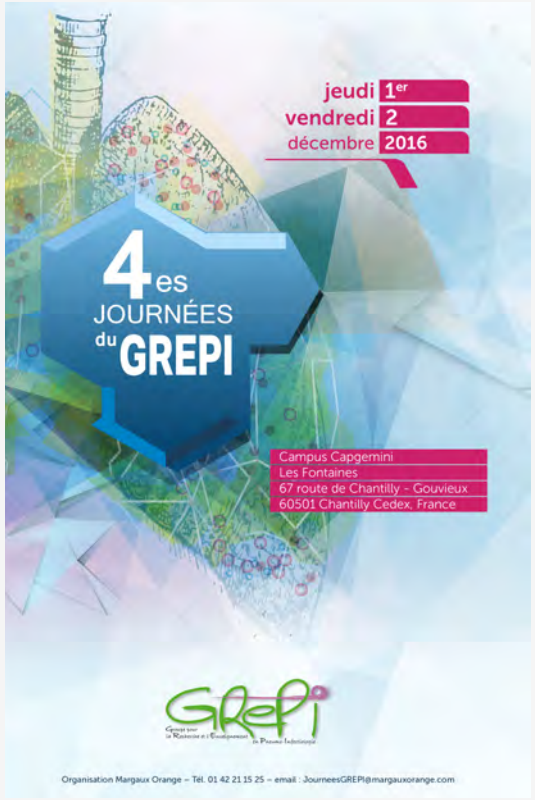


Pourquoi les vaccinations antigrippale et anti-pneumococcique sont-elles indiquées dans les pathologies respiratoires chroniques ? Comment évalue-t-on l'efficacité d'un vaccin ?

Elodie Blanchard

Service des Maladies Respiratoires

CHU Bordeaux

Plan

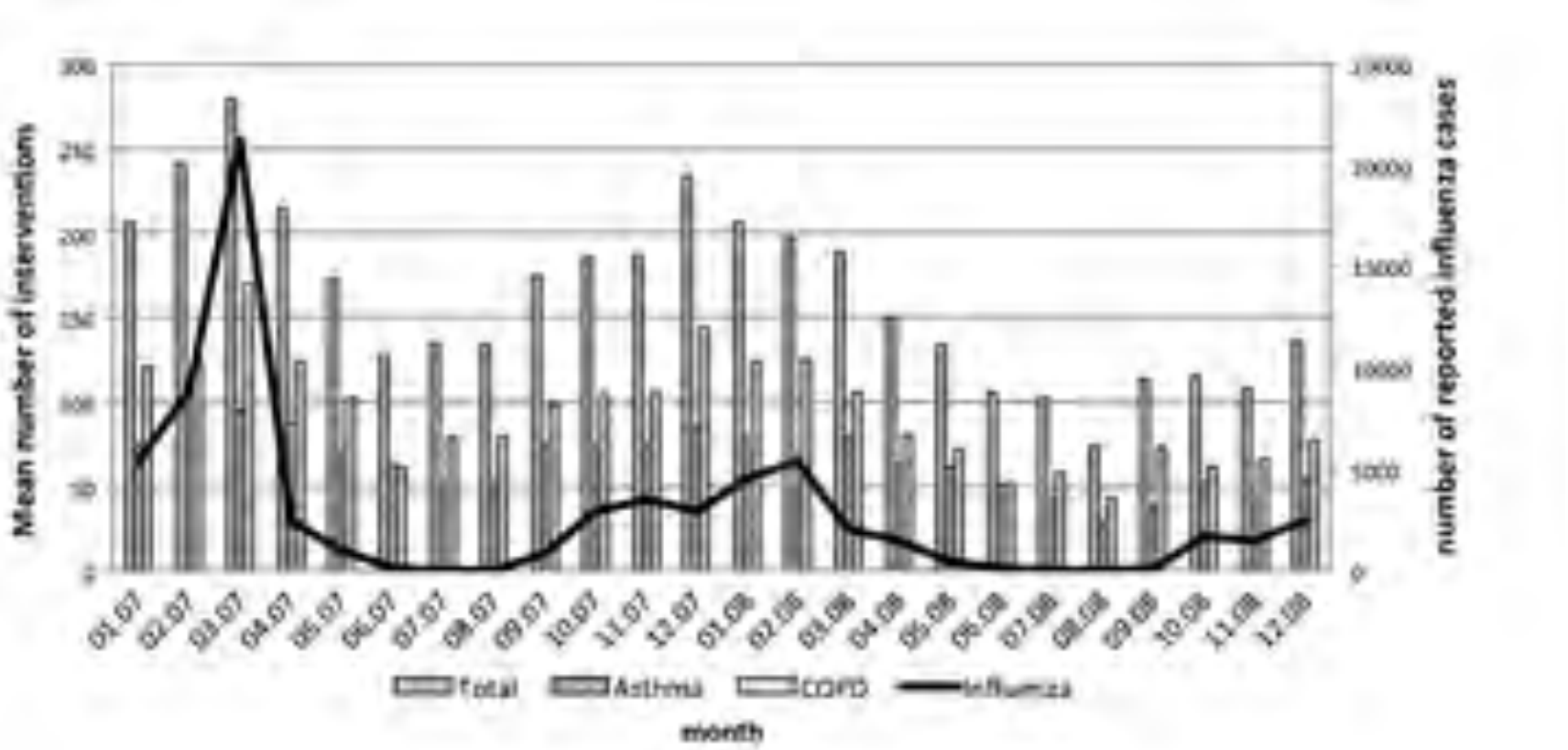
- Données épidémiologiques « Pathologies Respiratoires Chroniques » et
  - Grippe
  - Pneumocoque

