pathirana, J.; Olatunji, Y.; et al. Effect of the Introduction of Pneumococcal Conjugate Vaccination on Invasive Pneumococcal Disease in The Gambia: A Population-Based Surveillance Study. *Lancet Infect. Dis.* **2016**, *16*, 703–711. [CrossRef]

22. Kwambana-Adams, B.A.; Asiedu-Bekoe, F.; Sarkodie, B.; Afreh, O.K.; Kuma, G.K.; Owusu-Okyere, G.; Foster-Nyarko, E.; Ohene, S.-A.; Okot, C.; Worwui, A.K.; et al. An Outbreak of Pneumococcal Meningitis among Older Children (≥5 Years) and Adults after the Implementation of an Infant Vaccination Programme with the 13-Valent Pneumococcal Conjugate Vaccine in Ghana. *BMC Infect. Dis.* **2016**, *16*. [CrossRef] [PubMed]

23. Bozio, C.H.; Abdul-Karim, A.; Abenyeri, J.; Abubakari, B.; Ofosu, W.; Zoya, J.; Ouattara, M.; Srinivasan, V.; Vuong, J.T.; Opare, D.; et al. Continued Occurrence of Serotype 1 Pneumococcal Meningitis in Two Regions Located in the Meningitis Belt in Ghana Five Years after Introduction of 13-Valent Pneumococcal Conjugate Vaccine. *PLoS ONE* **2018**, *13*, e0203205. [CrossRef]

24. Kambiré, D.; Soeters, H.M.; Ouédraogo-Traoré, R.; Medah, I.; Sangaré, L.; Yaméogo, I.; Sawadogo, G.; Ouédraogo, A.-S.; Ouangraoua, S.; McGee, L.; et al. Early Impact of 13-Valent Pneumococcal Conjugate Vaccine on Pneumococcal Meningitis—Burkina Faso, 2014–2015. *J. Infect.* **2018**, *76*, 270–279. [CrossRef]

25. Deloria-Knoll, M.; Bennett, J.C.; Garcia Quesada, M.; Kagucia, E.W.; Peterson, M.E.; Feikin, D.R.; Cohen, A.L.; Hetrich, M.K.; Yangyupei, Y.; Sinkevitch, J.N.; et al. Global Landscape Review of Serotype-Specific Invasive Pneumococcal Disease Surveillance among Countries Using PCV10/13: The Pneumococcal Serotype Replacement and Distribution Estimation (PSERENADE) Project. *Microorganisms* **2021**, in press.

26. Hadfield, J.D. MCMC Methods for Multi-Response Generalized Linear Mixed Models: The MCMCglmm R Package. *J. Stat. Softw.* **2010**, *33*, 1–22. [CrossRef]

27. World Health Organization. *Strategic Advisory Group of Experts on Immunization Yellow Book*; World Health Organization Department of Immunization, Vaccines and Biologicals (IVB): Geneva, Switzerland, 2020; p. 8.

28. Traore, Y.; Tameklo, T.A.; Njanpop-Lafourcade, B.-M.; Lourd, M.; Yaro, S.; Niamba, D.; Drabo, A.; Mueller, J.E.; Koeck, J.-L.; Gessner, B.D. Incidence, Seasonality, Age Distribution, and Mortality of Pneumococcal Meningitis in Burkina Faso and Togo. *Clin. Infect. Dis.* **2009**, *48*, S181–S189. [CrossRef]

29. Klugman, K.P.; Madhi, S.A.; Adegbola, R.A.; Cutts, F.; Greenwood, B.; Hausdorff, W.P. Timing of Serotype 1 Pneumococcal Disease Suggests the Need for Evaluation of a Booster Dose. *Vaccine* **2011**, *29*, 3372–3373. [CrossRef] [PubMed]

30. Tsaban, G.; Ben-Shimol, S. Indirect (Herd) Protection, Following Pneumococcal Conjugated Vaccines Introduction: A Systematic Review of the Literature. *Vaccine* **2017**, *35*, 2882–2891. [CrossRef]

31. World Health Organization. Pneumococcal Conjugate Vaccines in Infants and Children under 5 Years of Age: WHO Position Paper. *Wkly. Epidemiol. Rec.* **2019**, *94*, 85–104.