

Streptococcus pneumoniae population structure in Germany in the pre- and post-immunization era.

Mark van der Linden

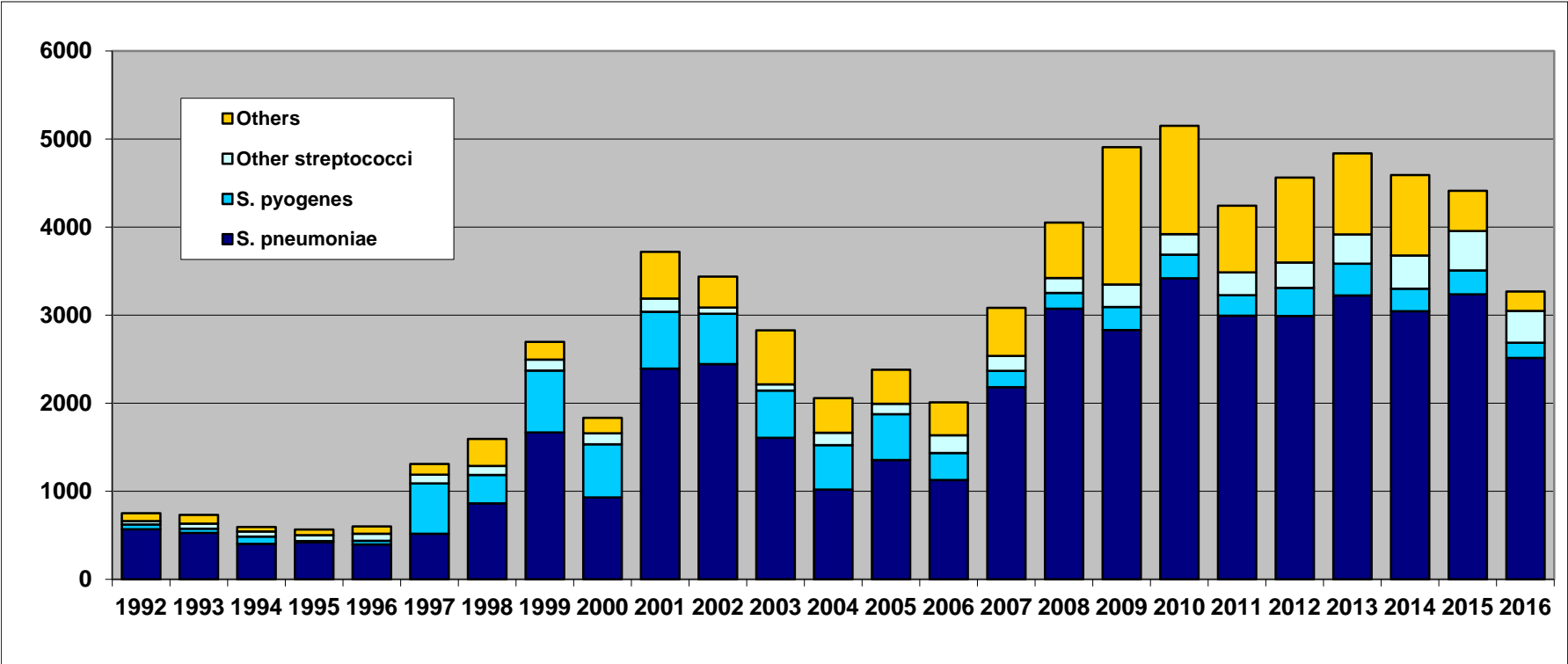
German National Reference Center for Streptococci (GNRCS)
www.pneumococcus.de



The German National Reference Center for Streptococci (GNRCS)

- Supported by the German Ministry of Health and the Robert Koch Institut
- Part of a network of 19 reference centers and 48 conciliar laboratories in Germany
- Tasks
 - Surveillance of streptococcal disease
 - Typing
 - Resistance surveillance
 - Support of vaccination programs

Numbers of isolates sent to the GNRCs 1992 - 2016





Surveillance of pneumococcal disease at the GNRCS

- >19 years surveillance of IPD in adults (n = 26.069) and children (n = 4.445)
- Strain collection
 - Total: n = 72.850
 - Streptococci: n = 60.394
 - Streptococcus pneumoniae*: n = 46.321
 - Streptococcus pyogenes*: n = 9.160
- Including clinical data



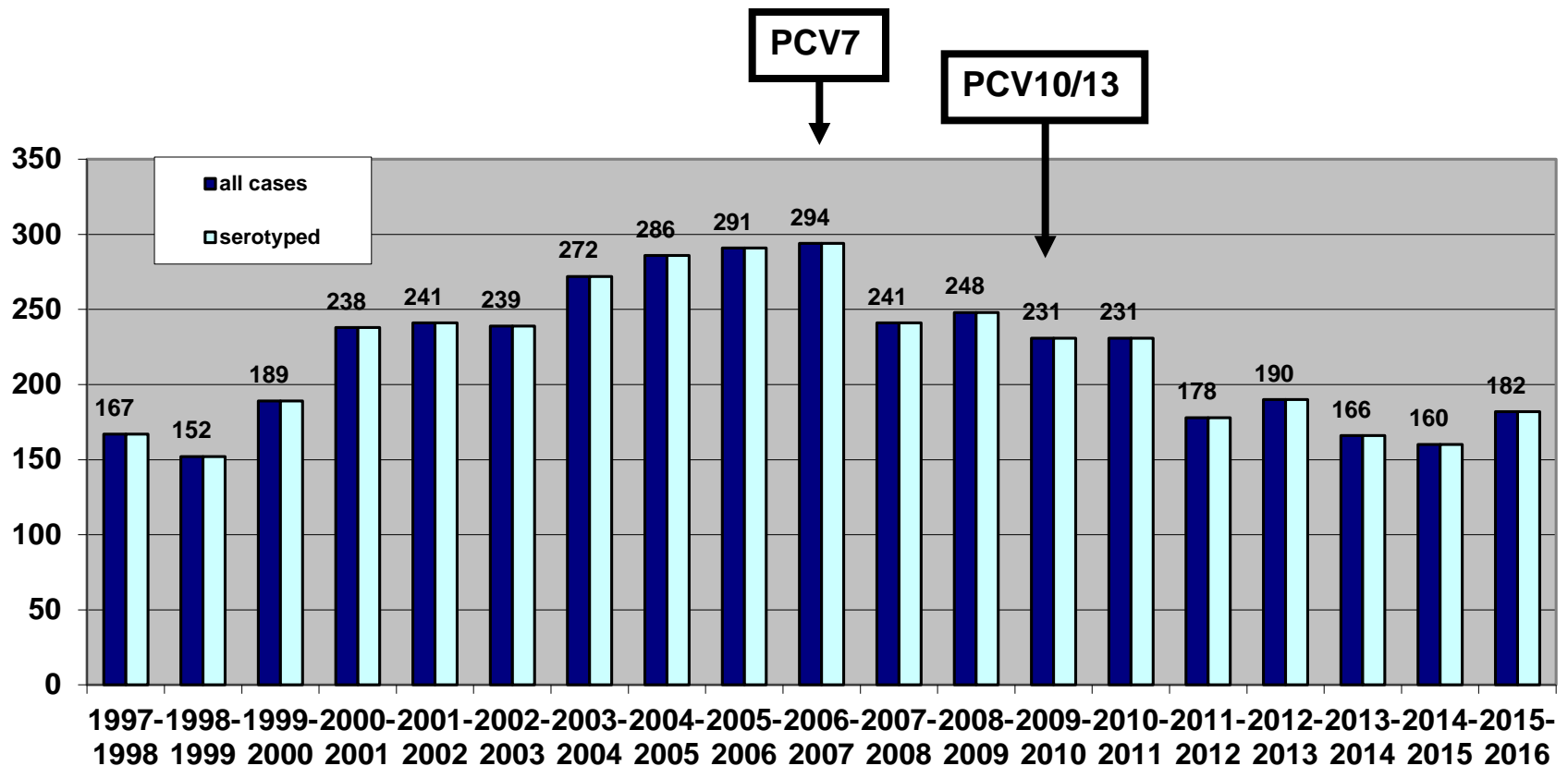
Pneumococcal vaccination in Germany

- June 1983: FDA approval of PPV23
- February 2001: EMA approval of PCV 7
- June 2001: STIKO recommendation of pneumococcal conjugate vaccination for children with elevated risk for IPD
- July 2006: STIKO recommendation of pneumococcal conjugate vaccination for all children < 2 years of age in Germany, 3+1 schedule, 2, 3, 4, 11-14 months
- April 2009: EMA approval of PCV 10
- December 2009: EMA approval of PCV 13 (children)
- October 2011: EMA approval of PCV13 (Adults 50 years and older)
- 2013: EMA approval of PCV13 (alle ages 6 weeks and older)
- August 2015: Change to 2+1 schedule, 2, 4, 11-14 months.