- Evaluation de l'efficacité d'un vaccin
  - Concepts d'immunogénicité et d'efficacité
  - Exemples dans la grippe et le pneumocoque

- Projet de recommandations vaccinales pneumologiques

Grippe

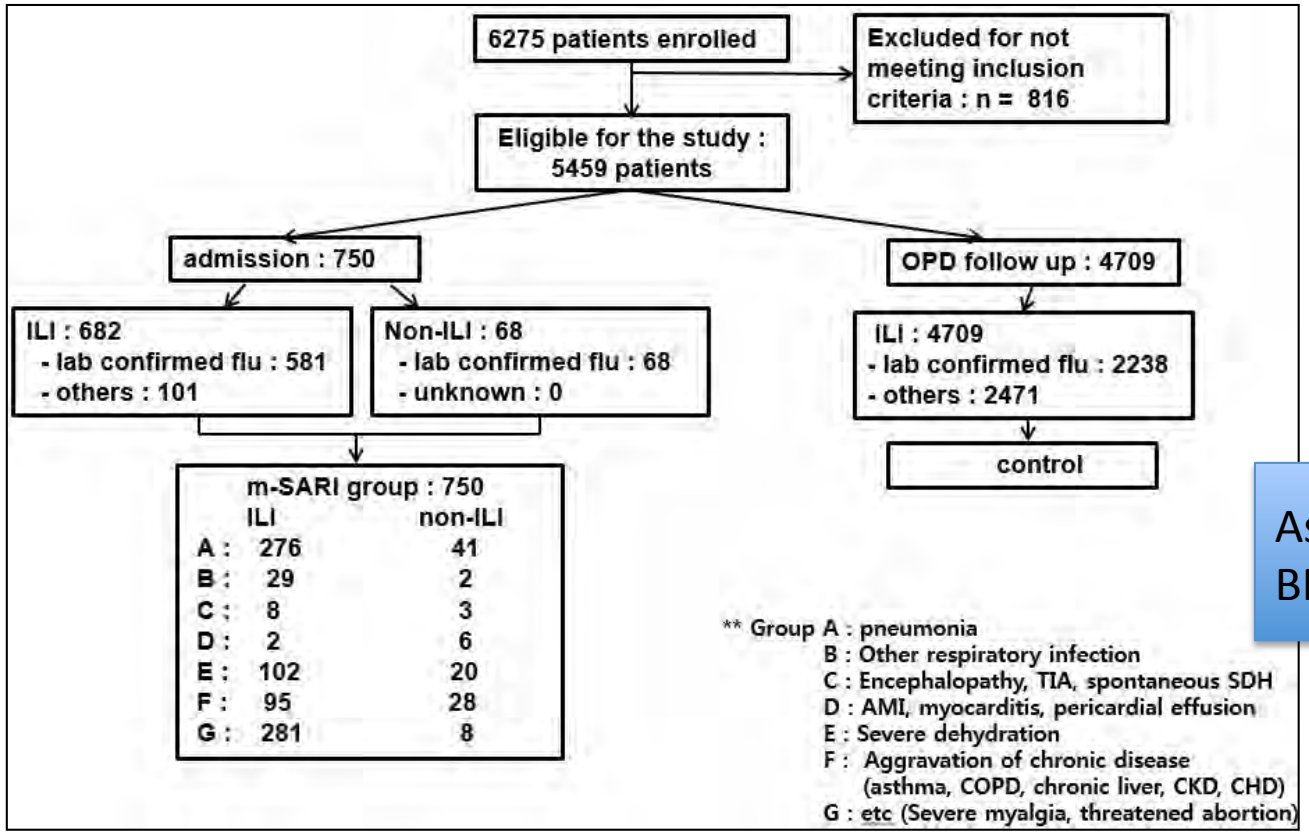
- Exacerbations de BPCO ou d'asthme + fréquentes en période d 'épidémie grippale



Brzezinzka-Pawlowska J Asthma 2016

Grippe

- Etude prospective coréenne saisons grippales 2011-2014
- Objectif: identifier les facteurs de risque de grippe hospitalisées et de pneumonie



