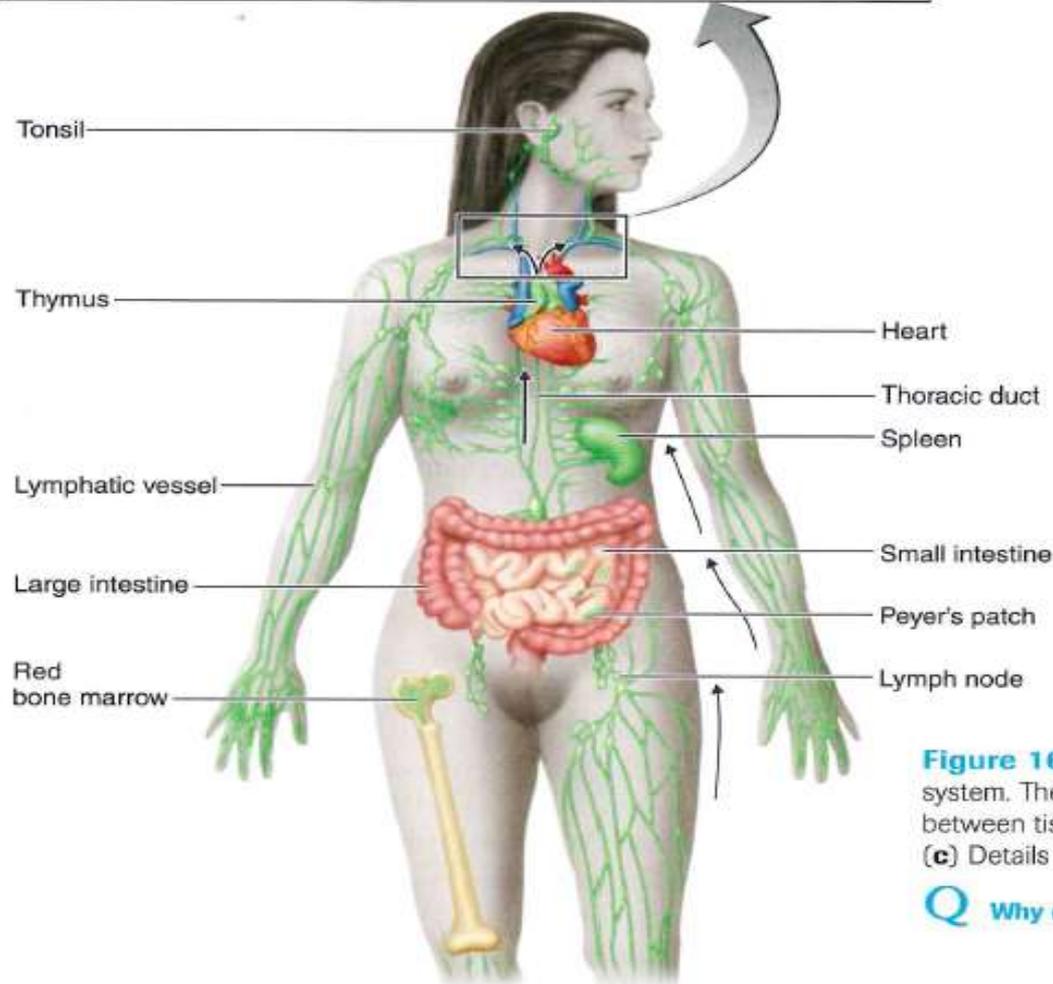
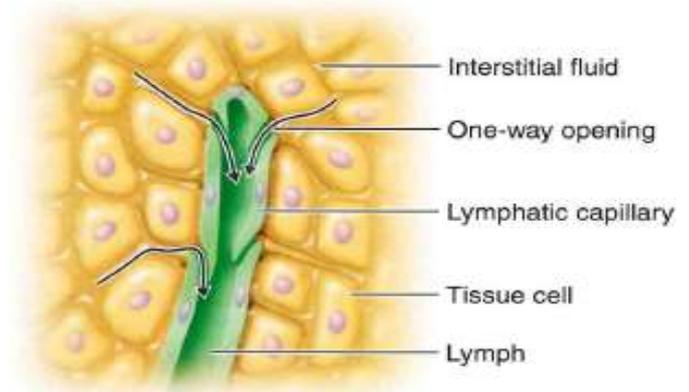


(b) Relationship of lymphatic capillaries to tissue cells and blood capillaries



(a) Components of lymphatic system



(c) Details of a lymphatic capillary

Figure 16.5 The lymphatic system. (a) Components of the lymphatic system. The arrows indicate the direction of lymph flow. (b) Fluid circulating between tissue cells (interstitial fluid) is picked up by lymphatic capillaries. (c) Details of a lymphatic capillary.

Q Why do lymph nodes swell during an infection?

Role of spleen

- Spleen consists of red pulp which is rich in red blood cells and white pulp which consists of organized lymphocytes and phagocytes
- Spleen and lymph nodes: secondary lymphoid organs
 - Macrophages: removal of opsonized microbes from the bloodstream
 - Production of some complement factors like properdin
 - Production of specific opsonizing antibodies → essential for activity of all phagocytic cells (granulocytes, monocytes, macrophages)

Long-term risks after splenectomy

- Spleen is a rediculoendothelial organ with important haemological and immunological functions including clearance of encapsulated bacteria (*Streptococcus pneumoniae*, *Neisseria meningitidis*, *Haemophilus influenzae type b*) and intraerythrocytic parasites (*Plasmodium spp*, *Babesia spp.* ...) from the blood and generation of immune responses to certain pathogens (risk = 0,23 – 0,43% annually, cumulative lifetime risk = 5%)
- Other adverse outcomes after splenectomy = thrombosis and cancer (platelet activation, thrombocytosis, disturbance endothelium, altered lipid profile).

Long-term risks after splenectomy among 8,149 cancer free American veterans

- Cohort study with up to 27 years follow-up, over four million veterans.
- Risk of being hospitalized:

Condition	Splenectomized	Not-splenectomized	RR	95% CI
Pneumococcal pneumonia	347	70647	2.06	1.85 - 2.3
Septicaemia	620	72216	3.88	3.12 - 3.67
Meningitis	40	6439	2.44	1.77 - 3.38
All pneumonias	1648	361053	1.94	1.84 - 2.04
Deep vein thrombosis	451	83460	2.18	1.99 - 2.4
Pulmonary embolisms	252	45420	2.24	1.97 - 2.55
Ischemic stroke	224	99080	1.06	0.93 - 1.21

Long-term risks after splenectomy among 8,149 cancer free American veterans

Type of cancer	Splenectomized	Not-splenectomized	RR	95% CI
Buccal	76	29170	1.26	1.0 – 1.58
Esophagus	32	10311	1.6	1.12 – 2.27
Liver	21	5139	1.88	1.23 – 2.89
Colon	54	12263	1.33	1.01 – 1.76
Pancreas	31	7608	1.87	1.27 – 2.75
Lung	253	102174	1.24	1.0 – 1.4
Prostate	146	653317	1.26	1.06 – 1.48
All leukemias	105	9730	5.2	4.23 – 6.39
All cancer	1094	370716	1.51	1.42 – 1.6

Conditions associated with the highest increased risk of invasive pneumococcal disease.