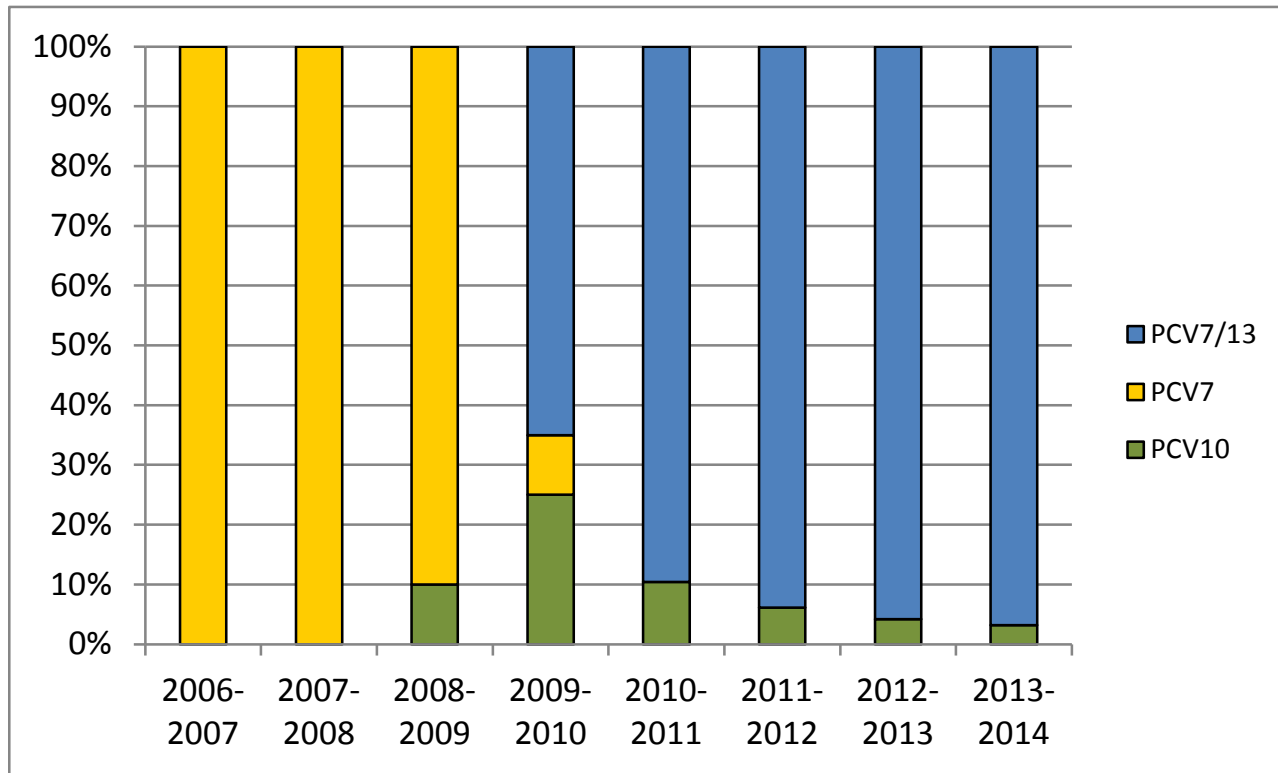
Children



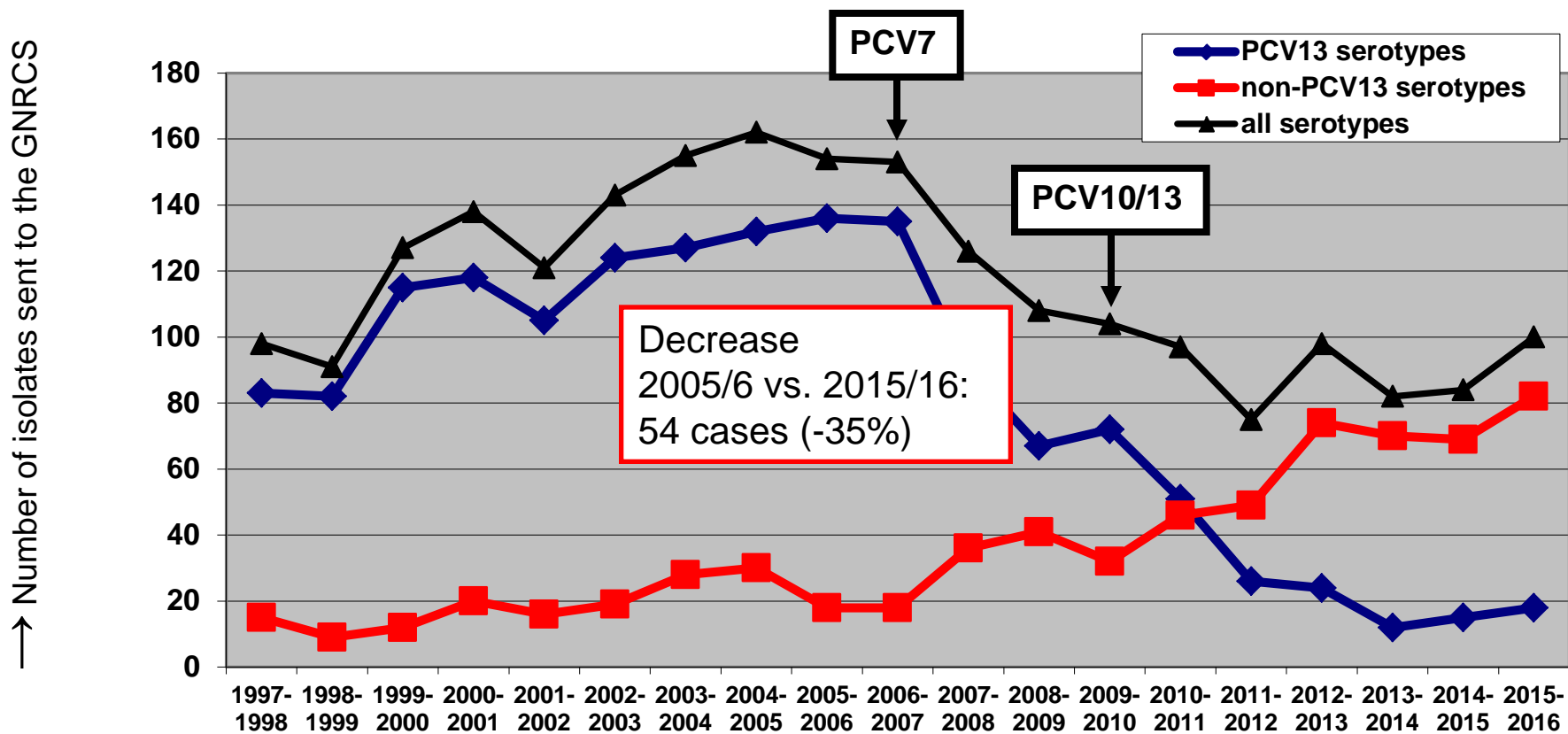
Isolates from children (0 - <16 y.) with invasive pneumococcal disease (IPD) 1997-2016



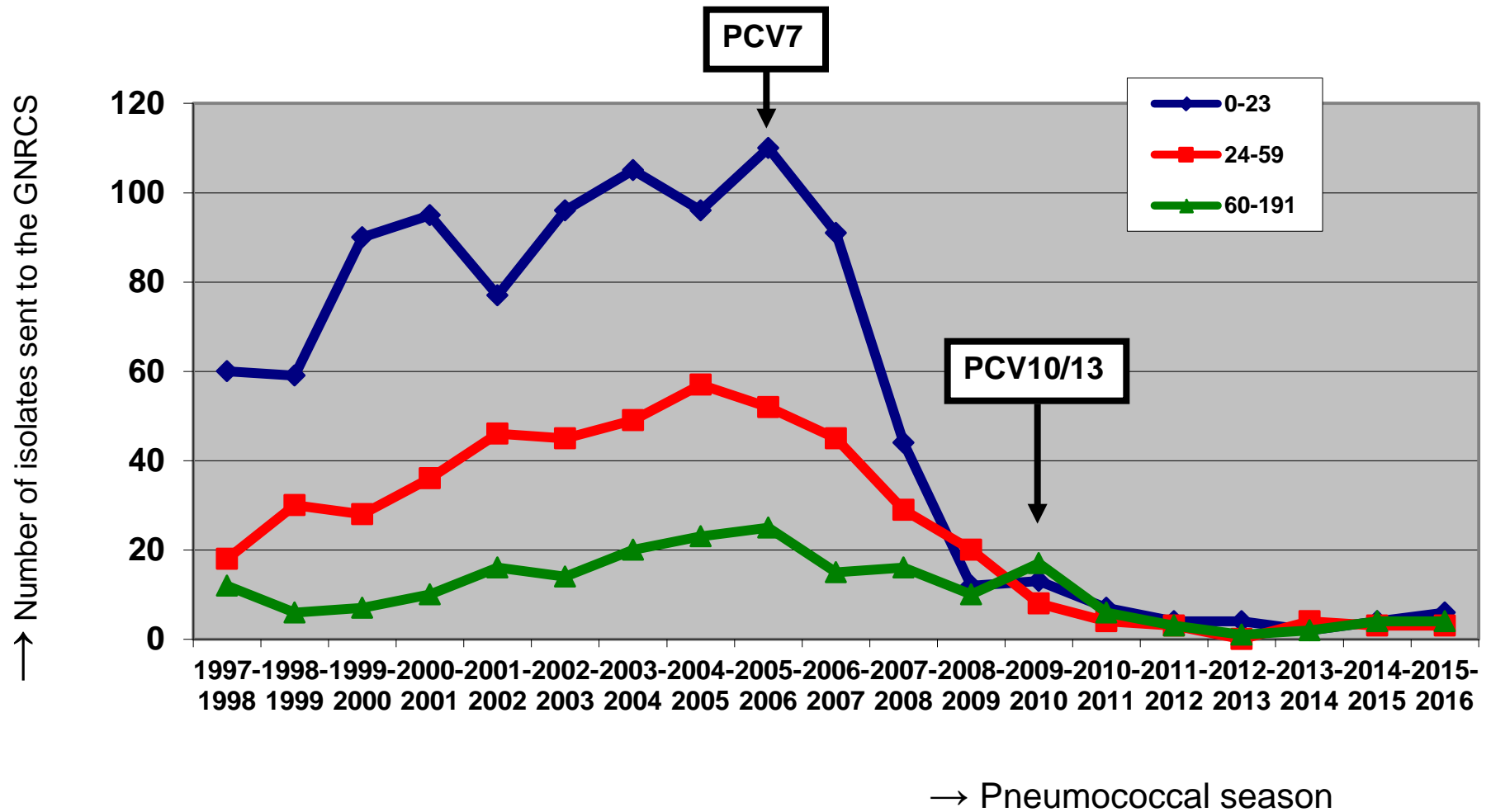
Vaccine sales in Germany 2006-2014



Effects of pneumococcal conjugate vaccination on IPD in children <2 y. in Germany