Asthme n=163
BPCO n=93

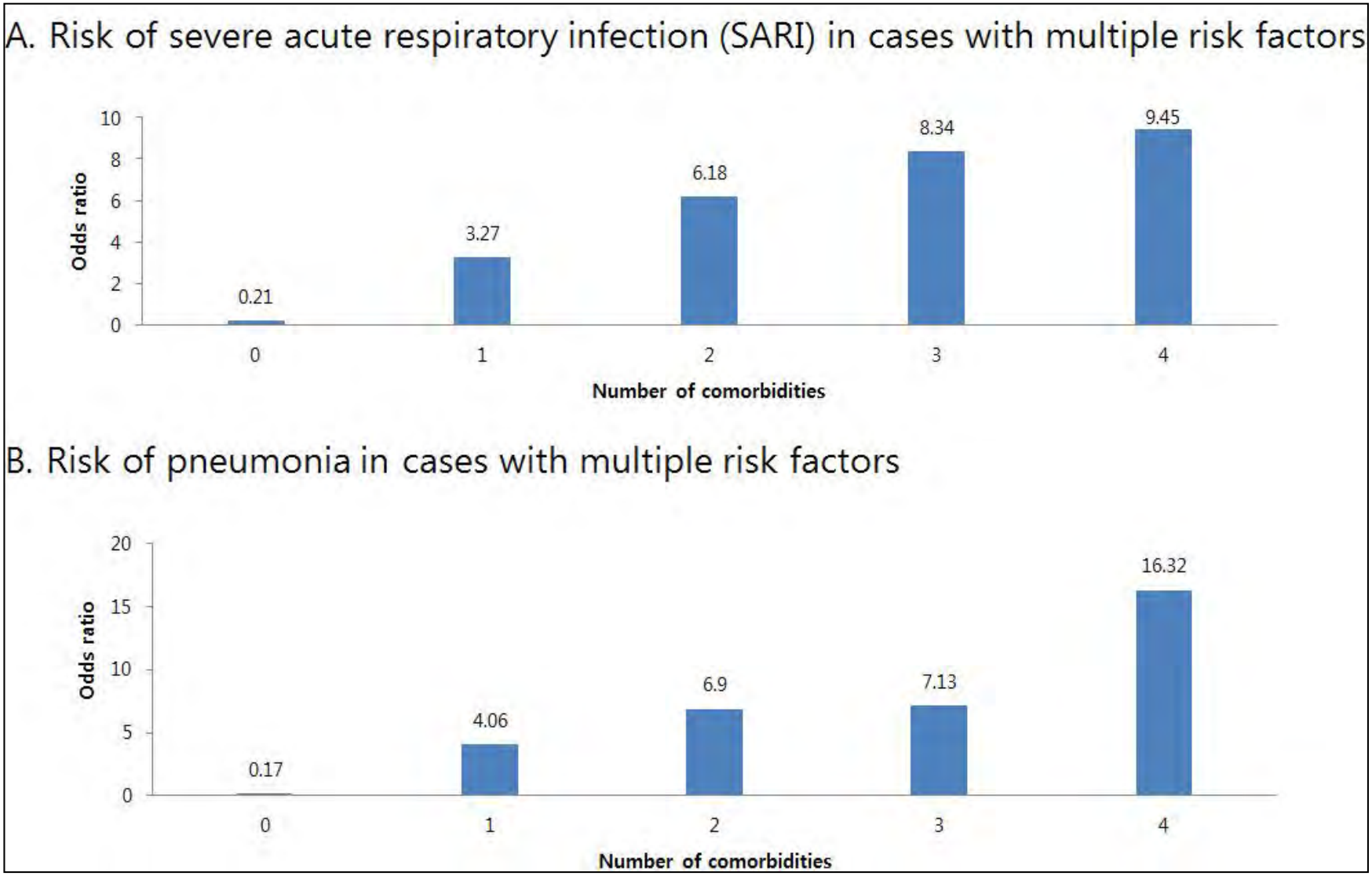
Kang Infection Chemotherapy 2016

Grippe

Table 2. Analysis of risk factors for severe acute respiratory infection among adult cases with acute respiratory illness				
	Control group (n = 4709)	Modified SARI (n = 750)	Univariate analysis	Multivariate analysis
			P value	Odds ratio (95% CI)
Age, mean years (SD)	46.7 (SD 19.2)	61.6 (SD 18.9)	<0.001	
Male sex - no. (%)	2,015 (42.8%)	326 (43.5%)	0,728	
Influenza vaccine[a]	1 365	305	<0.001	0.84 (0.68-1.03)
Pneumococcal vaccine[b]	564	92	<0.001	0.96 (0.70-1.3)
Age < 65	3291	270	<0.001	
Age ≥ 65	743	164	<0.001	
DM	506 (10.7%)	164 (3.5%)	<0.001	0.94 (0.73-1.20)
Chronic heart disease	189 (4%)	103 (13.7%)	<0.001	2.24 (1.68-2.98)
CVD	17,177 (3.8%)	79 (10.5%)	<0.001	1.49 (1.05-2.10)
Neuromuscular	56 (1.2%)	24 (3.2%)	<0.001	1.2 (0.67-2.13)
COPD	48 (1%)	45 (6%)	<0.001	2.34 (1.48-3.69)
Asthma	94 (2%)	69 (9.2%)	<0.001	2.33 (1.62-3.36)
CKD	95 (2%)	61 (8.1%)	<0.001	2.62 (1.73-3.98)
CLD	101 (2.1%)	29 (3.9%)	<0.004	1.71 (1.04-2.81)
Solid cancer	276 (5.9%)	80 (10.7%)	<0.001	1.17 (0.86-1.59)
Immunocompromised	51 (1.1%)	17 (2.3%)	0,007	1.71 (0.92-3.20)
-Hematologic malignancy	30	9		
-Solid organ transplant	8	3		
-BMT	1	0		
-HIV/AIDS	13	4		
Autoimmune disease	79 (1.7%)	34 (4.5%)	<0.001	2.53 (1.57-4.09)

Kang Infection Chemotherapy 2016

Grippe



Kang Infection Chemotherapy 2016

Grippe

PROTÉGEONS-NOUS, VACCINONS-NOUS.