Category A

- functional or anatomical asplenia
- immunocompromised conditions
 - congenital or acquired immune deficiency
 - immunosuppressive therapy (corticosteroid therapy ≥ 2 mg/kg)
 - haematological and other malignancies
 - solid organ transplant
 - HIV infection
 - chronic renal failure
- proven or presumptive cerebrospinal leak
- cochlear implants
- intracranial shunts

Epidemiology and outcome of invasive pneumococcal disease (2009-2011)

- collaboration of 50 hospitals, 1332 patients

<u>Type of IPD</u>	Total (n=1332)	age group n(%)		
		18-49y (n=220)	50-64y (n=370)	≥65y (n=742)
bacteraemic pneumonia	1049	170(77,3)	276 (74,6)	603 (81,3)
empyema	94	21 (9,5)	32 (8,6)	41 (5,5)
meningitis	73	8 (3,6)	32 (8,6)	33 (4,4)
bacteraemia without focus	73	8 (3,6)	17 (4,6)	48 (6,5)
other	43	13 (5,9)	13 (3,5)	17 (2,3)

J. Verhaegen et al. Eurosurveillance, 2014, 19, 7 August 2014

Epidemiology and outcome of invasive pneumococcal disease (2009-2011)

<u>Comorbidities</u>	age group n			P-value
	18-49y (n=220)	50-64y (n=370)	≥65y (n=742)	
any	118	274	627	<0,0001
COPD	15	89	231	<0,0001
cancer	13	81	203	<0,0001
heart failure	3	40	206	<0,0001
diabetes	11	47	146	<0,0001
renal insufficiency	3	32	144	<0,0001
immunosuppression	21	51	100	0,32
≥2 comorbidities	50 (45%)	154	399 (54%)	≤0,001

J. Verhaegen et al. Eurosurveillance, 2014, 19, 7 August 2014

Category	n	Admission to ICU n (%)	Outcome at discharge			Univariate OLR	
			Cured n (%)	Discharged with persisting symptoms n (%)	Death n (%)	Odds ratio (95% CI)	Overall p value
Total*	1,329	434 (33)	884 (67)	237 (18)	208 (16)	–	–
Age in years							
18–49	219	54 (25)	157 (72)	49 (22)	13 (6)	1	0.044
50–64	370	154 (42)	240 (65)	83 (22)	47 (13)	1.42 (0.98–2.04)	
≥65	740	226 (31)	487 (66)	105 (14)	148 (20)	1.52 (1.10–2.12)	
Type of invasive pneumococcal disease							
Bacteraemic pneumonia	1,049	303 (29)	722 (69)	169 (16)	155 (15)	1	0.0049
Empyema	94	49 (52)	49 (52)	35 (37)	10 (11)	1.61 (1.07–2.45)	
Meningitis	73	59 (81)	38 (52)	16 (22)	19 (26)	2.06 (1.31–3.25)	
Bacteraemia without focus	73	12 (16)	51 (70)	4 (6)	18 (25)	1.12 (0.69–1.84)	
Other (e.g. septic arthritis, endocarditis, or peritonitis)	43	11 (26)	24 (56)	13 (30)	6 (14)	1.53 (0.84–2.79)	

CI: confidence interval; ICU: intensive care unit; OLR: ordinal logistic regression; SD: standard deviation.

* Data missing for three patients.

TABLE 4

Disease outcome at discharge for patients with invasive pneumococcal disease, by comorbidity, Belgium, 2009–2011 (n=1,329)*

Category	n	Outcome at discharge			Univariate OLR		Multivariate OLR	
		Cured n (%)	Discharged with persisting symptoms n (%)	Death n (%)	Odds ratio (95% CI)	P value	Odds ratio (95% CI)	P value
Total*	1,329	884 (67)	237 (18)	208 (16)	–	–	–	–
Comorbidity								
No	313	217 (69)	67 (21)	29 (9)	1	–	–	–
Any	1,016	667 (66)	170 (17)	179 (18)	1.29 (0.98–1.69)	0.067	1.20 (0.91–1.60)	0.20
Number of comorbidities, mean ± SD	1,323	1.43 ± 1.19	1.4 ± 1.22	1.88 ± 1.28	1.18 (1.08–1.29)	0.0004	–	–
COPD	335	226 (68)	56 (17)	53 (16)	0.97 (0.75–1.26)	0.83	0.90 (0.69–1.19)	0.47
Asthma	68	47 (69)	12 (18)	9 (13)	0.88 (0.52–1.48)	0.63	0.88 (0.51–1.51)	0.65
Heart failure	249	141 (57)	44 (18)	64 (26)	1.85 (1.41–2.43)	<0.0001	1.70 (1.26–2.30)	0.0006
Renal insufficiency	179	103 (58)	25 (14)	51 (29)	1.82 (1.34–2.48)	0.0001	1.63 (1.16–2.29)	0.0047
Hepatic disease	104	62 (60)	15 (14)	27 (26)	1.56 (1.05–2.31)	0.027	1.38 (0.91–2.10)	0.13
Immunosuppression	172	116 (67)	28 (16)	28 (16)	0.99 (0.71–1.38)	0.93	0.96 (0.67–1.39)	0.84
HIV infection	24	18 (75)	3 (13)	3 (13)	0.68 (0.27–1.70)	0.41	0.96 (0.37–2.50)	0.93
Cancer	296	192 (65)	48 (16)	56 (19)	1.17 (0.90–1.52)	0.26	1.16 (0.87–1.54)	0.31
Diabetes	203	136 (67)	37 (18)	30 (15)	0.98 (0.72–1.34)	0.91	0.83 (0.59–1.15)	0.26
Asplenia	11	6 (55)	1 (9)	4 (36)	2.15 (0.70–6.55)	0.18	2.18 (0.69–6.87)	0.18
Alcoholism	59	28 (48)	13 (22)	18 (31)	2.37 (1.45–3.86)	0.0006	2.79 (1.65–4.73)	0.0001
Hypertension	78	54 (69)	12 (15)	12 (15)	0.89 (0.55–1.45)	0.65	0.92 (0.56–1.52)	0.74
Smoking	26	21 (81)	4 (15)	1 (4)	0.44 (0.16–1.20)	0.11	0.59 (0.13–1.62)	0.30
Previous IPD	14	7 (50)	4 (29)	3 (21)	1.82 (0.67–4.97)	0.24	1.84 (0.65–5.19)	0.25
Tuberculosis	8	5 (63)	0 (0)	3 (38)	1.68 (0.44–6.37)	0.45	2.04 (0.52–7.91)	0.31
Other	154	101 (66)	29 (19)	24 (16)	1.05 (0.74–1.48)	0.79	1.05 (0.73–1.51)	0.78

CI: confidence interval; COPD: chronic obstructive pulmonary disease; HIV: human immunodeficiency virus; IPD: invasive pneumococcal disease; OLR: ordinal logistic regression; SD: standard deviation.