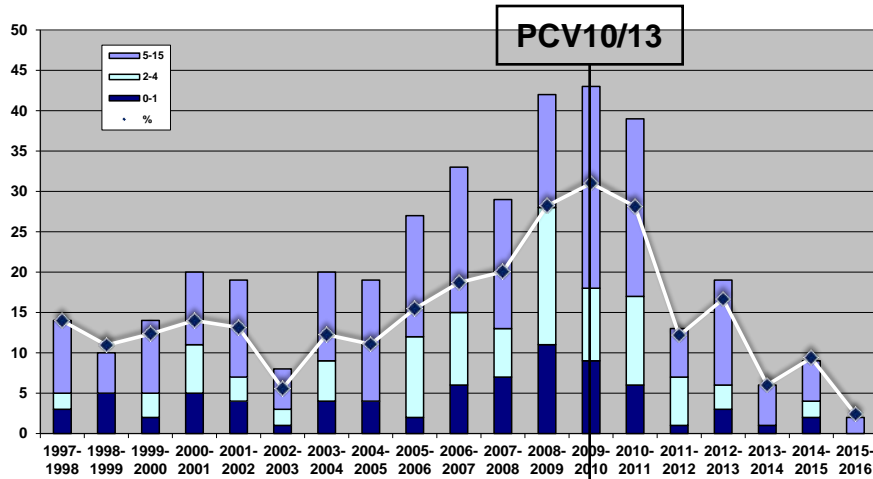


IPD caused by PCV7 serotypes among children <2 y. in Germany

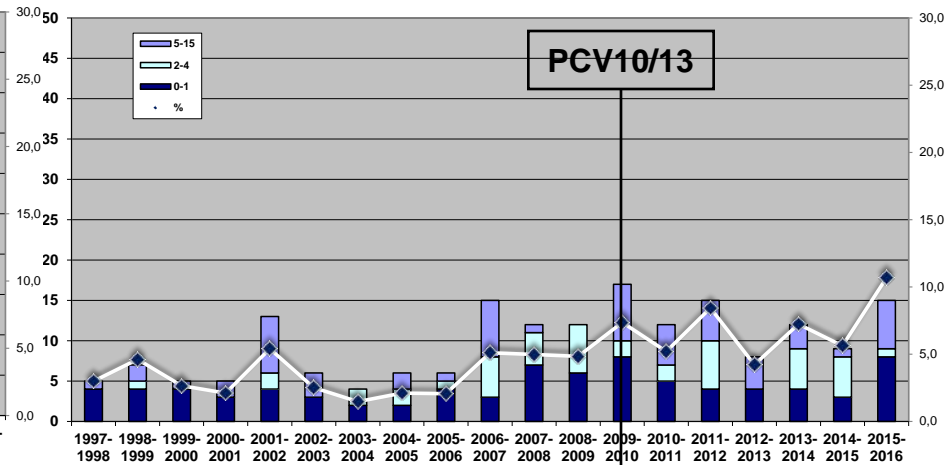


IPD caused by serotypes 1, 3, 7F and 19A

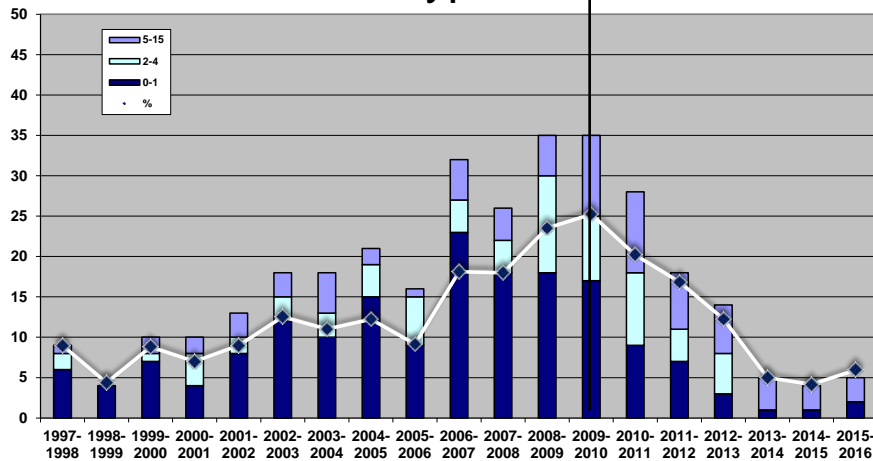
Serotype 1



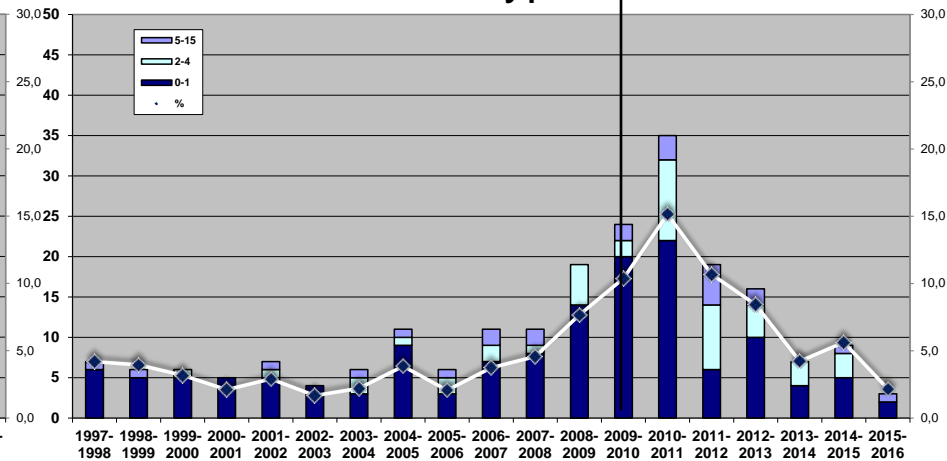
Serotype 3



Serotype 7F



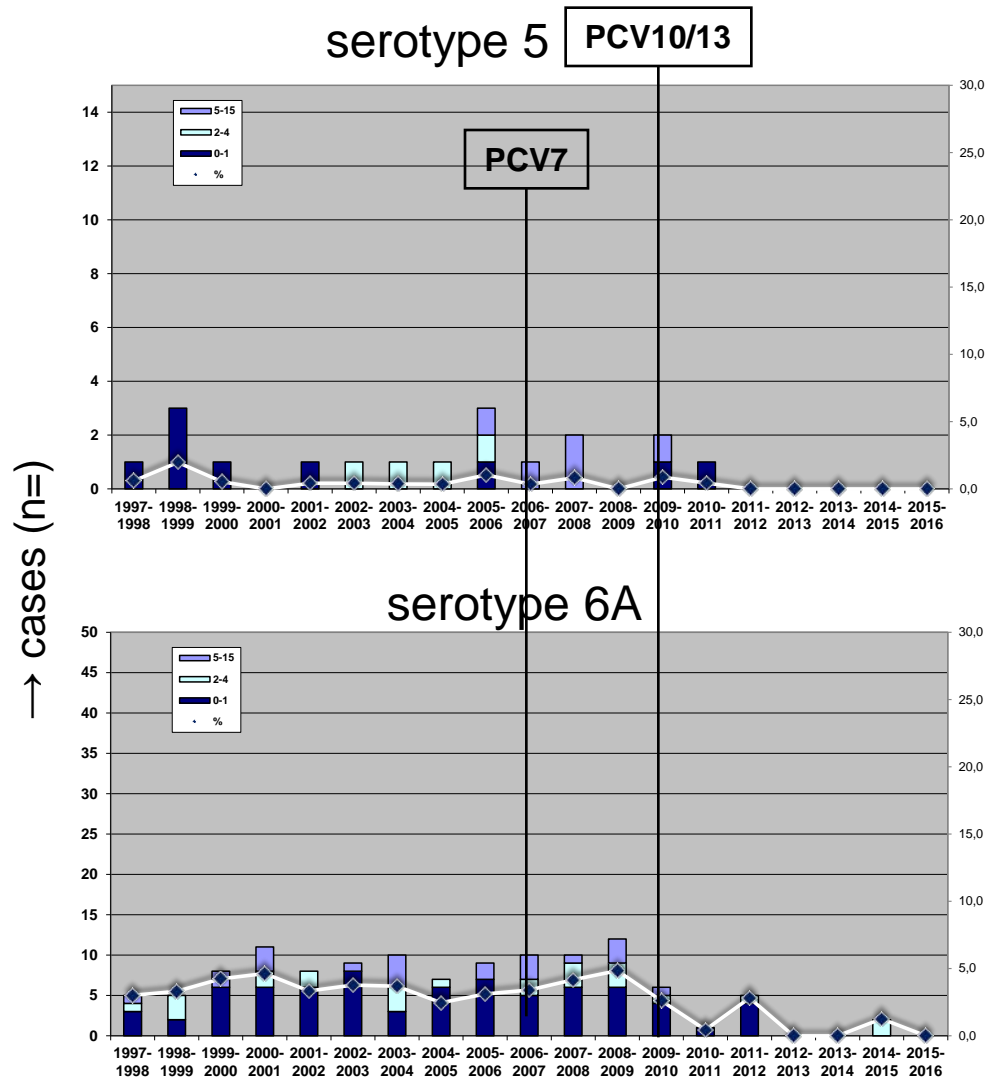
Serotype 19A



→ Pneumococcal season

→ Cases (n=)

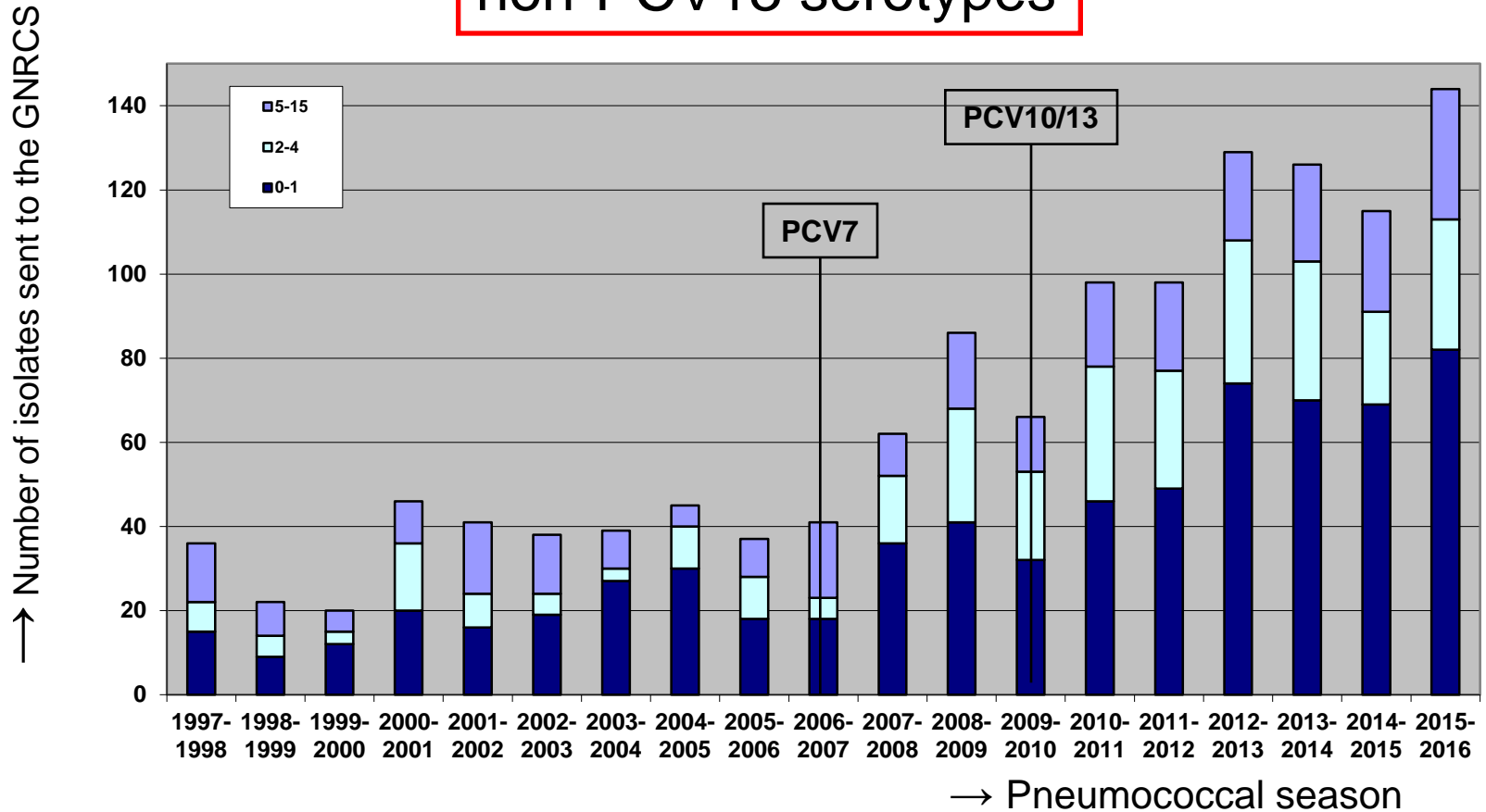
IPD caused by serotypes 5 and 6A



→ Pneumococcal season

IPD among children <2 y. with non-PCV13 serotypes (per season)