- Vaccination annuelle pour
  - tous les sujets > 65 ans
  - femme enceinte
  - affections broncho-pulmonaires chroniques répondant aux critères de l'ALD 14 (asthme et BPCO)
  - insuffisances respiratoires chroniques obstructives ou restrictives quelle que soit la cause
  - maladies respiratoires chroniques ne remplissant pas les critères de l'ALD mais susceptibles d'être aggravées ou décompensées par une affection grippale, dont asthme, bronchite chronique, bronchiectasies, hyperréactivité bronchique
  - dysplasies broncho-pulmonaires
  - mucoviscidose

Calendrier vaccinal 2016

Pneumocoque

Thorax

Which individuals are at increased risk of pneumococcal disease and why? Impact of COPD, asthma, smoking, diabetes, and/or chronic heart disease on community-acquired pneumonia and invasive pneumococcal disease

Antoni Torres,[1] Francesco Blasi,[2] Nathalie Dartois,[3] Murat Akova[4]

Table 1 Overview of risk factors associated with community-acquired pneumonia and pneumococcal disease

Risk factor	Cohort studies		Case-control studies	
	Number of cohorts*	Risk range†	Number of cohorts*	Risk range†
Pneumococcal pneumonia				
Chronic respiratory diseases	6¶	Rate ratio: 3.7–9.8	0	–
Current smoking status	3	Rate ratio: 3.0–4.4	0	–
Diabetes mellitus	6	RR: 2.3 Rate ratio: 1.5–3.1	0	–
Chronic heart disease	3	Rate ratio: 3.8–5.1	0	–
Invasive pneumococcal disease				
Chronic respiratory diseases	9**	OR: 2.1–16.8 Rate ratio: 2.5–7.7	4††	OR: 1.3–4.7
Current smoking status	5	OR: 2.2 RR: 2.7 Rate ratio: 3.6–4.3	1	OR: 1.1
Diabetes mellitus	10	OR: 1.4–4.6 Rate ratio: 1.5–3.9	2	OR: 1.5–1.7
Chronic heart disease	5	OR: 3.0–6.9 Rate ratio: 2.9–3.9	4	OR: 1.7–9.9

Torres Thorax 2015

Pneumocoque

Table 2. No. of cases of invasive pneumococcal disease, no. of adults (≥18 years) with a given medical condition, incidence rates, and relative risks (RRs) for healthy adults and adults with select chronic conditions—United States, 1999–2000.

Category	Cases of invasive pneumococcal disease, no.		Adults with condition, no.		Incidence rate (95% CI), cases/100,000 persons[a]	RR (95% CI)	
	ABCs	US projection	NHIS	US projection		Unadjusted[b,c]	Adjusted[b,c,d]
Healthy	1570	28,495	50,434	326.0×10^6	8.8 (8.5–9.0)	Referent	Referent
Diabetes	629	11,633	3942	22.6×10^6	51.4 (49.2–53.9)	5.8 (1.6–21.0)	3.4 (1.8–6.4)
Chronic heart disease	1225	20,564	3761	22.0×10^6	93.7 (87.4–100.9)	10.4 (3.6–30.6)	6.4 (3.7–10.9)
Chronic lung disease	741	13,852	3647	22.1×10^6	62.9 (59.8–66.3)	6.9 (1.7–28.1)	5.6 (3.2–9.9)
Solid cancer	511	9557	551	3.3×10^6	300.4 (272.6–334.6)	32.2 (7.8–132.2)	22.9 (11.9–44.3)
HIV/AIDS	515	8726	374	2.1×10^6	422.9 (378.3–479.4)	48.8 (7.9–302.3)	48.4 (24.8–94.6)
Hematological cancer	265	4928	155	1.0×10^6	503.1 (422.2–622.3)	52.2 (7.9–345.6)	38.3 (15.9–92.2)
Alcohol abuse	518	9163	1464	9.1×10^6	100.4 (94.1–107.7)	11.5 (2.2–60.8)	11.4 (5.9–21.9)
≥1 condition[e]							
HIV/AIDS or hematological cancer not included	1598	29,167	9330	55.8×10^6	52.3 (50.5–54.3)	5.7 (1.9–17.4)	3.9 (2.1–6.9)
Any condition	2765	50,208	9597	57.3×10^6	87.5 (84.5–90.8)	9.6 (2.9–31.5)	7.4 (3.2–16.9)
≥2 conditions[e]							
HIV/AIDS or hematological cancer not included	620	11,536	1909	11.0×10^6	104.5 (98.4–111.3)	11.7 (3.3–42.1)	7.5 (2.9–19.6)
Any condition	815	14,993	2025	11.7×10^6	128.4 (121.0–136.7)	14.5 (4.1–50.6)	9.6 (3.8–24.2)