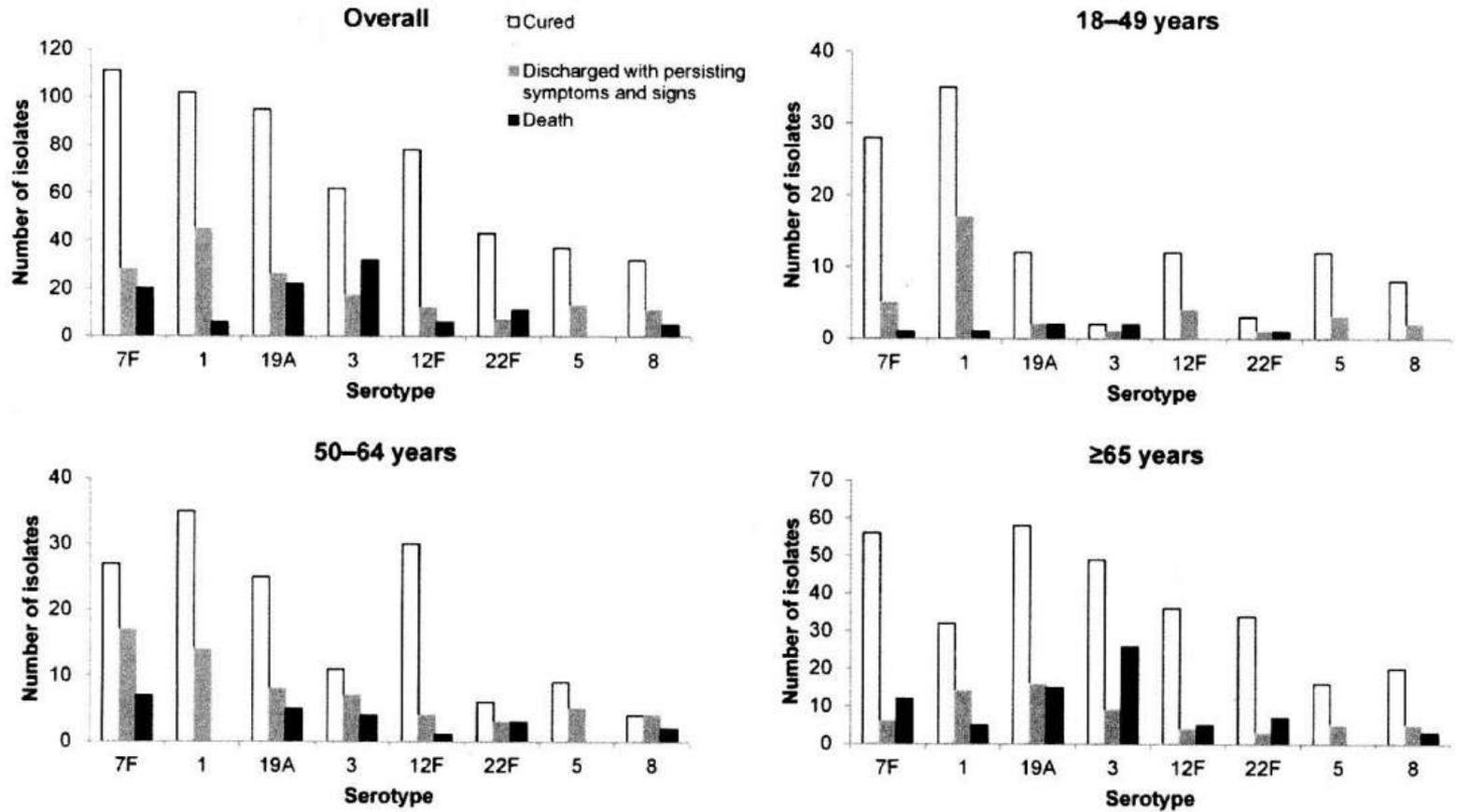
* Data missing for three patients.

Disease outcome at discharge by age and type of IPD

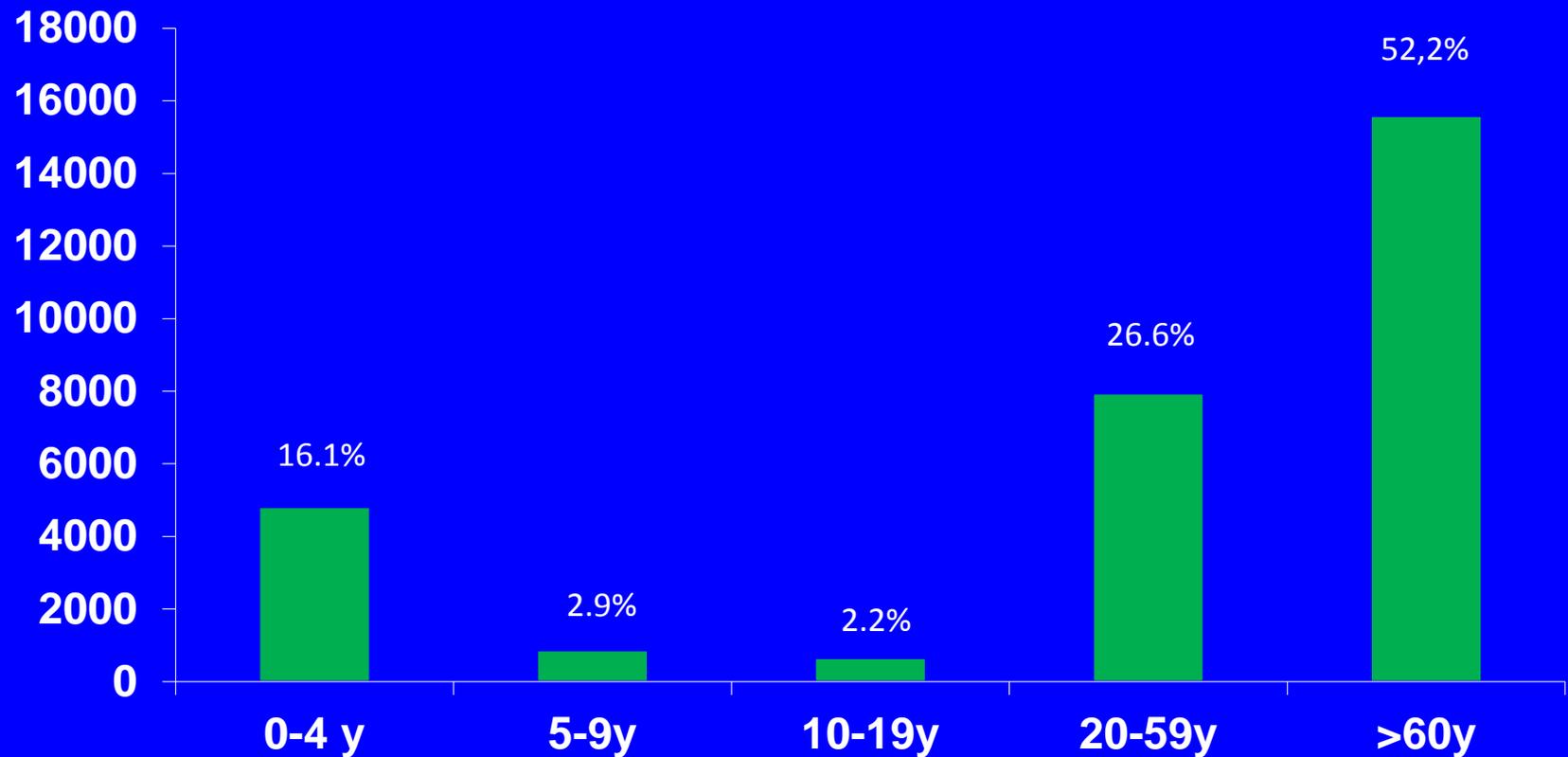
category	n	admission ICU n(%)	Outcome at discharge			P-value overall
			cured n(%)	with symptoms n (%)	death n (%)	
total	1329	434 (32,7)	884 (66,5)	237 (17,8)	208 (15,7)	
<u>age</u>						0,044
18-49y	219	54 (24,5)	157 (71,7)	49 (22,4)	13 (5,9)	
50-64y	370	154 (41,6)	240 (64,9)	83 (22,4)	47 (12,7)	
≥65y	740	226 (30,6)	487 (65,8)	105 (14,2)	148 (20,0)	
<u>type of IPD</u>						
bacteraemia pneumonia	1049	303 (28,9)	722 (69,0)	169 (16,2)	155 (14,8)	0,0049
empyema	94	49 (52,1)	49 (52,1)	35 (37,2)	10 (10,6)	
meningitis	73	59 (80,8)	38 (52,1)	16 (21,9)	19 (26)	
bacteraemia without focus	73	12 (16,4)	51 (69,9)	4 (5,5)	18 (24,7)	
other	43	11 (25,6)	24 (55,8)	13 (30,2)	6 (14,0)	