non-PCV13 serotypes

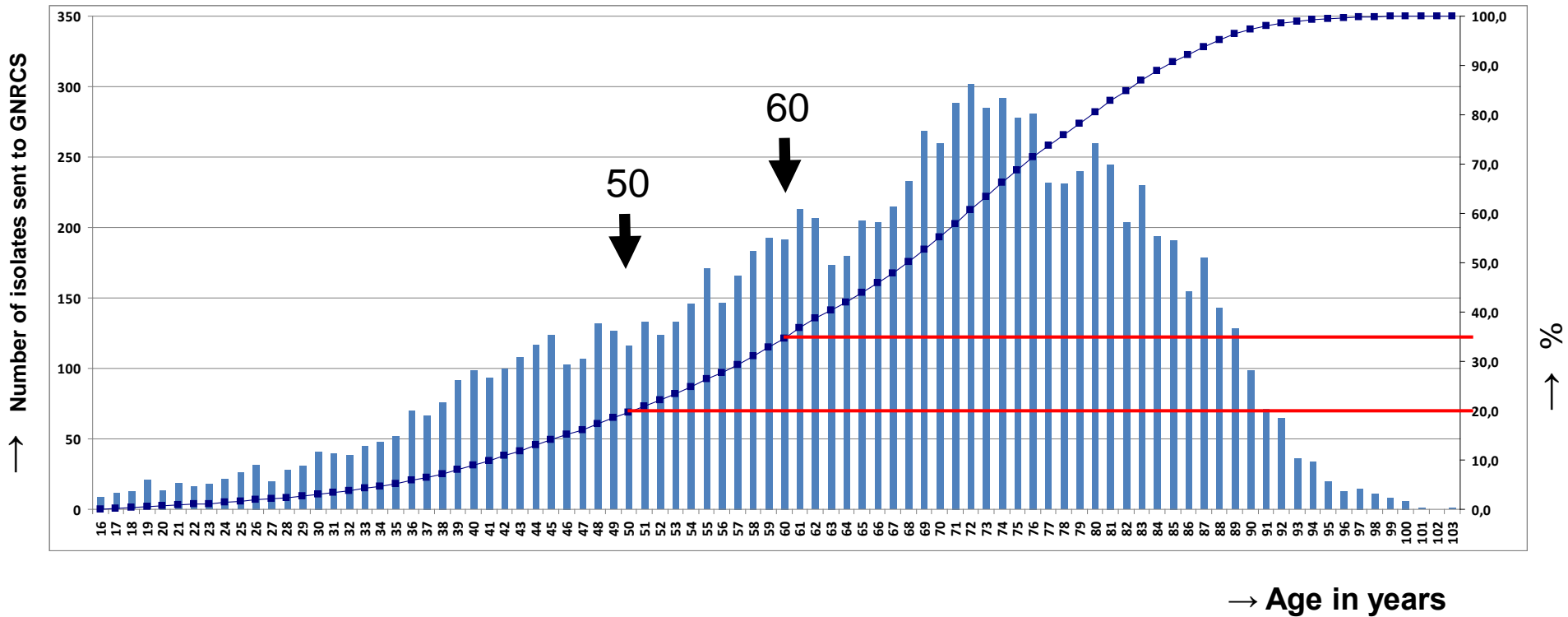


Adults

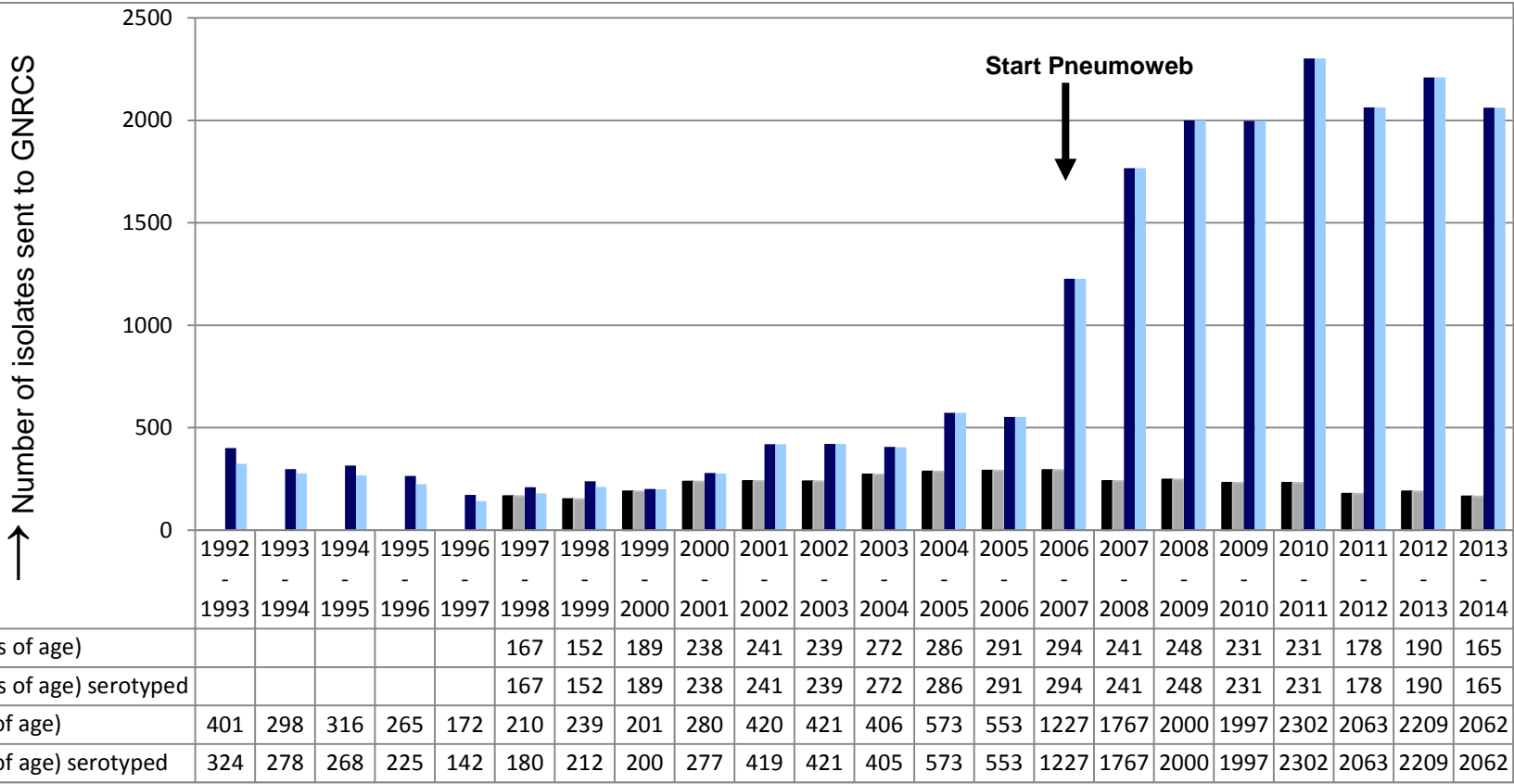


Age distribution IPD adults

- 2008-2013, n=10,567-

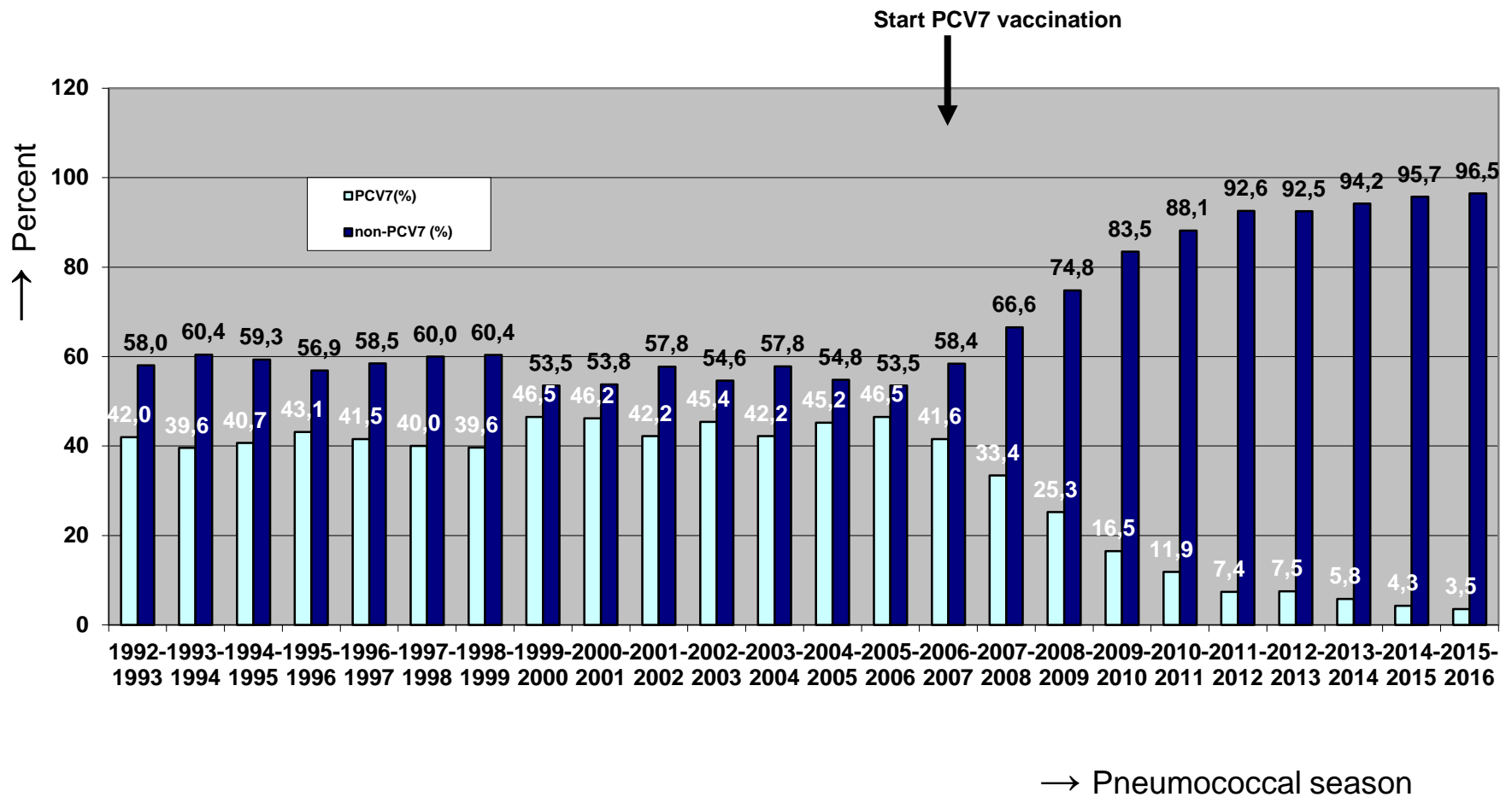


Reported cases of IPD among adults

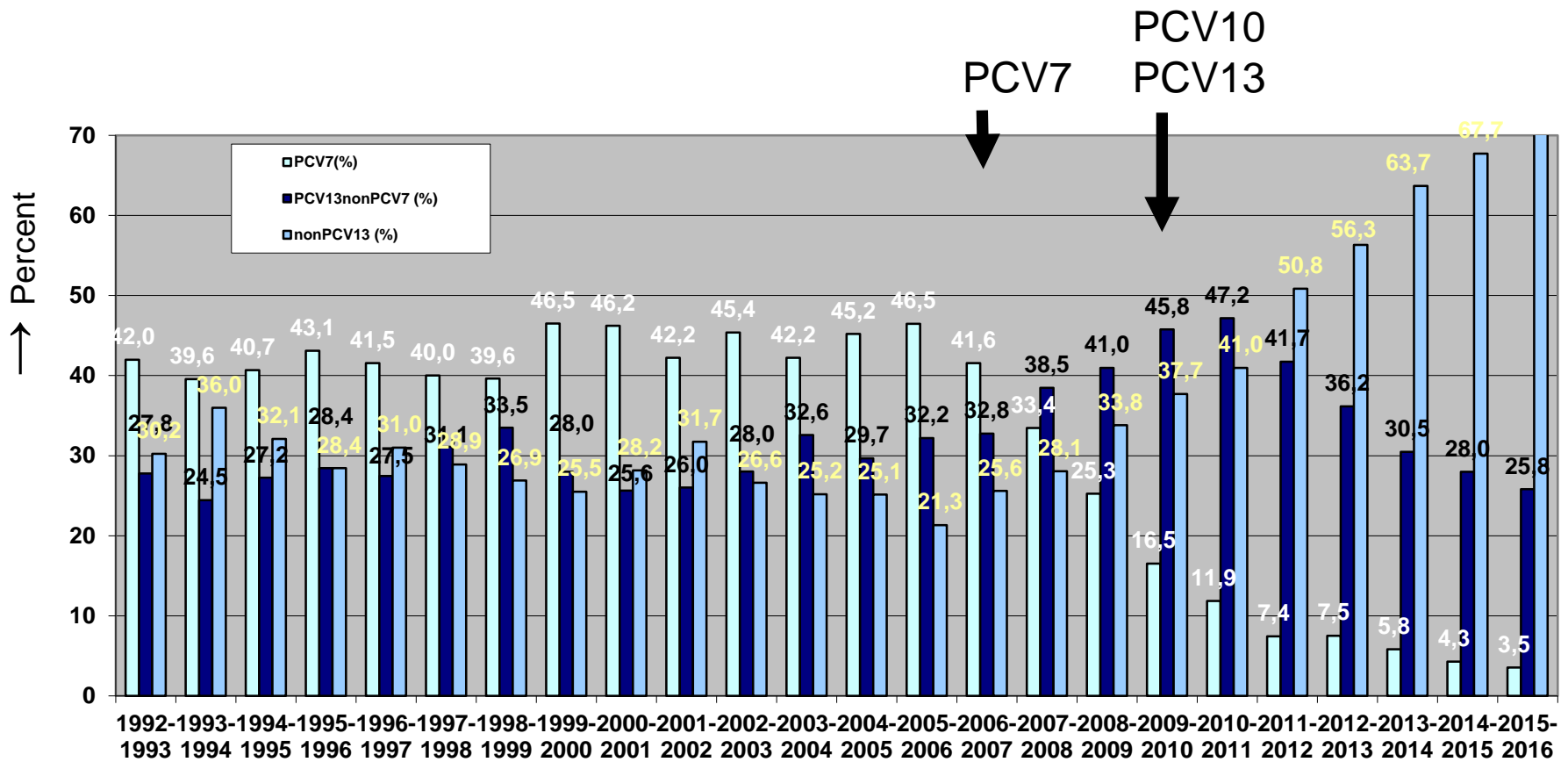


→ Pneumococcal season

Herd protection effect PCV7 on IPD among adults



Herd protection effect PCV7 and PCV13 on IPD among adults

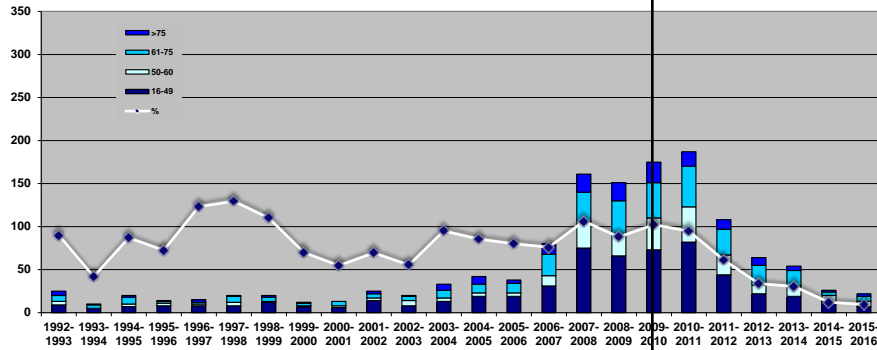