Kyaw JID 2005

Pneumocoque

Table 5. Multivariate Analysis of the Risk of Developing Severe Community-acquired Pneumonia in the Study Patients

Factor	n	Severe	OR	95% CI	p value
Age (>65 yrs)	578	100	2.428	(1.554, 3.792)	<0.001
Chronic obstructive pulmonary disease	166	34	1.909	(1.194, 3.053)	0.007
Congestive heart failure	35	10	2.652	(1.190, 5.911)	0.017
Diabetes mellitus	107	25	2.441	(1.434, 4.154)	0.001
Dementia	13	5	4.230	(1.242, 14.400)	0.021
Legionella spp.	53	18	2.867	(1.499, 5.485)	0.001
Number of pathogens					
Single	493	79	Reference	–	[<0.001]
Polymicrobial	95	24	1.917	(1.107, 3.322)	0.020
Unknown	444	30	0.376	(0.236, 0.600)	<0.001

- Augmentation du risque de PAC liée à la corticothérapie inhalée dans la BPCO

Ishiguro Int Med 2013, Kew Cochrane Database Rev Syst 2014

Pneumocoque

- Etude américaine
- Contexte:
  - Indication PCV 13 pour les > 65 ans et les immunodéprimés
  - Non immunodéprimés < 65 ans ➔ PPSV 23

- Groupe des « non immunodéprimés» < 65 ans hétérogène
- Y a-t-il des populations plus à risque au sein des « non-immunodéprimés » ?
- N=1549 inf invasives à pneumocoques
- 2008-2014

	Adjusted relative risk	95% confidenc interval
Non-immunocompromising (Non-IC) conditions		
Alcoholism	1.6	1.2–2.0
Asthma	1.8	1.6–2.1
Chronic liver disease	2.1	1.5–2.8
Cigarette smoking	1.6	1.4–1.8
Chronic kidney disease stage 3,4	1.2	1.0–1.4
Congestive heart failure	1.5	1.2–1.7
Chronic obstructive pulmonary disease	2.1	1.8–2.5
Dementia	1.3	0.9–1.9
Diabetes mellitus	1.3	1.2–1.5
Stroke	1.0	0.6–1.6
Immunocompromising (IC) conditions		
Asplenia	4.2	0.7–12.9
Cerebrospinal fluid leak	6.4	1.6–16.7
Chemotherapy	2.1	1.6–2.7
Congenital immunodeficiency	2.4	1.8–3.1
End stage renal disease	3.7	2.8–4.7
Generalized malignancy	1.8	1.4–2.3
HIV	7.0	4.9–9.7
Immunocompromising meds	2.5	2.0–3.0
Leukemia	4.3	3.1–5.9
Lymphoma	3.9	2.9–5.1
Multiple myeloma	11.9	8.9–15.7
Myelofibrosis	1.5	0.1–6.8
Nephrotic syndrome	0.6	0.2–1.2

Baxter Vaccine 2016

Pneumocoque

- Etude américaine
- Contexte:
  - Indication PCV 13 pour les > 65 ans et les immunodéprimés
  - Non immunodéprimé < 65 ans ➔ PPSV 23

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Baxter Vaccine 2016

Pneumocoque

- Près de 50% des inf invasives à pneumocoques surviennent chez des patients vaccinés par le PPSV23
- Le cumul des comorbidités augmente le risque de développer une infection invasive à pneumocoque
- Exemple: un BPCO toujours fumeur et diabétique = 3 comorbidités soit un RR ajusté 5,2 versus 6,8 pour un « immunodéprimé »

Table 4
Relative Risk of IPD, for one or multiple non-immunocompromising conditions, compared to the healthy population. The stacking model (Adjusted Relative Risk) controls for age, sex, year, PPSV23, and medical conditions, and adds an interaction term for patients with immunocompromising and non-immunocompromising conditions.

		Relative risk	95% confidence interval
Age Group (ref = 18 to <50)	50 to <65 years	1.9	1.7–2.2
	65 to <80 years	2.4	2.0–2.9
	⩾80 years	4.6	3.8–5.5
Race (ref = White)	Asian	0.7	0.6–0.8
	Black	1.3	1.1–1.5
	Hispanic	1.0	0.8–1.1
	Other	1.3	0.8–2.0
Pneumovax (ref = NO)	YES	1.3	1.1–1.5
Sex (ref = Male)	F	0.9	0.8–1.0
Year (ref = 2014)	2008	1.5	1.3–1.8
	2009	1.6	1.3–1.9
	2010	1.6	1.3–1.9
	2011	1.3	1.1–1.6
	2012	1.1	0.9–1.3
	2013	1.1	0.9–1.4
Non-IC conditions (ref = Healthy)	Unadjusted Relative risk	Adjusted Relative risk	95% confidence interval
1 Condition	3.0	2.2	1.9–2.5
2 Conditions	5.5	2.9	2.5–3.5
⩾3 Conditions	13.4	5.2	4.4–6.1
IC Conditions	24.0	6.8	6.1–7.7

IC = immunocompromising; IPD = invasive pneumococcal disease.