Disease outcome at discharge by age and serotype

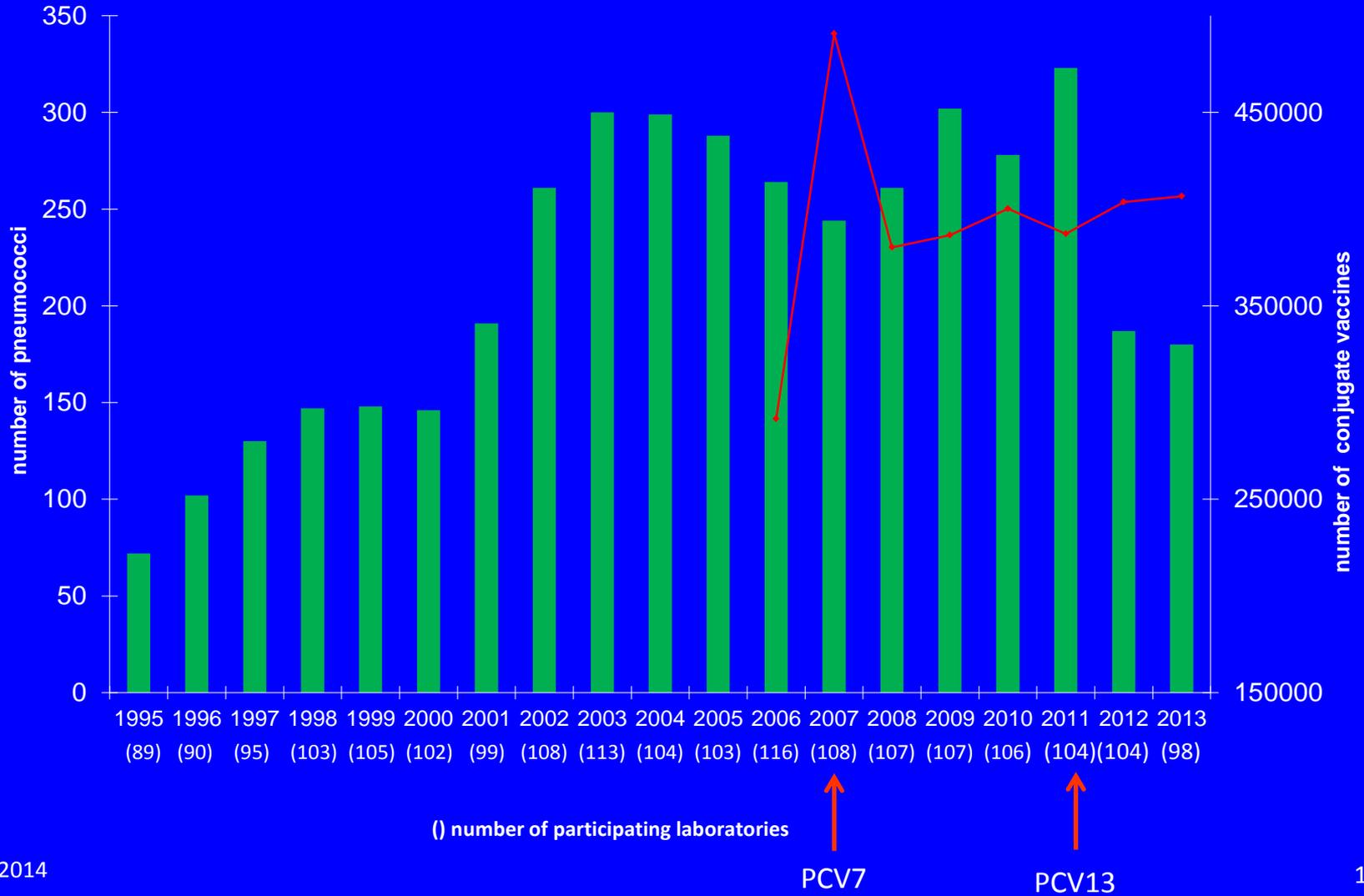
Figure 1



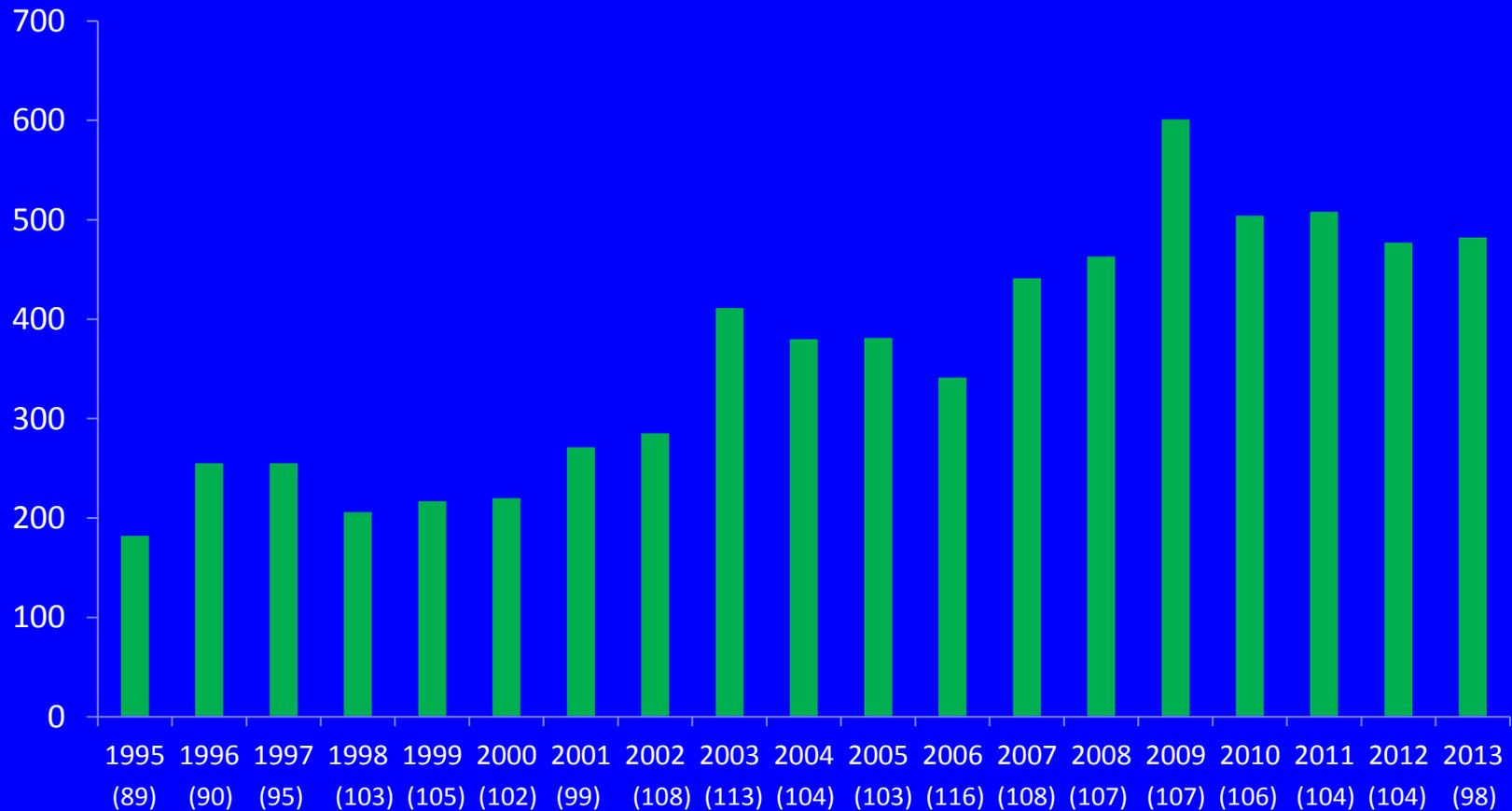
Age distribution of 29869 patients with pneumococcal bacteraemia (Belgium 1980-2013)



Evolution of number of pneumococci isolated from blood and pleural fluid cultures in young children (≤ 4 years) (1995-2013)