→ Pneumococcal season

IPD caused by serotypes 1, 3, 7F and 19A

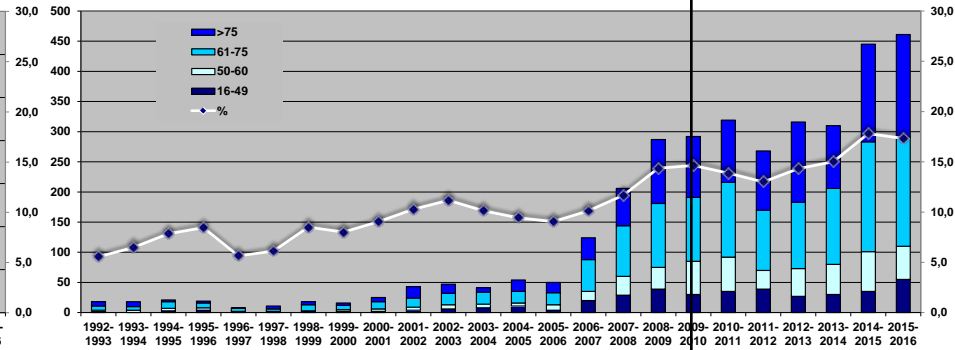
Serotype 1

PCV10/13

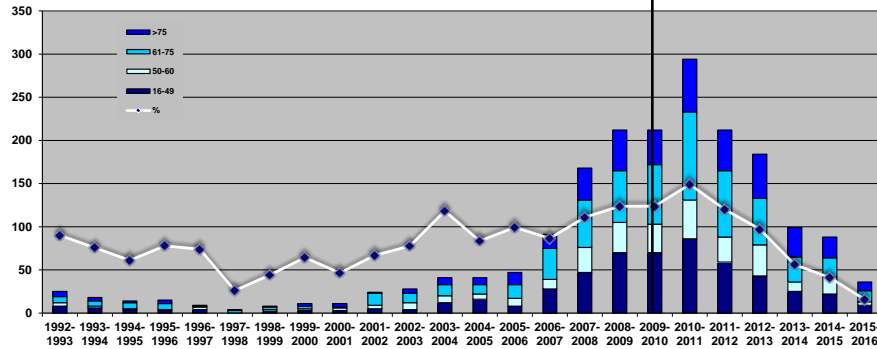


Serotype 3

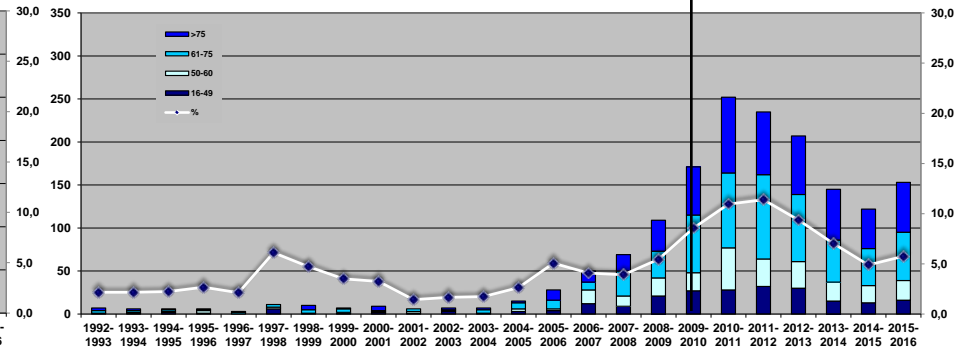
PCV10/13



Serotype 7F



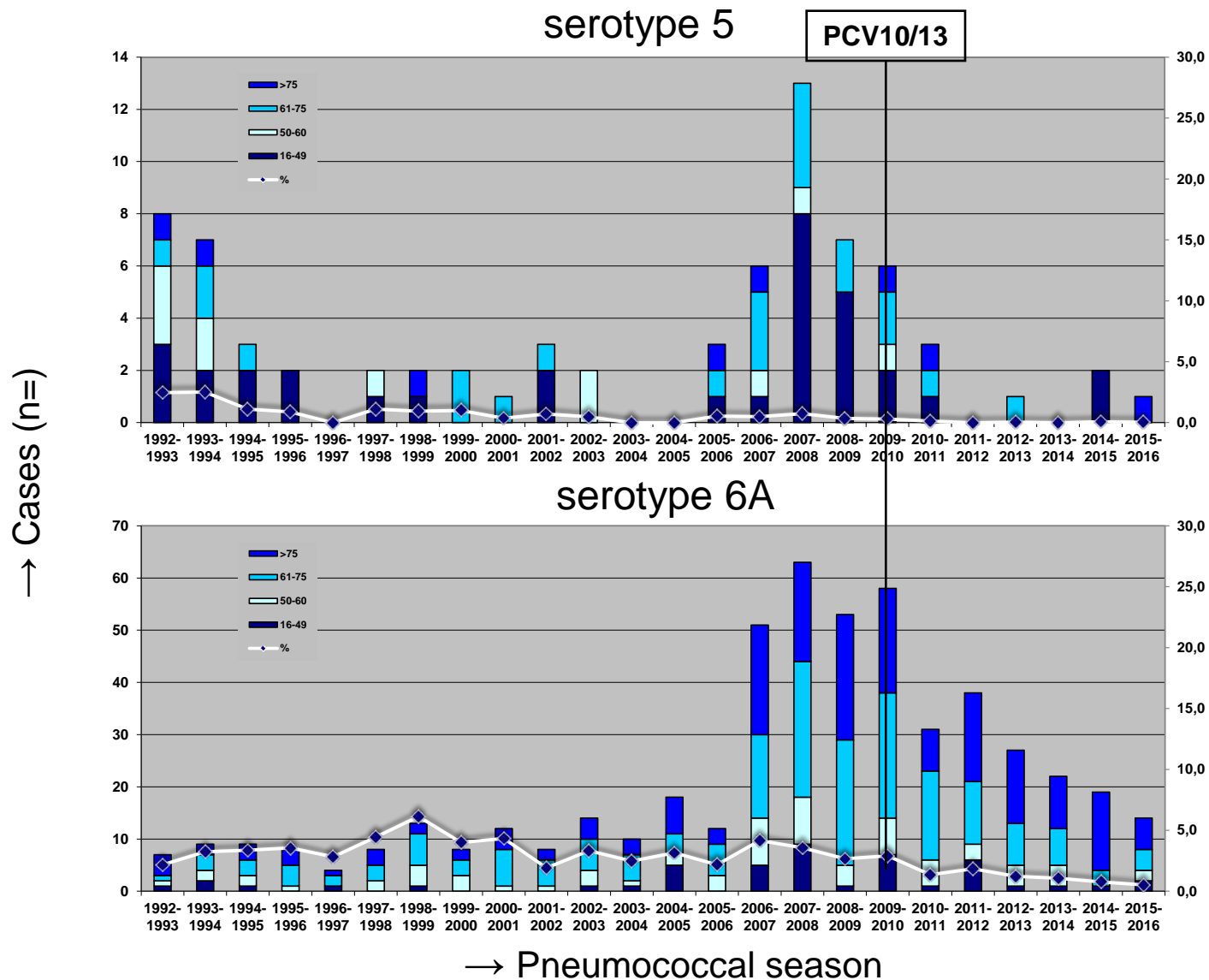
Serotype 19A



→ Pneumococcal season

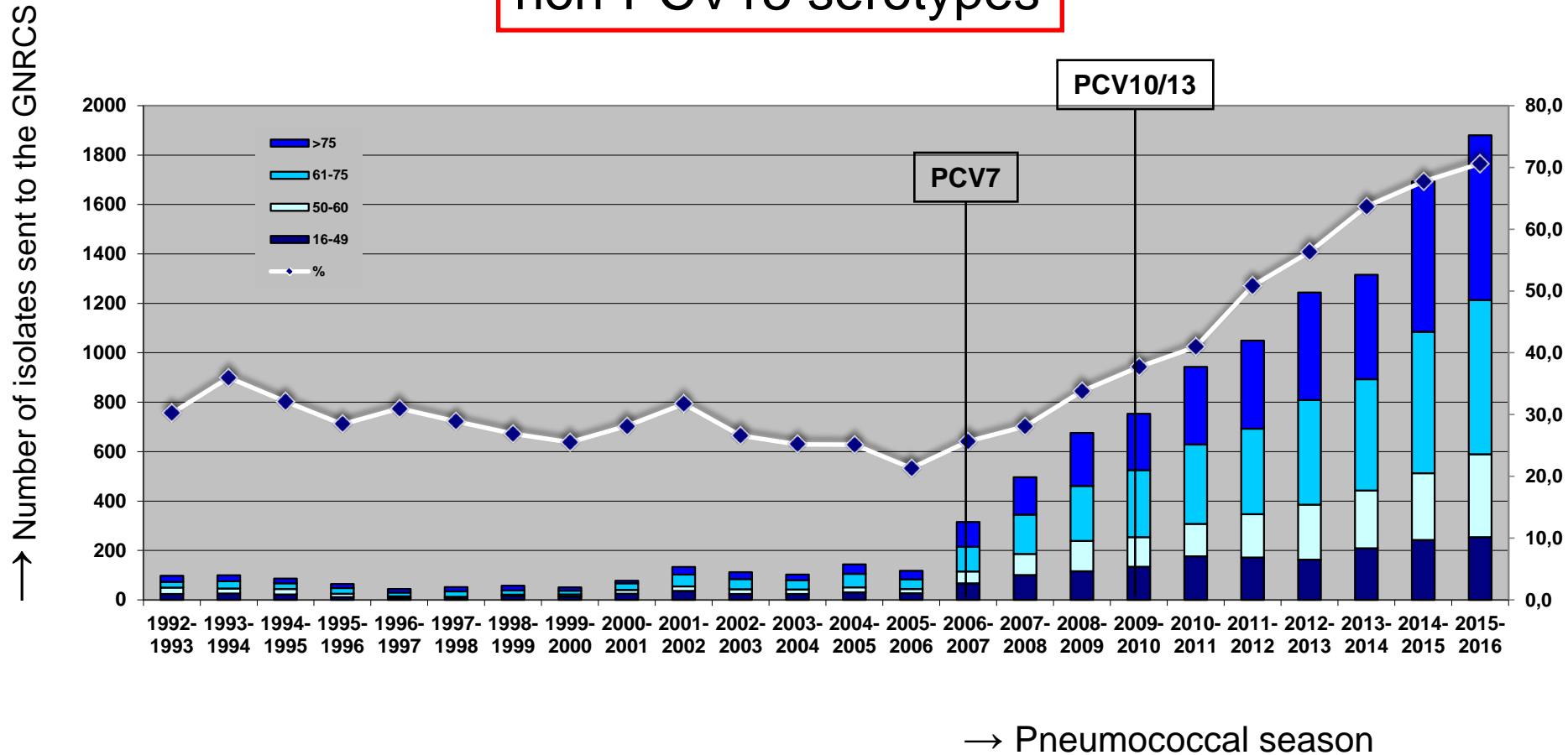
→ Cases (n=)

IPD caused by serotypes 5 and 6A



IPD among adults ≥ 16 y. with non-PCV13 serotypes (per season)