Baxter Vaccine 2016

Pneumocoque

Insuffisant respiratoire chronique
BPCO
Emphysème
Asthme sévère sous traitement continu

→ Vaccin polysacharidique Pneumo 23®

Si corticothérapie systémique (poso ?)

→ Vaccin conjugué Prevenar 13®
+
≥ 8 semaines + tard
Vaccin polysacharidique Pneumo 23®

Il n'existe pas actuellement de données permettant de recommander la pratique de revaccinations ultérieures.

Calendrier vaccinal 2016, Vaccination des immunodéprimés HCSP 2014

Comment évalue-t-on l'efficacité d'un vaccin ?

- Concept d'**immunogénicité** d'un vaccin

  Capacité à induire une réponse immunitaire adaptative capable de protéger l'individu contre l'agent pathogène (exemples: titre seuil d'Ac ou doublement du titre après vaccin ...)

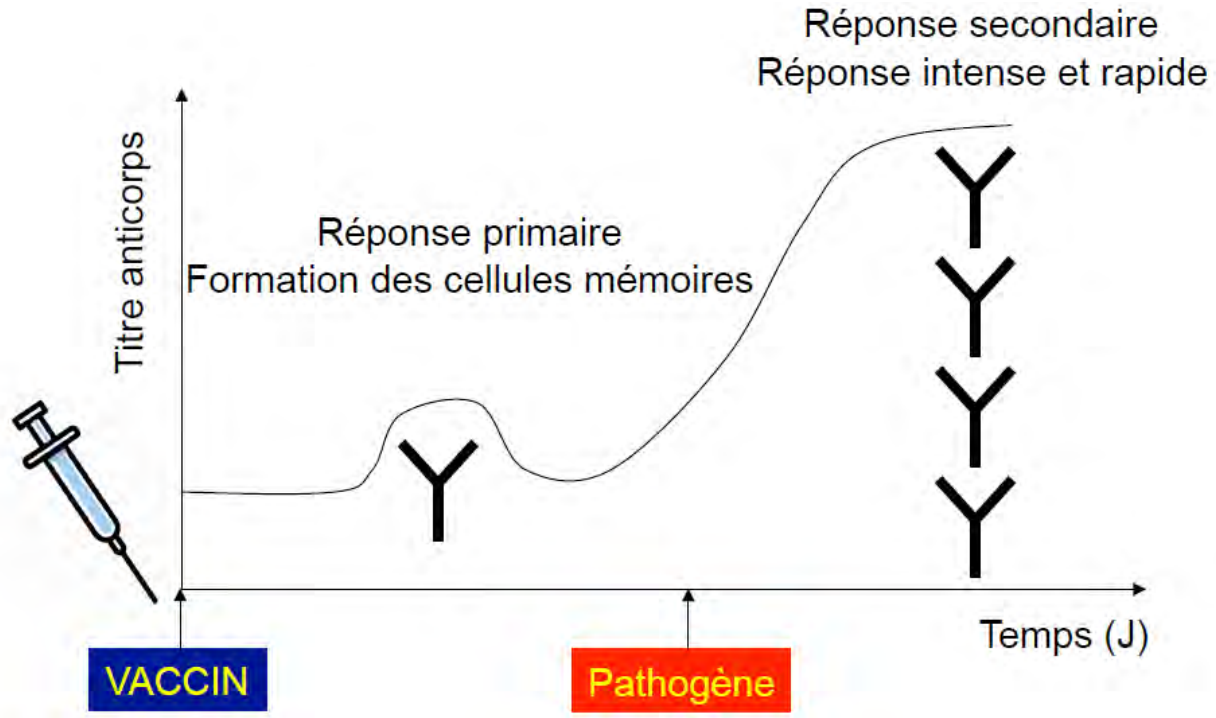


Schéma F. Batteux

Comment évalue-t-on l'efficacité d'un vaccin ?

- Concept d'**efficacité** d'un vaccin

- Essais cliniques randomisés vaccinés / non vaccinés
  - Critère de jugement principal: développer la maladie
  - « Efficacy » des anglo-saxons
  - Réduction relative du risque de développer la maladie grâce à la vaccination

- Etudes observationnelles chez des sujets vaccinés
  - Critère de jugement principal: développer la maladie
  - « Effectiveness » des anglo-saxons
  - Réduction relative du risque de développer la maladie chez un sujet vacciné

Efficacité vaccinale anti-grippale

- Méta-analyse
- Grippe confirmée par PCR ou culture
- « Efficacy»: essais cliniques randomisés *vs* placebo