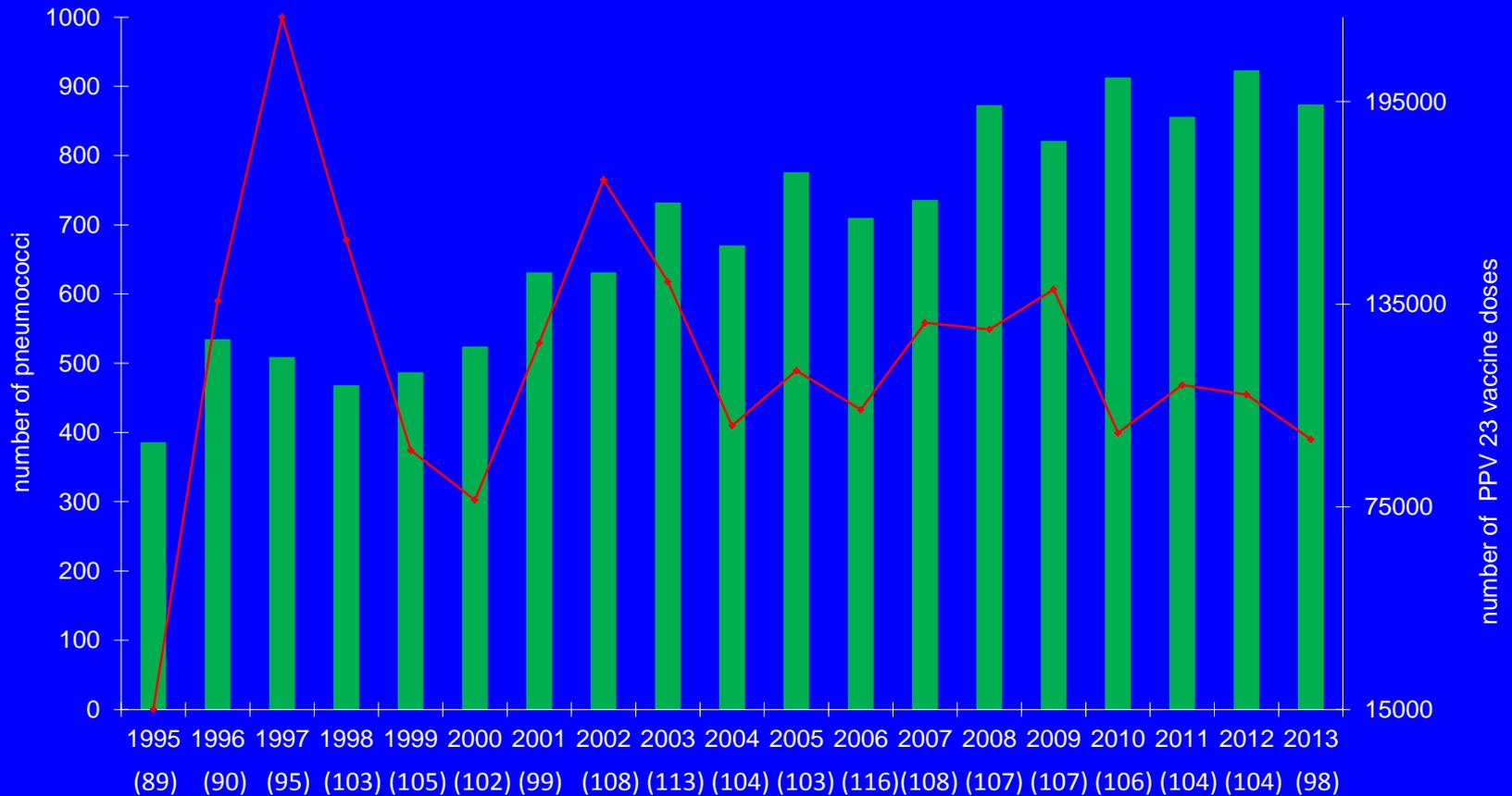


Evolution of number of pneumococci isolated from blood and pleural fluid cultures in adults (>20-<60 years) (1995-2013)



() number of participating laboratories

Evolution of number of pneumococci isolated from blood and pleural fluid cultures in elderly (>60 years) and number of 23-valent-vaccines (1995-2013)



() number of participating laboratories

Pneumococcus capsular typing

- Danish nomenclature (Kauffman und Lund, 1954)
 - Nine pooled sera = A-I
 - 93 serovars
 - 26 sera of a single serotype
 - 20 group sera = 2 to 4 cross-reacting serovars (e.g. serogroup 7 = 7F, 7A, 7B, 7C)



Isaac Sheehymelster

Figure 29.11 *Streptococcus pneumoniae*. India ink negative stain of cells of *Streptococcus pneumoniae*. An extensive capsule surrounds the cells, which are 1.0–1.2 μm in diameter.

Distribution by capsular type or group of 36760 pneumococci (Belgium 1980-2013)

<u>SGT's</u>	<u>Number</u>	<u>% of total</u>
19 (F, A, B)	4559	12.4
1	4425	12
14	3339	9.1
6 (A, B, C)	2748	7.5
3	2672	7.3
9 (A, L, N, V)	2244	6.1
23 (F, A, B)	2206	6.6
7 (F, A, B, C)	2507	6.8
4	1252	3.4
8	1249	3.4
18 (F, A, B, C)	817	2.2
Other 26 SGT's	8742	23.8

Red: included in PCV7

Green: also included in PCV13

Pneumococcal polysaccharide vaccine

- 23-valent vaccine (Pneumo 23)
 - 0,5 ml single dose vial containing purified capsular polysaccharide from each of the 23 types of *S. pneumoniae* (1, 2, 3, 4, 5, 6B, 7F, 8, 9N, 9V, 10A, 11A, 12F, 14, 15B, 17F, 18C, 19F, 19A, 20 22F, 23F)
 - This vaccine induces B-cell type-specific protective antibody without a contribution of helper T-cells
 - Low antibody titers, particularly in children less than 18 months of age