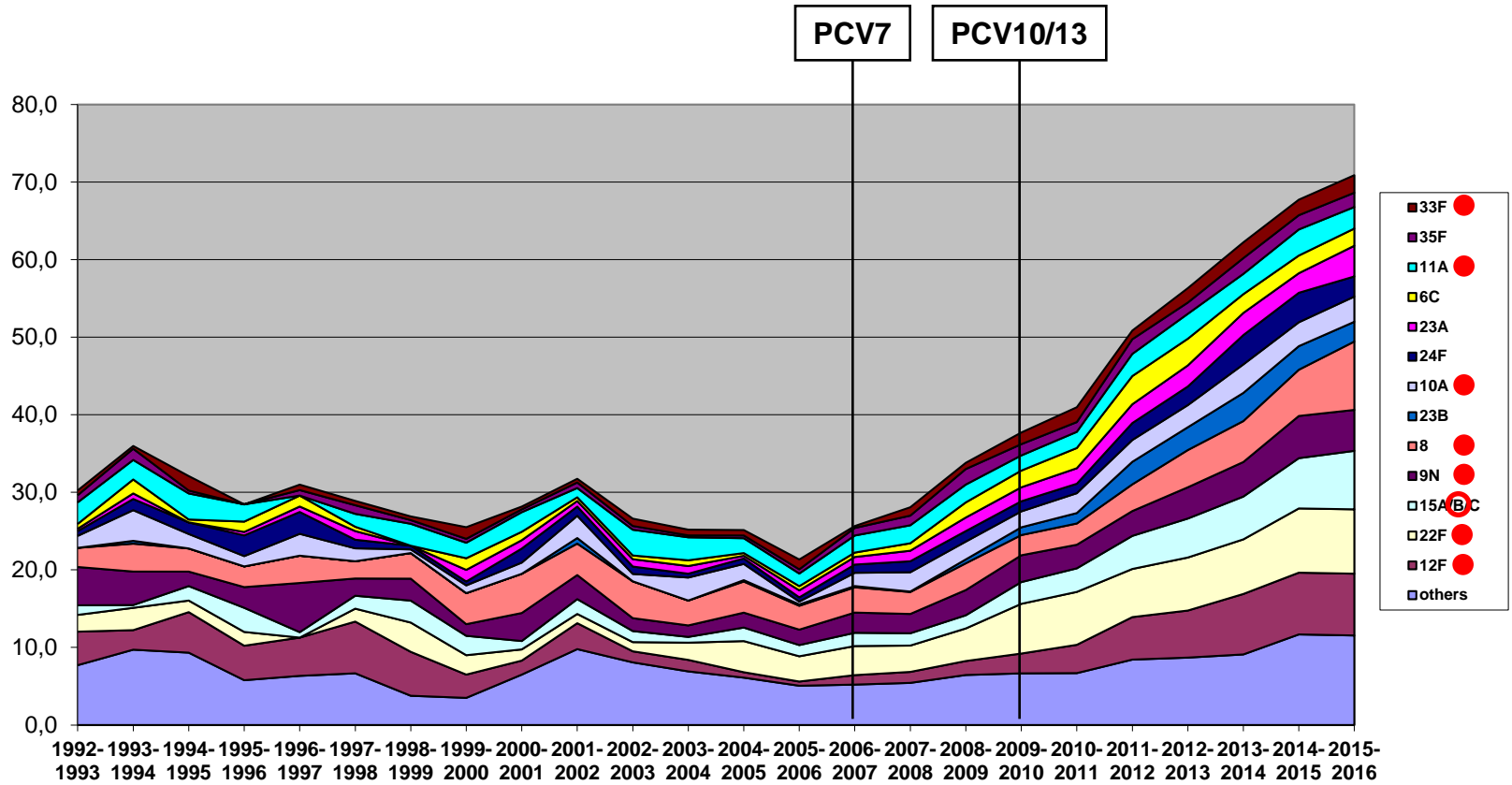
non-PCV13 serotypes



IPD caused by non-PCV13 serotypes

- Adults >16 y. -

→ Cases non-PCV13 serotypes (%)

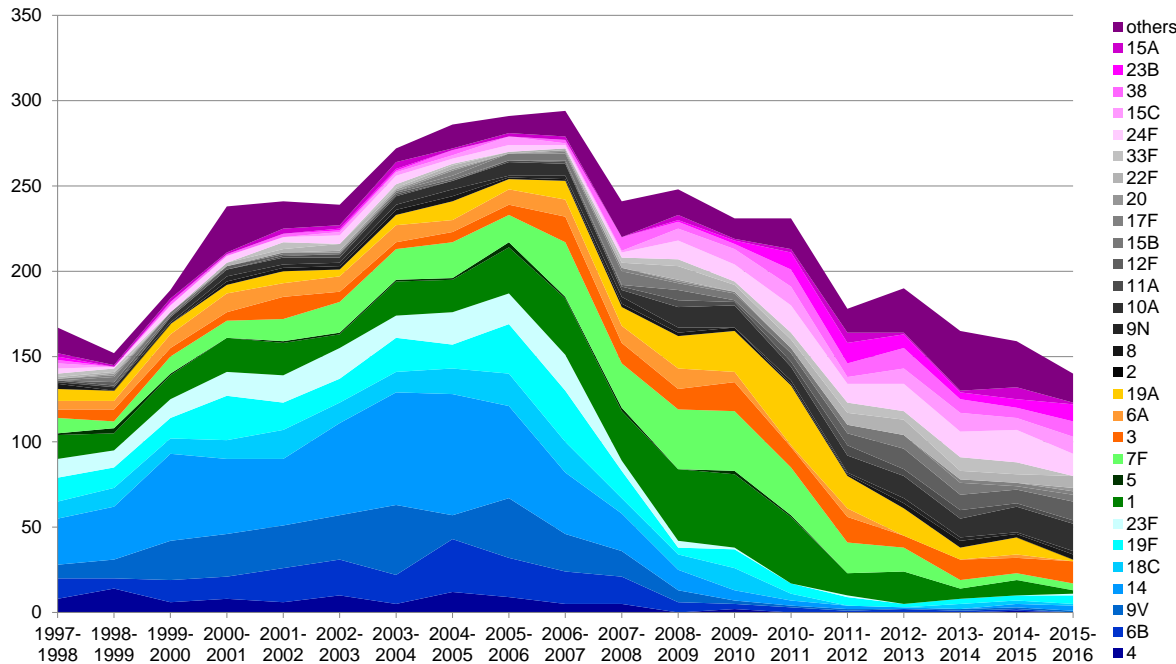


→ Pneumococcal season

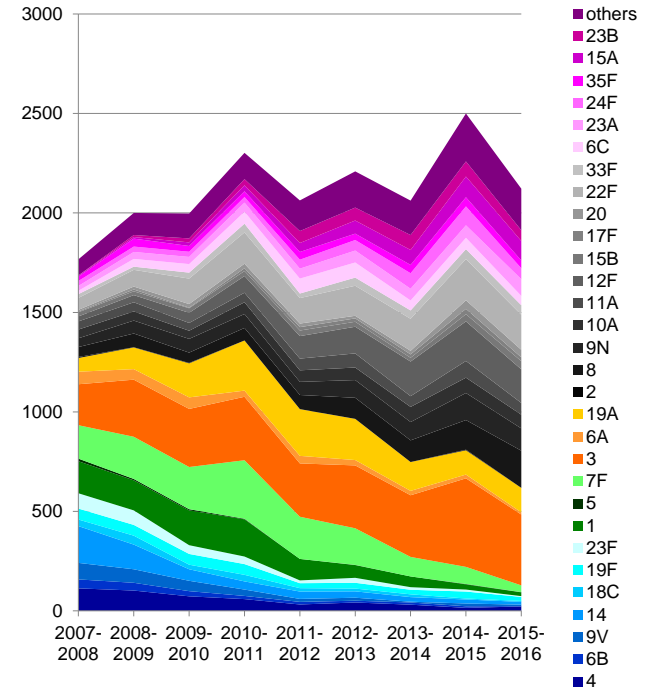
What will happen after higher valent
vaccination?

What will happen after higher valent vaccination?

Children



Adults



Serotype distribution of IPD cases among children (1997–2016) and adults (2007–2016) in Germany.

Most prevalent serotypes among children (IPD, <16 years)

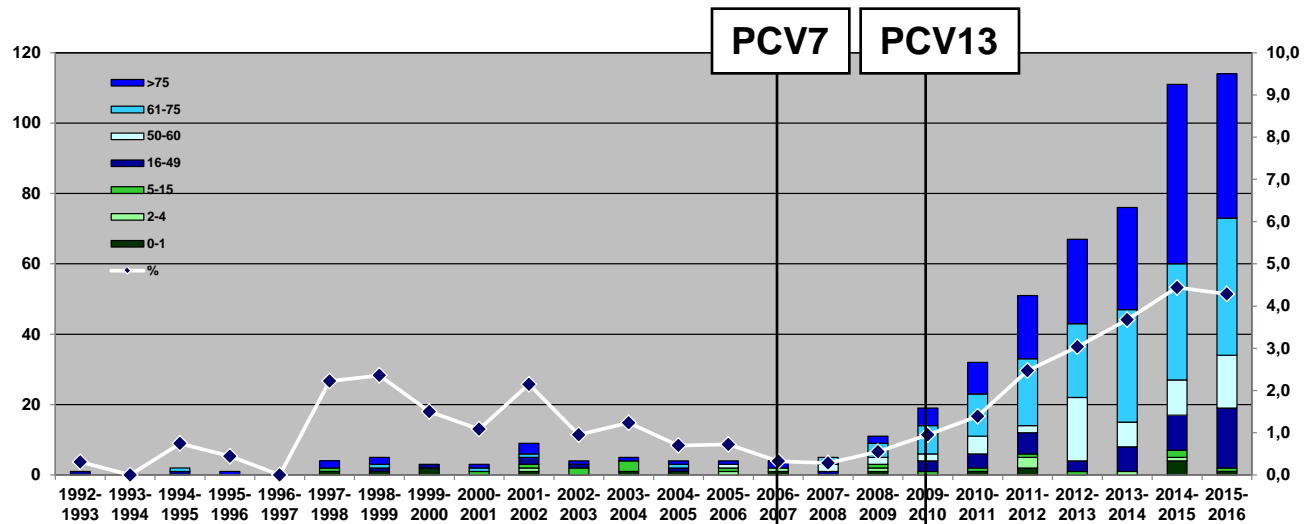
Serotype	average 1997-2006	%	Serotype	2012-2013	%	Serotype	2013-2014	%	Serotype	2014-2015	%	Serotype	2015-2016	%
total	231	100,0	total	190	100,0	total	166	100,0	total	159	100,0	total	182	100,0
PPV23	201	87,0	PPV23	118	62,1	PPV23	92	55,4	PPV23	86	54,1	PPV23	108	59,3
PCV13	195	84,4	PCV13	61	32,1	PCV13	38	22,9	PCV13	44	27,7	PCV13	38	20,9
PCV10	174	75,3	PCV10	38	20,0	PCV10	19	11,4	PCV10	23	14,5	PCV10	20	11,0
PCV7	142	61,5	PCV7	5	2,6	PCV7	8	4,8	PCV7	10	6,3	PCV7	13	7,1
14	49	21,2	1	19	10,0	24F	15	9,0	24F	19	11,9	10A	24	13,2
9V	23	10,0	19A	16	8,4	3	12	7,2	10A	15	9,4	3	15	8,2
19F	17	7,4	24F	16	8,4	10A	12	7,2	19A	10	6,3	12F	15	8,2
6B	17	7,4	7F	14	7,4	15C	11	6,6	1	9	5,7	24F	14	7,7
1	17	7,4	10A	13	6,8	12F	9	5,4	3	9	5,7	15C	13	7,1
23F	14	6,1	38	12	6,3	38	8	4,8	12F	8	5,0	23B	12	6,6
7F	13	5,6	12F	12	6,3	33F	8	4,8	15A	7	4,4	38	10	5,5
18C	13	5,6	15C	9	4,7	19A	7	4,2	15C	7	4,4	22F	10	5,5
4	9	3,9	22F	9	4,7	15B	7	4,2	33F	7	4,4	19F	6	3,3
6A	8	3,5	15B	8	4,2	1	6	3,6	38	6	3,8	15B	6	3,3
19A	6	2,6	23B	8	4,2	7F	5	3,0	23A	6	3,8	7F	5	2,7
3	6	2,6	3	7	3,7	34	5	3,0	22F	5	3,1	8	5	2,7
10A	4	1,7	33F	5	2,6	11A	5	3,0	23B	5	3,1	9N	4	2,2
24F	4	1,7	21	4	2,1	22F	5	3,0	35F	5	3,1	14	3	1,6
9A	2	0,9	11A	4	2,1	6C	5	3,0	7F	4	2,5	19A	3	1,6
9N	2	0,9	35B	4	2,1	8	4	2,4	35B	4	2,5	23A	3	1,6
15A	2	0,9	8	3	1,6	23A	4	2,4	19F	3	1,9	35B	3	1,6
8	2	0,9	6C	3	1,6	23B	4	2,4	14	2	1,3	6C	3	1,6
15B	2	0,9	9N	3	1,6	35F	4	2,4	18C	2	1,3	18C	2	1,1
15C	2	0,9	6B	2	1,1	18C	3	1,8	6A	2	1,3	1	2	1,1
18B	2	0,9	19F	2	1,1	19F	3	1,8	8	2	1,3	20	2	1,1
22F	2	0,9	34	2	1,1	28F	3	1,8	21	2	1,3	21	2	1,1
5	1	0,4	37	2	1,1	35B	3	1,8	34	2	1,3	31	2	1,1
38	1	0,4	23A	2	1,1	37	2	1,2	11A	2	1,3	11A	2	1,1

Most prevalent serotypes among adults (IPD, ≥16 years)