	Population (dates)	Patients randomly allocated to receive TIV and placebo	Vaccine efficacy (95% CI)	Reported antigenic match
Adults (18–64 years)				
Ohmit et al (2006)[24]	Healthy adults aged 18–46 years (2004–05)	728	75% (42 to 90)	Type A: drifted H3N2; type B: mixed lineage
Ohmit et al (2008)[25]	Healthy adults aged 18–48 years (2005–06)	1205	16% (−171 to 70)	Type A: drifted H3N2; type B: lineage mismatch (1 isolate)
Beran et al (2009)[26]	Healthy adults aged 18–64 years (2005–06)	6203	22% (−49 to 59)	Type A: similar H3N2 and H1N1; type B: lineage mismatch
Beran et al (2009)[27]	Healthy adults aged 18–64 years (2006–07)	7652	62% (46 to 73)	Type A: similar H3N2; type B: lineage mismatch
Monto et al (2009)[28]	Healthy adults aged 18–49 years (2007–08)	1139	68% (46 to 81)	Type A: drifted H3N2; type B: lineage mismatch
Jackson et al (2010)[21]	Healthy adults aged 18–49 years (2005–06)	3514	50%† (14 to 71)	Type A: similar H3N2; type B: lineage mismatch
Jackson et al (2010)[21]	Healthy adults aged 18–49 years (2006–07)	4144	50%† (−3 to 75)	Type A: similar H3N2; type B: mixed lineage
Frey et al (2010)[29]	Healthy adults aged 18–49 years (2007–08)	7576	63% (one-sided 97·5% lower limit of 47%)	Type A: mixed strains; type B: lineage mismatch
Madhi et al (2011)[30]	Adults aged 18–55 years with HIV infection (2008–09)	506	76% (9 to 96)	Type A: drifted H1N1; type B: not reported

Osterholm Lancet Inf Dis 2012

Efficacité vaccinale anti-grippale

- « Effectiveness»: études observationnelles chez les sujets vaccinés

	Population (dates)	Participants	Vaccine effectiveness against medically attended influenza (95% CI)
Eisenberg et al (2008)[39]	All patients aged 6–59 months admitted to hospital, seen in emergency department or by primary-care doctors for acute respiratory illness (2003–05)	2003–04 (927 patients); 2004–05 (1502 patients)	44% (−42 to 78); 57% (28 to 74)
Szilagyi et al (2008)[40]	All patients aged 6–59 months admitted to hospital, seen in emergency department (inpatient) or by primary-care doctors (outpatient) for acute respiratory illness (2003–05)	2003–04 (4760 inpatients); 2003–04 (696 outpatients); 2004–05 (4708 inpatients); 2004–05 (742outpatients)	12% (−120 to 60); 52% (−100 to 90); 37% (−50 to 70); 7% (−80 to 50)
Belongia et al (2009)[41]	Residents recommended for vaccination by ACIP with acute respiratory illness: <24 months, ≥65 years, or high-risk (2004–05); <24 months, ≥50 years, or high-risk (2005–06); <59 months, ≥50 years, or high risk (2006–07)	2004–05 (818 patients); 2005–06 (356 patients); 2006–07 (932 patients)	10% (−36 to 40); 21% (−52 to 59); 52% (22 to 70)
Skowronski et al (2009)[42]	All patients aged ≥9 years presenting with ILI to sentinel primary-care practitioners	841	47% (18 to 65)
Heinonen et al (2011)[43]	Cohort of patients aged 6–35 months presenting with ILI enrolled in a randomised controlled trial for antivirals (2007–08)	340	72% (35 to 88)
Savulescu et al (2010)[44]	All patients ≥65 years old presenting with ILI (2008–09)	103	79% (−26 to 96)
Kissling et al (2009)[45]	All patients ≥65 years old presenting with ILI (2008–09)	292	59% (15 to 80)
Kelly et al (2011)[46]	All patients aged 6–59 months presenting with ILI (2008)	289	68%* (26 to 86)
Talbot et al (2011)[47]	Adults aged >50 years admitted to hospital with respiratory symptoms or non-localising fever (2006–09)	2006–07 (168 patients); 2007–08 (68 patients); 2008–09 (181 patients)	57% (−44 to 87)† 56% (−63 to 88)† 73% (−15 to 9[illegible])†