Pneumococcal conjugate vaccines

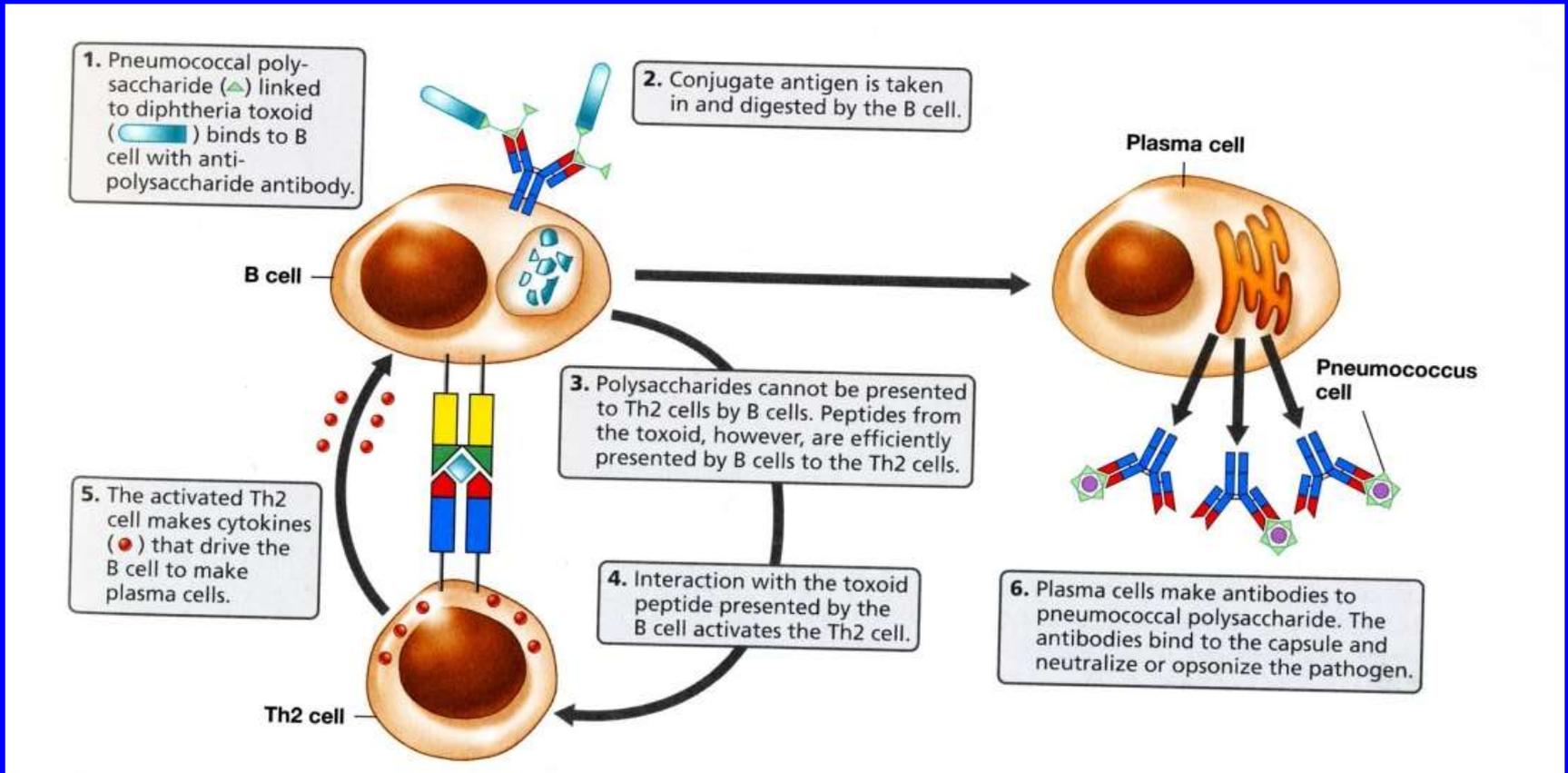
- 7-valent vaccine (PREVENAR)
 - 2 µg of 6 capsular polysaccharides: 4, 9V, 14, 18C, 19F, 23F
4 µg of polysaccharide 6B
 - conjugated to 20 µg mutant non-toxic *C. diphtheriae* CRM₁₉₇ protein
 - no longer available and replaced in 2011 by 13-valent vaccine
 - 10-valent vaccine (SYNFLORIX)
 - 1 µg of 7 capsular polysaccharides: **1**, **5**, 6B, **7F**, 9V, 14, 23F
 - 3 µg of 3 capsular polysaccharides: 4, 18C, 19F
 - conjugated to 9-16 µg protein D *Haemophilus influenzae* or 10 µg (Tetanus anatoxine (18C) or 6 µg *C. diphtheriae* anatoxine (19F)
 - 13-valent vaccine (PREVENAR 13)
 - 13 capsular polysaccharides: 1, **3**, 4, 5, **6A**, 6B, 7F, 9V, 14, 18C, **19A**, 19F, 23F
 - conjugated to 20 µg mutant non-toxic *C. diphtheriae* CRM₁₉₇ protein
-

Basisvaccinatieschema Vlaanderen 2014

leeftijd	IPV-DTP _a -Hib-HBV	Pn _c -13	MBR	MenC	IPV-DTP _a	HPV	dTp _a
8 weken	X	X					
12 weken	X						
16 weken	X	X					
12 maand		X	X				
15 maand	X			X			
6 jaar					X		
10 jaar			X				
12 jaar*						XX	
14 jaar							X

gebruikte symbolen voor vaccins	
IPV	geïnactiveerd injecteerbaar vaccin tegen polio
D	vaccin tegen difterie (d: verlaagde dosis)
T	vaccin tegen tetanus
P _a	acellulair vaccin tegen pertussis (p _a verlaagde dosis)
Hib	vaccin tegen <i>Haemophilus influenzae</i> type b
HBV	vaccin tegen hepatitis B
MBR	vaccin tegen mazelen, bof en rubella
Pn _c -13	geconjugeerd vaccin tegen pneumokokken
MenC	vaccin tegen meningokokken van serogroep C
HPV	vaccin tegen Humaan Papillomavirus

vaccins gratis beschikbaar in Vlaanderen - 2014	
vaccinatie	merknaam
IPV-DTP _a -Hib-HBV	Hexyon
Pn _c -13	Prevenar 13
MBR	Priorix
MenC	NeisVac-C
IPV-DTP _a	Infanrix-IPV
HBV	Engerix B 20 (volwassenen)
HPV	Cervarix (enkel meisjes 1 ^{ste} jaar S.O.)
dTp _a	Boostrix (enkel 3 ^{de} jaar secundair)
dT	Tedivax pro adulto
IPV	Imovax polio