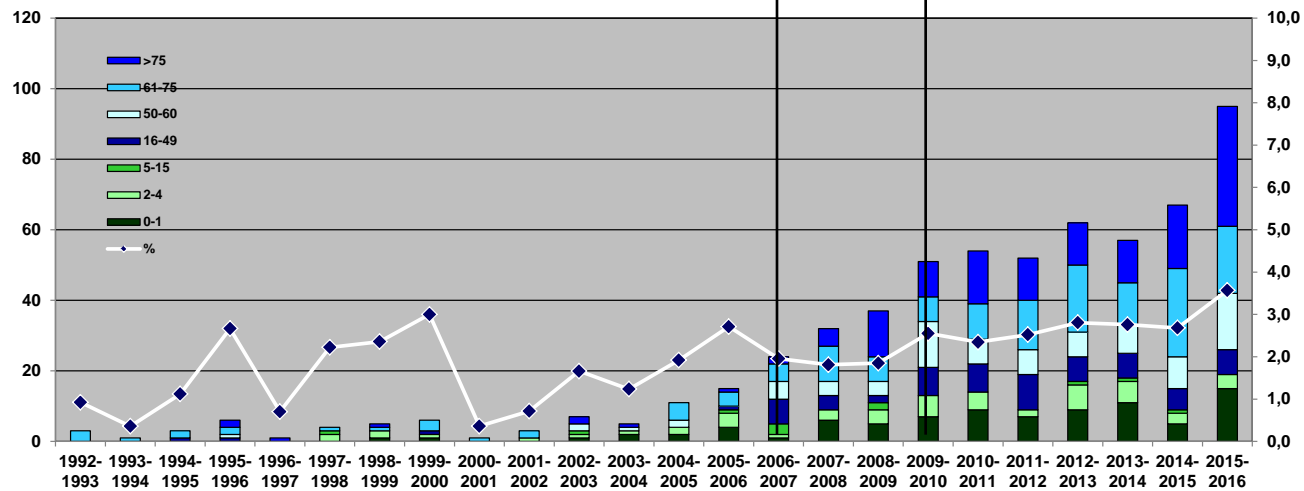
Serotype	all 1992-2006	%	Serotype	2012-2013	%	Serotype	2013-2014	%	Serotype	2014-2015	%	Serotype	2015-2016	%
all	4477	100,0	total	2209	100,0	total	2066	100,0	total	2500	100,0	total	2661	100,0
PPV23	3911	87,4	PPV23	1648	74,6	PPV23	1492	72,2	PPV23	1799	72,0	PPV23	1900	71,4
PCV13	3238	72,3	PCV13	965	43,7	PCV13	750	36,3	PCV13	807	32,3	PCV13	781	29,3
PCV10	2581	57,7	PCV10	415	18,8	PCV10	273	13,2	PCV10	221	8,8	PCV10	153	5,7
PCV7	1943	43,4	PCV7	166	7,5	PCV7	120	5,8	PCV7	107	4,3	PCV7	94	3,5
14	591	13,2	3	316	14,3	3	310	15,0	3	445	17,8	3	461	17,3
3	389	8,7	19A	207	9,4	12F	176	8,5	22F	207	8,3	8	242	9,1
4	368	8,2	7F	184	8,3	22F	161	7,8	12F	199	8,0	22F	218	8,2
1	307	6,9	22F	151	6,8	19A	145	7,0	8	149	6,0	12F	211	7,9
7F	296	6,6	12F	134	6,1	8	109	5,3	9N	136	5,4	19A	153	5,7
9V	286	6,4	8	106	4,8	7F	99	4,8	19A	122	4,9	9N	138	5,2
23F	257	5,7	9N	89	4,0	9N	92	4,5	15A	104	4,2	15A	112	4,2
6B	183	4,1	6C	76	3,4	24F	78	3,8	24F	95	3,8	23A	105	3,9
8	160	3,6	11A	71	3,2	10A	76	3,7	7F	86	3,4	10A	79	3,0
19F	153	3,4	15A	66	3,0	15A	75	3,6	11A	84	3,4	23B	76	2,9
6A	140	3,1	23B	65	2,9	23B	75	3,6	10A	77	3,1	11A	74	2,8
19A	128	2,9	1	64	2,9	23A	59	2,9	23B	76	3,0	24F	66	2,5
12F	120	2,7	10A	63	2,9	1	54	2,6	23A	63	2,5	6C	60	2,3
9N	119	2,7	23A	60	2,7	11A	54	2,6	6C	57	2,3	33F	56	2,1
18C	105	2,3	24F	53	2,4	6C	50	2,4	33F	50	2,0	38	51	1,9
22F	103	2,3	4	42	1,9	33F	42	2,0	35F	46	1,8	31	50	1,9
11A	101	2,3	33F	41	1,9	35F	42	2,0	20	43	1,7	35F	50	1,9
10A	80	1,8	14	32	1,4	35B	34	1,6	35B	42	1,7	20	47	1,8
24F	47	1,0	35B	32	1,4	4	31	1,5	31	40	1,6	15B	45	1,7
20	38	0,8	35F	32	1,4	38	25	1,2	15B	36	1,4	7F	36	1,4
5	35	0,8	19F	29	1,3	14	24	1,2	19F	35	1,4	35B	35	1,3
33F	35	0,8	38	28	1,3	16F	24	1,2	16F	32	1,3	15C	31	1,2
6C	32	0,7	6A	27	1,2	19F	23	1,1	38	29	1,2	16F	28	1,1
23A	31	0,7	16F	27	1,2	31	23	1,1	17F	27	1,1	19F	27	1,0

Strongly increasing serotypes 15A, 15B/C

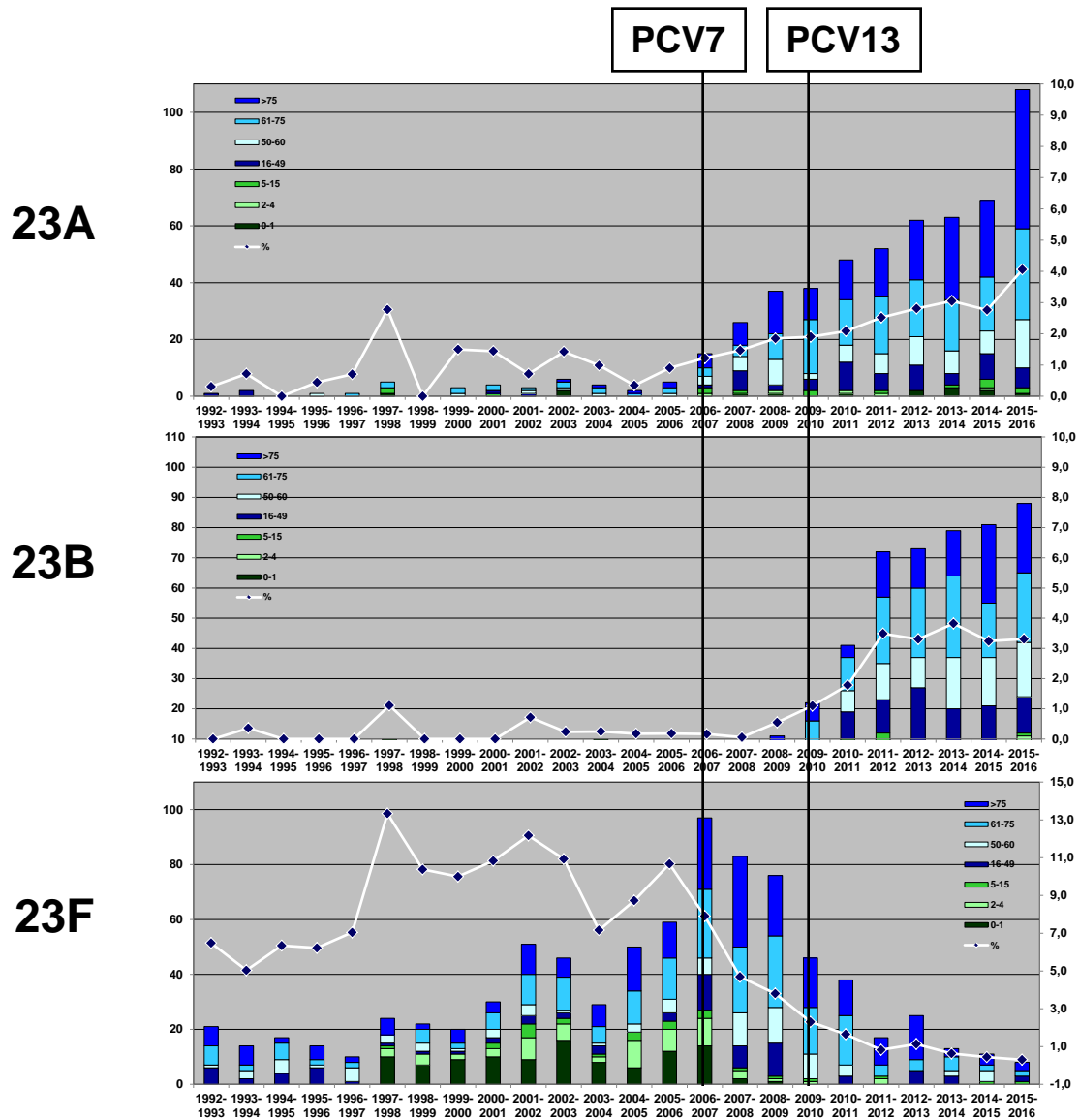
15A



15B/C



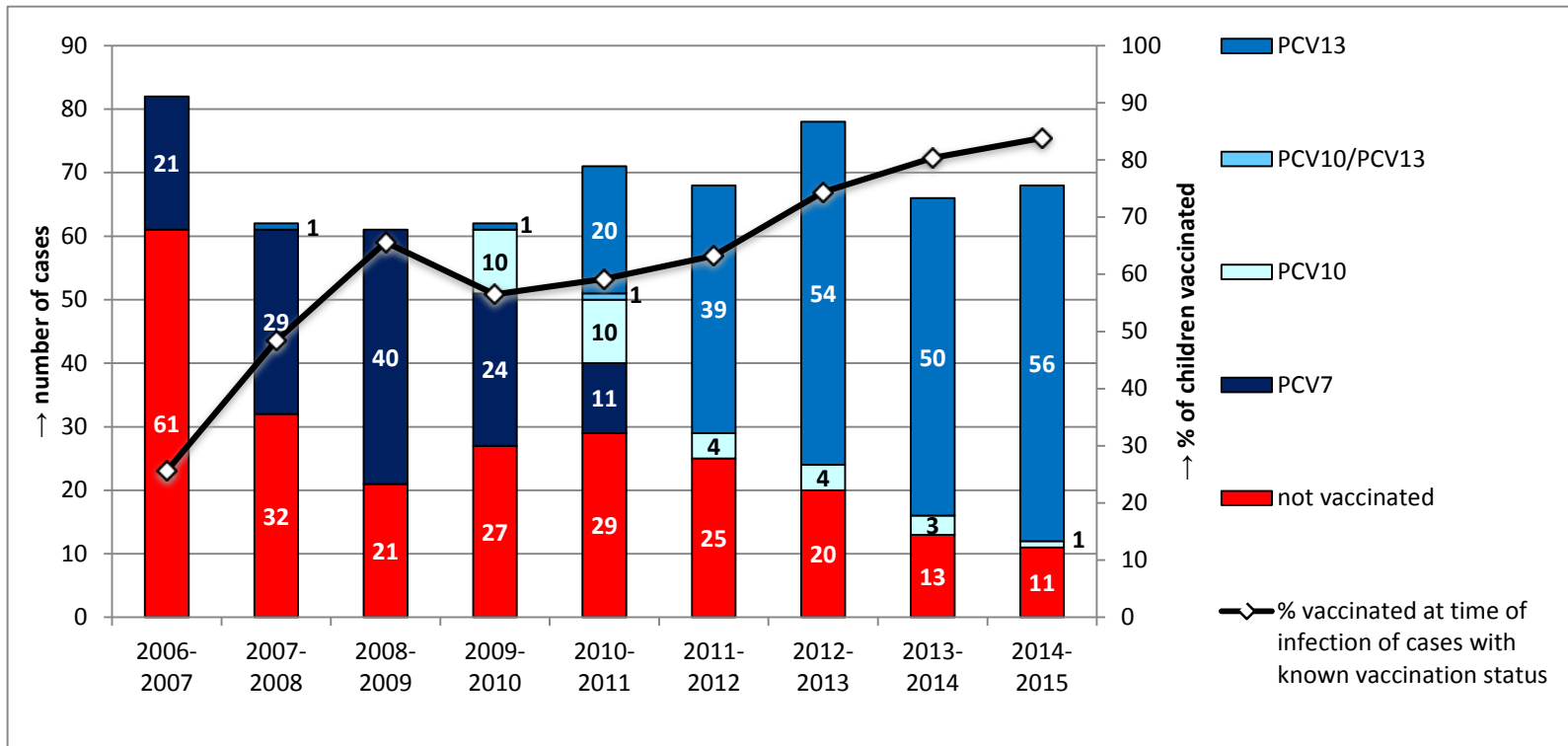
Strongly increasing serotypes 23A, 23B



Vaccination Effectiveness
and
Vaccination Compliance

Study on Vaccine Effectiveness (VE) Pfizer IIR

- July 2006 until June 2015
- 921 IPD cases
- vaccination status for 618 children (67.1%)
- 379 (61.3%) vaccinated, 239 (38.7%) not vaccinated