conjugate vaccines

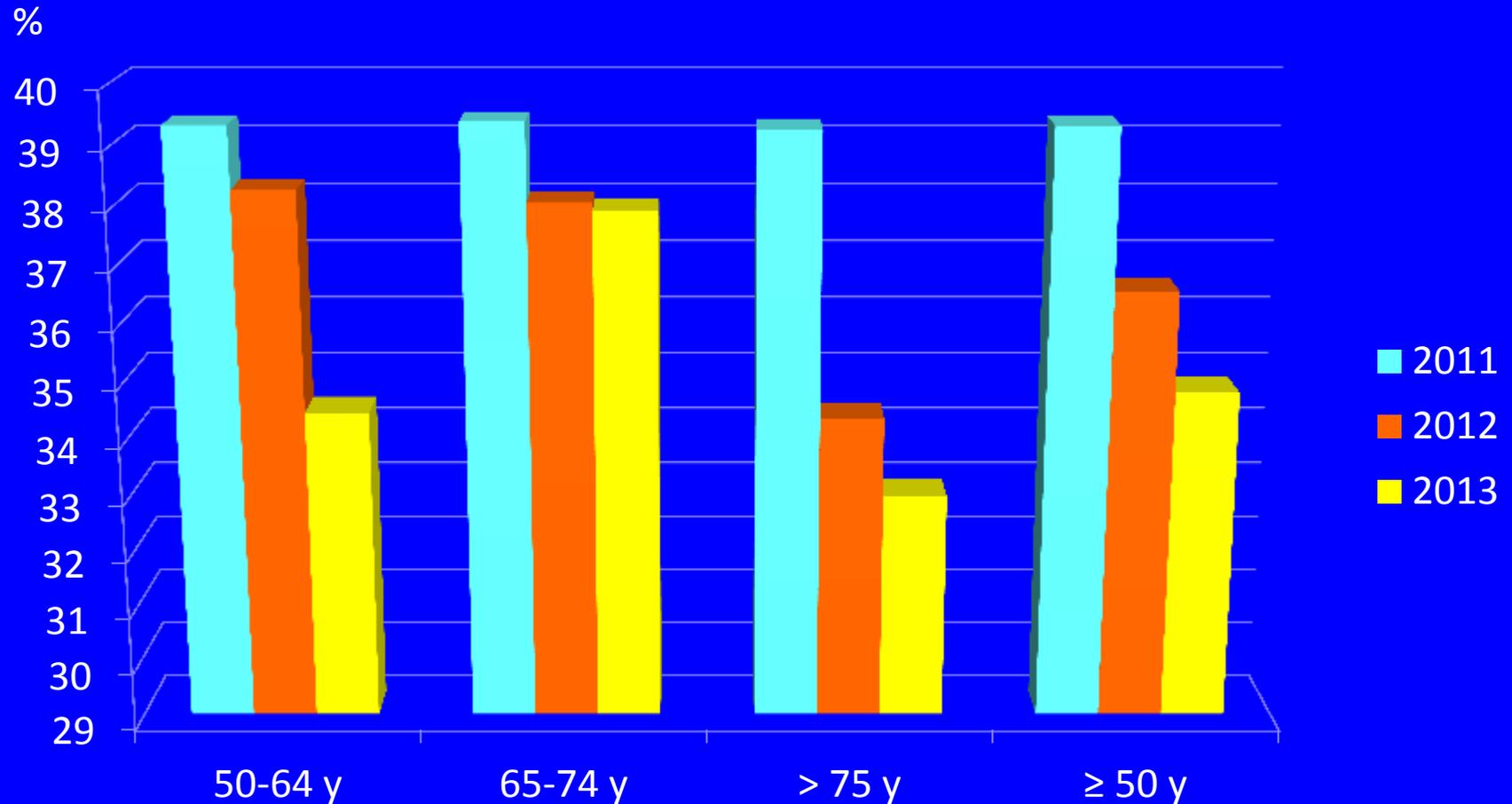
Efficacy of pneumococcal vaccines

- Conjugated vaccines
 - Review of clinical trials: efficacy of 80% against vaccine-type invasive pneumococcal disease in children < 2 years (Cochrane)
 - “replacement by other capsular types” (1, 7F, 19A) in Belgium and other countries
 - Effectiveness against pneumonia is lower (~ 27%)
- Polysaccharide vaccine
 - Review of clinical trials: overall efficacy of 74% against invasive pneumococcal disease (Cochrane)
 - 52% in older adults and adults with increased risk of invasive pneumococcal disease
 - 29% against all-cause pneumonia

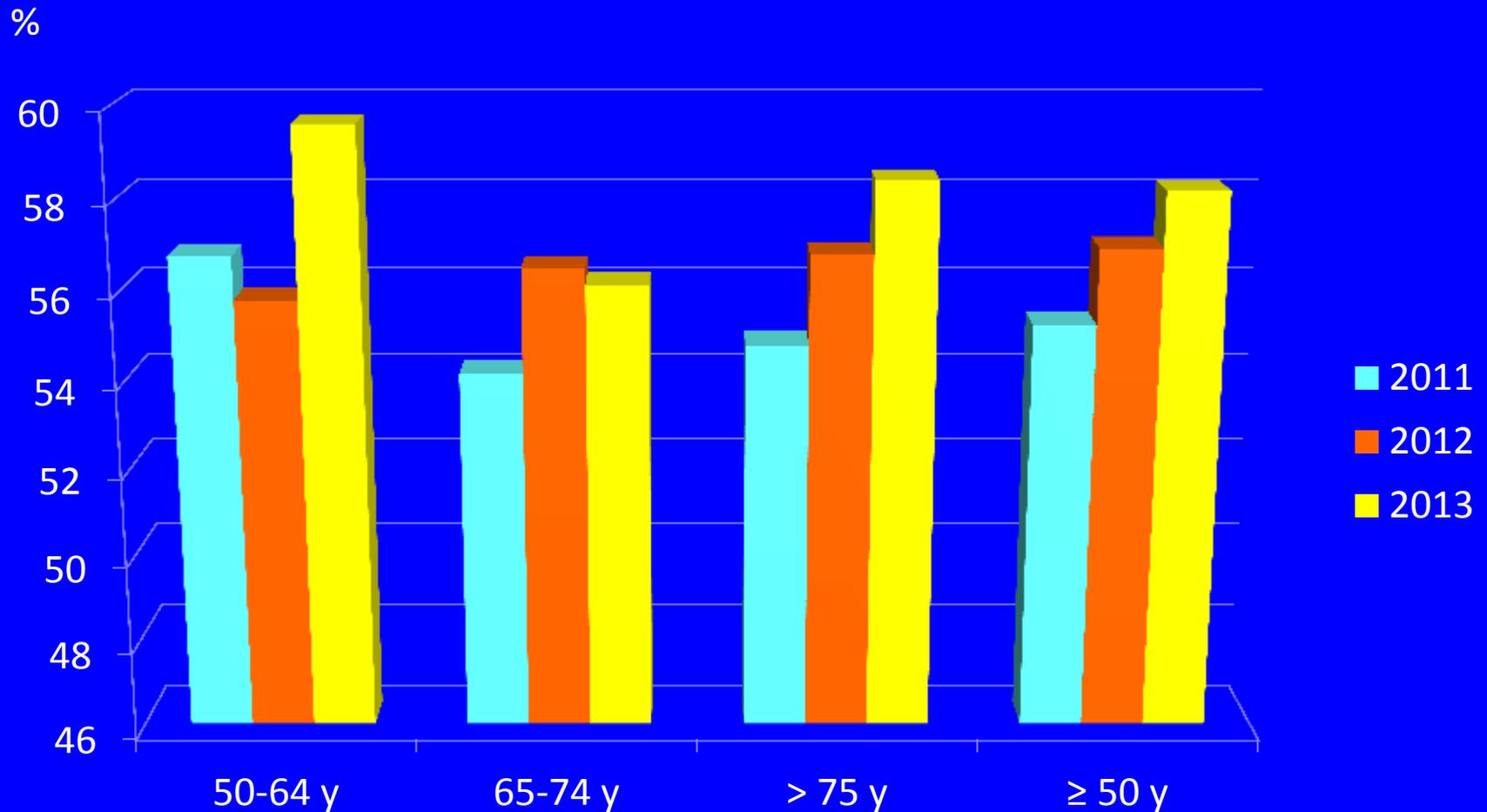
Overzicht distributie kapseltypen (bloed + lumbaalvocht) PCV13-PPV23 (2011-2013)

Kapsel- type	50-64 jr			65-74 jr			>75 jr			50->75 jr		
	2011	2012	2013	2011	2012	2013	2011	2012	2013	2011	2012	2013
1	43	51	51	35	35	27	31	25	19	109	111	97
3	26	27	34	20	28	30	51	43	46	97	98	110
4	6	2	6	5	2	2	2	3	2	13	7	10
5	15	10	5	13	6	5	15	6	5	43	22	15
6	14	13	9	12	13	16	26	28	33	52	54	58
7	46	35	29	30	27	23	56	33	25	132	95	77
9	7	17	14	14	7	4	11	21	21	32	45	39
14	3	3	2	4	7	5	17	8	7	24	18	14
18	4	4	0	1	1	0	2	1	1	7	6	1
19	44	54	29	34	36	33	87	79	59	165	169	127
23	11	13	11	8	11	13	10	19	14	29	43	38
Subtotaal PCV13	219	229	190	176	173	158	308	266	232	703 (39.3%)	668 (36.5%)	586 (34.8%)
8	9	14	21	8	16	14	7	15	25	24	45	60
10	5	9	4	6	3	2	5	9	12	16	21	18
11	6	13	8	8	8	3	14	24	11	28	45	22
12	34	40	56	23	25	25	30	49	49	87	114	130
15	12	12	13	7	9	9	19	24	19	38	45	47
17	6	3	4	1	3	4	4	5	9	11	11	17
20	2	1	4	0	4	2	2	2	2	4	7	8
22	15	16	17	11	11	13	31	34	37	57	61	67
33	8	7	12	2	5	4	10	12	15	20	24	31
Subtotaal PPV23	316	334	329	242	257	234	430	440	411	988 (55.3%)	1041 (56.9%)	980 (58.2%)
Andere	22	26	33	29	25	25	47	69	61	98 (5.5%)	120 (6.6%)	119 (7%)
totaal	557	599	552	447	455	417	785	775	704	1789	1829	1685

PCV13 and IPD coverage Belgium, 2011-2013



PPV23 and IPD coverage Belgium, 2011-2013



Aanbevelingen Hoge Gezondheidsraad – vaccinatie tegen pneumokokken (2013)

1. Volwassenen van 19 tot 75 jaar met **verhoogd risico**
 - immuniteitsstoornis **anatomische of functionele asplenie**, sickle cell disease, hemoglobinopathie, lek cerebrospinaalvocht, cochleair implantaat)
 - Primo-vaccinatie: PCV13 gevolgd door POV23 na 8 weken
 - Revaccinatie: PPV23 om de 5 jaren
2. Volwassenen van 50 tot 75 jaar met **comorbiditeit** (chronisch hartlijden, chronisch longlijden of rokers, chronisch leverlijden of ethyllabusus, chronisch nierlijden) en gezonde personen tussen 65 en 75 jaar.
Primovaccinatie: PPV23 of PCV13 gevolgd door PPV23 na 8 weken.
Revaccinatie: éénmalige revaccinatie met PPV23 na 5 jaren.