Vaccine Effectiveness PCV7 (2006-2010)

2006-2010		cases vaccinated: unvaccinated	controls vaccinated: unvaccinated	crude vaccine effectiveness (95% CI)	adjusted vaccine effectiveness (95% CI)
PCV7 serotypes + 6A					
	at least one dose	20:94	94:60	84% (72 to 91)	80% (63 to 89)
	post primary	1:49	38:27	98% (91 to 100)	97% (89 to 100)
	post booster	0:44	11:19	98% (84 to 100)	95% (57 to 100)
Serotype 4					
	at least one dose	0:1	94:60	79% (-307 to 100)	70% (-636 to 100)
	post primary	0:1	38:27	76% (-364 to 100)	51% (-1088 to 100)
	post booster	0:1	11:19	44% (-1054 to 100)	-86% (-50978 to 99) [†]
Serotype 6B					
	at least one dose	2:20	94:60	92% (74 to 98)	90% (66 to 98)
	post primary	0:15	38:27	98% (82 to 100)	97% (72 to 100)
	post booster	0:14	11:19	94% (48 to 100)	85% (-89 to 100)
Serotype 9V					
	at least one dose	0:4	94:60	93% (32 to 100)	89% (-13 to 100)
	post primary	0:2	38:27	86% (-85 to 100)	83% (-158 to 100)
	post booster	0:2	11:19	66% (-367 to 100)	-16% (-18054 to 99) [†]
Serotype 14					
	at least one dose	2:24	94:60	93% (79 to 99)	90% (68 to 98)
	post primary	0:12	38:27	97% (77 to 100)	97% (71 to 100)
	post booster	0:15	11:19	95% (52 to 100)	89% (-20 to 100)
Serotype 18C					
	at least one dose	4:6	94:60	56% (-52 to 88)	8% (-239 to 76)
	post primary	0:3	38:27	90% (-11 to 100)	79% (-137 to 100)
	post booster	0:4	11:19	81% (-103 to 100)	66% (-635 to 100)
Serotype 19F					
	at least one dose	5:11	94:60	69% (14 to 90)	55% (-34 to 87)
	post primary	1:6	38:27	84% (15 to 98)	73% (-44 to 97)
	post booster	0:4	11:19	81% (-103 to 100)	72% (-301 to 100)
Serotype 23F					
	at least one dose	3:8	94:60	74% (11 to 94)	61% (-62 to 92)
	post primary	0:6	38:27	95% (50 to 100)	89% (-23 to 100)
	post booster	0:3	11:19	76% (-184 to 100)	33% (-9761 to 100)
Serotype 6A					
	at least one dose	4:7	94:60	62% (-26 to 90)	73% (1 to 93)
	post primary	0:4	38:27	92% (21 to 100)	91% (8 to 100)
	post booster	0:1	11:19	43% (-1054 to 100)	74% (-478 to 100)

* Serotype 6A is not included in PCV7, but antibodies against serotype 6B are crossprotective towards 6A.

† This value can not be strictly interpreted due to insufficient number of events

Vaccine Effectiveness PCV13 (2010-2015)

2010-2015		cases vaccinated: unvaccinated	controls vaccinated: unvaccinated	crude vaccine effectiveness (95% CI)	adjusted vaccine effectiveness (95% CI)
PCV13 serotypes					
	at least one dose	25:55	194:43	90% (82 to 94)	86% (74 to 93)
	post primary	10:22	74:20	87% (70 to 95)	85% (62 to 94)
	post booster	2:13	33:16	91% (65 to 98)	91% (61 to 99)
PCV13-non-PCV7 serotypes					
	at least one dose	23:43	194:43	88% (78 to 93)	82% (66 to 91)
	post primary	10:16	74:20	82% (57 to 93)	80% (46 to 93)
	post booster	2:12	33:16	90% (62 to 98)	90% (54 to 98)
PCV7 serotypes in PCV13					
	at least one dose	2:12	194:43	96% (84 to 99)	94% (78 to 99)
	post primary	0:6	74:20	98% (81 to 100)	99% (80 to 100)
	post booster	0:1	33:16	84% (-225 to 100)	83% (-240 to 100)
Serotype 1					
	at least one dose	2:5	194:43	90% (56 to 98)	83% (15 to 97)
	post primary	1:2	74:20	84% (-31 to 99)	49% (-614 to 96)
	post booster	0:1	33:16	84% (-225 to 100)	82% (-328 to 100)
Serotype 3					
	at least one dose	6:5	194:43	74% (10 to 92)	74% (2 to 93)
	post primary	1:2	74:20	84% (-31 to 99)	80% (-68 to 98)
	post booster	1:2	33:16	70% (-140 to 97)	63% (-393 to 97)
Serotype 5					
	at least one dose	0:0	194:43		
	post primary	0:0	74:20		
	post booster	0:0	33:16		
Serotype 6A					
	at least one dose	0:4	194:43	95% (55 to 100)	96% (56 to 100)
	post primary	0:1	74:20	91% (-78 to 100)	84% (-214 to 100)
	post booster	0:2	33:16	90% (-30 to 100)	84% (-224 to 100)
Serotype 7F					
	at least one dose	1:12	194:43	97% (88 to 100)	84% (18 to 98)
	post primary	0:2	74:20	95% (29 to 100)	86% (-116 to 100)
	post booster	0:0	33:16	51% (-9185 to 100)	32% (-8066 to 99)
Serotype 19A					
	at least one dose	14:17	194:43	81% (60 to 92)	77% (47 to 90)
	post primary	8:9	74:20	75% (30 to 92)	73% (18 to 92)
	post booster	1:7	33:16	90% (49 to 99)	88% (25 to 99)

Vaccination status of children <2 y. with IPD with PCV13 serotype

2011-2016		
Vaccination status	n=	%
unvaccinated	57	60,6
incomplete	17	18,1
according to age	13	13,8
unknown	7	7,4
Total	94	100,0

2015-2016

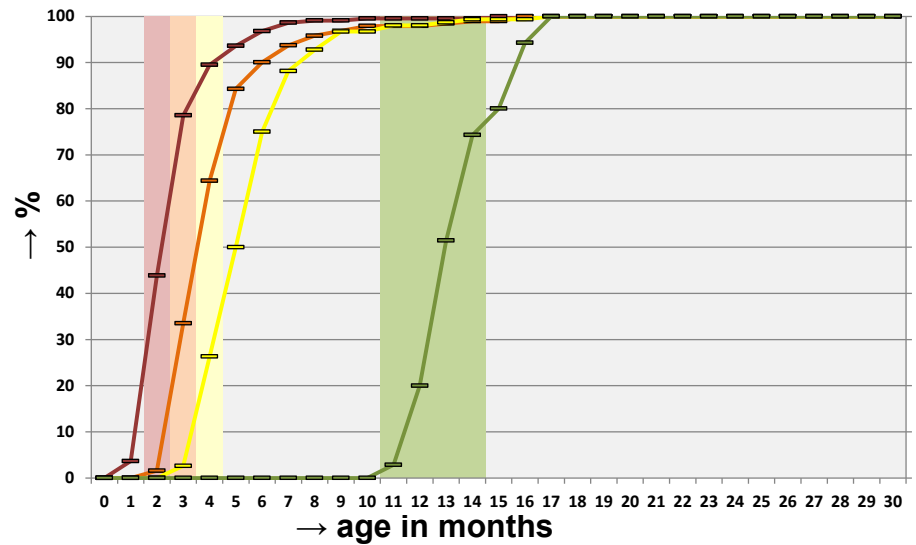
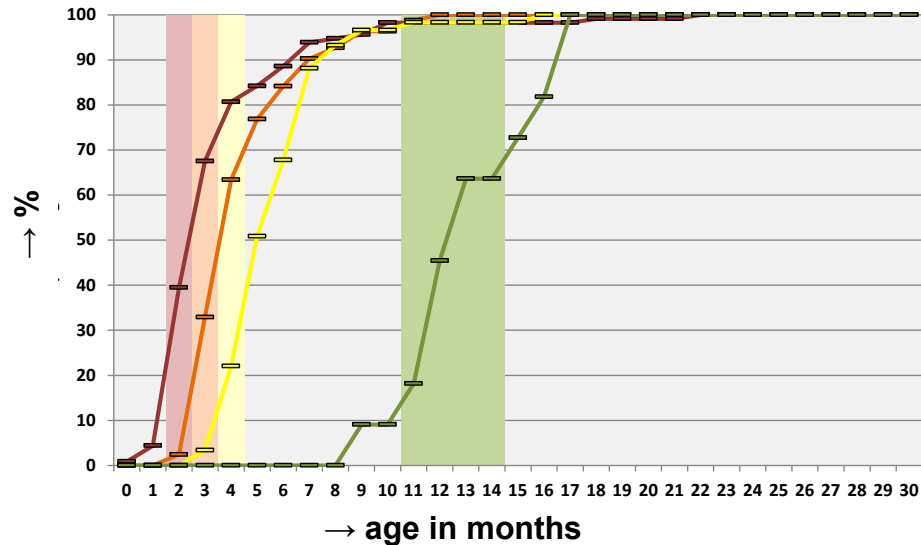
Study	Number	Local number	Diagnosis	Age in Months	SeroType	Vaccination status	Conclusion
RKI	5143	68872	meningitis	1	3	not vaccinated	not vaccinated
RKI	5265	70842		14	3	not vaccinated	not vaccinated
RKI	5333	72140		3	3	not vaccinated	not vaccinated
RKI	5201	69822	pneumonia, pleuritis, pleuraempyema	7	3	PCV10	vaccinated acc. to age
RKI	5284	71385	pneumonia	23	3	PCV13	vaccinated acc. to age
RKI	5357	72462	sepsis	22	3	PCV13	vaccinated acc. to age (2+1 schedule)
RKI	5119	68364		1	3	unknown	
RKI	5214	70152	otitis media, mastoiditis	3	3	unknown	
RKI	5135	68712	pneumonia	20	14	not vaccinated	not vaccinated
RKI	5336	72184	otitis media, pneumonia	21	19A	PCV13	vaccinated acc. to age
RKI	5372	72752	pneumonia	13	19A	PCV13	vaccinated acc. to age (no booster)
RKI	5228	70435		0	19F	not vaccinated	not vaccinated
RKI	5242	70582		1	19F	not vaccinated	not vaccinated
RKI	5205	69880		8	19F	not vaccinated	not vaccinated
RKI	5303	71710		13	19F	unknown	
RKI	5346	72292	unclear cause of death	5	19F	unknown	
RKI	5320-1	71968		5	7F	not vaccinated	not vaccinated
RKI	5126	68589		5	7F	PCV13	one dose 4 days before onset

Administration of PCV doses

- children <2 y. with IPD -

PCV7	administered on time
1st dose	39,5%
2nd dose	32,9%
3rd dose	22,0%
booster	63,6%

PCV13	administered on time
1st dose	43,8%
2nd dose	33,5%
3rd dose	26,3%
booster	74,3%



Conclusions

- Most children in Germany are vaccinated with PCV13 (>95%)
- Pneumococcal conjugate vaccination (PCV7/PCV10/PCV13) shows strong effects on IPD among children
- A strong herd protection effect is observed among adults both for PCV7 serotypes as well as for PCV13-non-PCV7 serotypes
- The herden protection effect is not the same for all serotypes
 - No reduction in IPD caused by serotype 3 among adults

Conclusions

- Non-PCV13 serotypes increase both among children and among adults
 - children: 10A, 12F, 23B, 24F, 38
 - adults: 6C, 12F, 15A, 22F, 23B
- 15A and 23B are strongly increasing and often penicillin non-susceptible
- Vaccine effectiveness for PCV7 and PCV13 is high, including for serotype 3
- Residual PCV13 cases mainly among non-vaccinated or incompletely vaccinated children
- Children in Germany receive their PCV vaccination doses too late. Delay: 2-3 Months

Thank you for your attention!