*Bij gebruik van beide vaccins verdient het aanbeveling om eerst PCV₁₃ toe te dienen omwille van de hyporesponsiviteit na eerdere revaccinatie met PPV₂₃. Een tijdsinterval van minstens 8 weken wordt in acht genomen.

Aanbevelingen Hoge Gezondheidsraad. Vaccinatie tegen pneumokokken (2013)

3. Volwassenen ouder dan 75 jaar

- primovaccinatie: PPV23 of PCV13 gevolgd door PPV23 na 8 weken
- Geen revaccinatie
- weinig evidentie voor effectiviteit boven de leeftijd van 80 jaar

Prevention of severe bacterial infections for persons with functional or anatomical asplenia

- elective splenectomy: vaccination completed 2 weeks before operation
- unplanned splenectomy: start with vaccination 1 week after operation
- children with splenic dysfunction: also antibiotic prophylaxis until at least 5 years of age
- importance that persons with asplenia are informed of the life-long increased risk of severe bacterial infection even if they have been appropriately vaccinated

Recommendations for vaccination in adults with asplenia

- Pneumococcal vaccine
 - If a PCV13 dose has not previously been given, give a single dose, preferably prior to PPV23. The recommended minimum interval between a PCV13 dose and a subsequent PPV23 dose is 2 months. If PCV13 follows PPV23, a minimum interval of 12 months is recommended.
 - There is a maximum limit of 3 doses of PPV23

Recommendations for vaccination in adults with asplenia

- Meningococcal vaccine
 - 2 doses of 4valent (A, C, W135, Y) conjugated vaccine 8 weeks apart
 - one dose every 5 years thereafter
- *Haemophilus influenzae* type b
 - If Hib vaccination is complete (3 vaccine doses as infant) additional/repeat doses are not required
- Influenza vaccine
 - 1 dose annually
 - influenza infection can be complicated by secondary invasive pneumococcal infection

Advisory Committee Statement for the splenectomized traveller

“... splenectomized travellers should seek expert advice regarding malaria risk and prevention before travel and should be particularly attentive to following those recommendations closely ...”

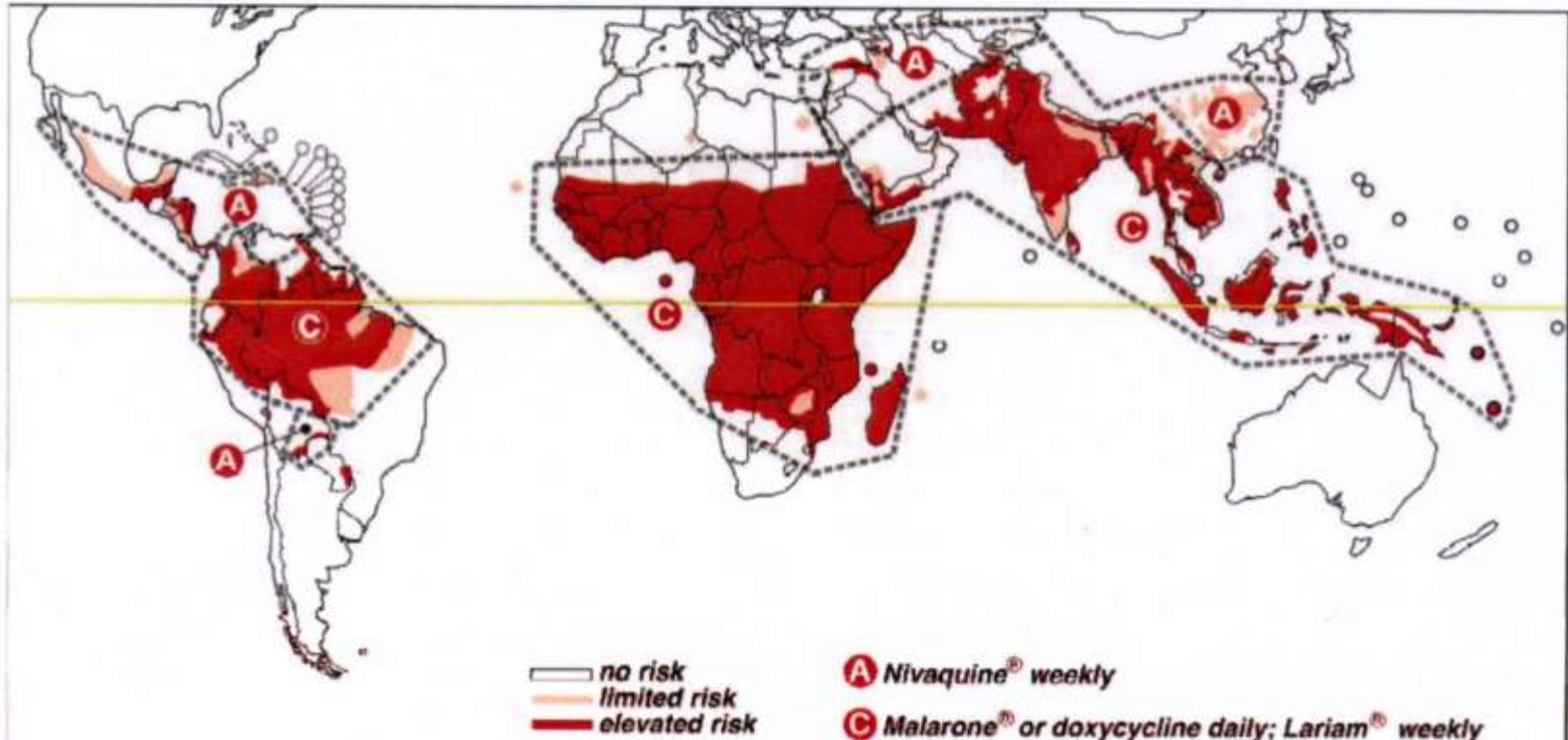
ABCD principles for malaria prophylaxis

- **Awareness:** being aware of the risk, main symptoms, incubation time
- **Bites:** avoidance of being bitten by *Anopheles* mosquitoes
 - remaining indoors, screens over doors and windows
 - Application of insect repellent (di-ethyltolbutamide) to exposed skin between dusk and dawn
 - utilization of a mosquito net (if possible pyrethroid treated)
 - protective clothing outdoors
- **Chemoprophylaxis** where appropriate
 - Drugs should be taken regularly, with food and plenty of water
- **Diagnosis**
 - Early diagnosis and treatment
 - Be aware that no prophylactic regimen offers complete protection

VERSPREIDING VAN MALARIA

<http://www.itg.be/itg/Uploads/MedServ/malariaworld2005.jpg>

Malaria 2010-2011 (source WHO 2009)



A Nivaquine[®] weekly

C Malarone[®] or doxycycline daily; Lariam[®] weekly

for details : see www.itg.be

Principles for malaria prophylaxis

- Zone A:
 - risk is general low and seasonal
 - *P. falciparum* absent or sensitive to chloroquine
 - chloroquine sulphate 300 mg po 1x/week
- Zone C:
 - risk high in Africa, risk low in Asia and America (high in Amazon basin)
 - atovaquone (250 mg) plus proguanil (100 mg) q 24h po (max duration = 28 days)
 - doxycycline (100 mg) q 24h po
 - mefloquine (250 mg) 1x/week po