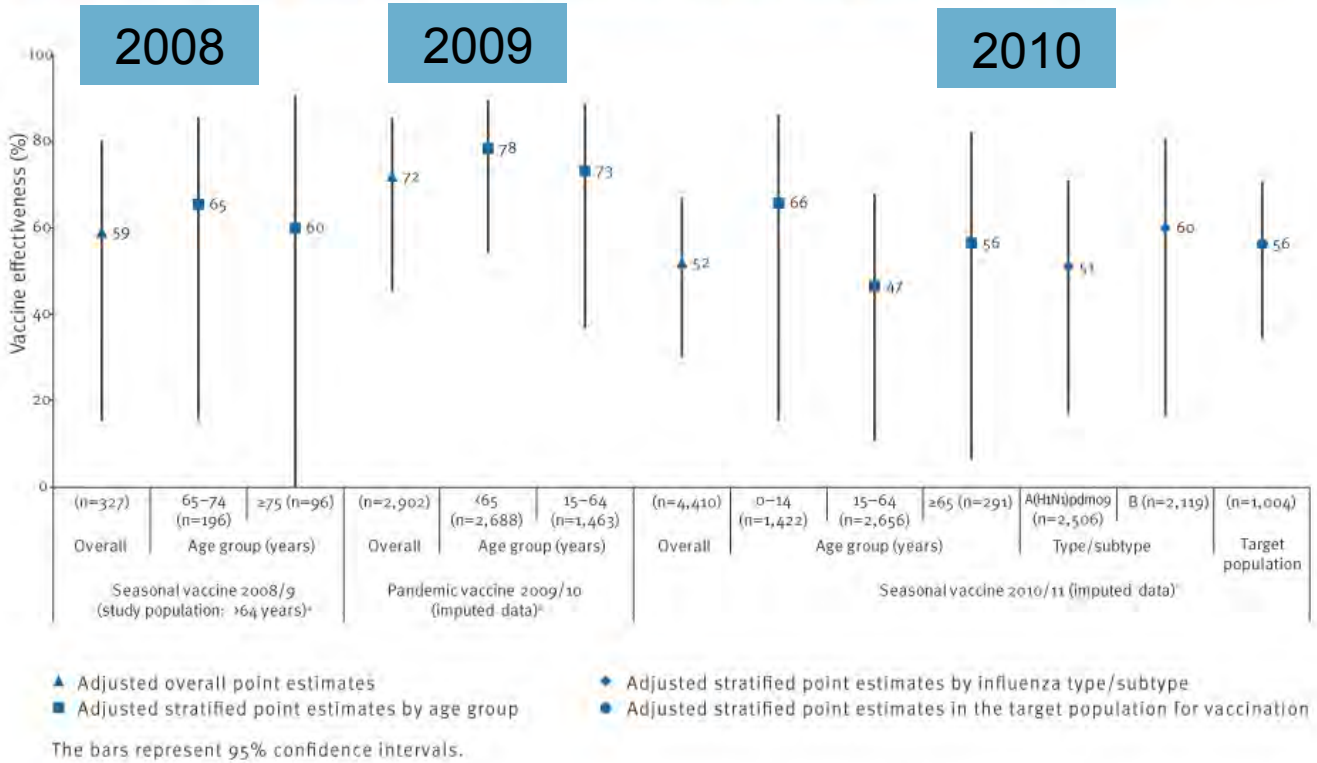
Osterholm Lancet Inf Dis 2012

Efficacité vaccinale anti-grippale

- I-MOVE: Influenza - Monitoring Vaccine Effectiveness (Europe)

FIGURE 2

Adjusted overall and stratified influenza vaccine effectiveness against medically attended laboratory-confirmed influenza, I-MOVE multicentre case–control study, 2008/09 (5 study sites), 2009/10 (7 study sites), 2010/11 (8 study sites)



I-MOVE: Influenza monitoring vaccine effectiveness.

[a] Adjusted for previous season influenza vaccination, at least one chronic disease, sex, at least one hospitalisation in previous 12 months, current smoker, age group (not included in the age-group strata), functional status.

[b] Adjusted for any influenza vaccination in the two previous seasons, 2009/10 seasonal influenza vaccination, at least one chronic disease, sex, at least one hospitalisation for chronic disease in previous 12 months, current smoker, age group, practitioners vists in previous 12 months, month of symptom onset.

[c] Adjusted for influenza vaccination in previous 2 seasons, at least one chronic disease, sex, at least one hospitalisation for chronic disease in previous 12 months, current smoker, age group, practitioners visits in previous 12 months, week of symptom onset.

Efficacité anti-grippale: saison 2014-2015

TABLE 2. Number and percentage receiving 2014–15 seasonal influenza vaccine among 2,321 outpatients with acute respiratory illness and cough, by influenza test result status, age group, and vaccine effectiveness* against all influenza A and B and against virus type A (H3N2) — U.S. Influenza Vaccine Effectiveness Network, United States, November 10, 2014–January 2, 2015

	Influenza positive			Influenza negative			Vaccine effectiveness			
							Unadjusted		Adjusted	
Influenza type/Age group	No. vaccinated	Total sample	(%)	No. vaccinated	Total sample	(%)	(%)	(95% CI)	(%)	(95% CI)
Influenza A and B										
Overall	**465**	**950**	**(49)**	**771**	**1,371**	**(56)**	**(25)**	**(12–37)**	**(23)**	**(8–36)**
Age group (yrs)										
6 mos–17	159	410	(39)	285	583	(49)	(34)	(14–49)	(24)	(0–43)
18–49	114	268	(43)	193	400	(48)	(21)	(-8–42)	(16)	(-18–41)
≥50	192	272	(71)	293	388	(76)	(22)	(-10–45)	(23)	(-14–47)
Influenza A (H3N2)										
Overall	**407**	**841**	**(48)**	**771**	**1,371**	**(56)**	**(27)**	**(13–39)**	**(22)**	**(5–35)**
Age group (yrs)										
6 mos–17	143	375	(38)	285	583	(49)	(35)	(16–50)	(26)	(2–45)
18–49	100	235	(43)	193	400	(48)	(21)	(-10–43)	(12)	(-26–39)
≥50	164	231	(71)	293	388	(76)	(21)	(-15–45)	(14)	(-31–43)

< 30 %

Flannery, Morb Mortal Wkly Rep CDC 2015

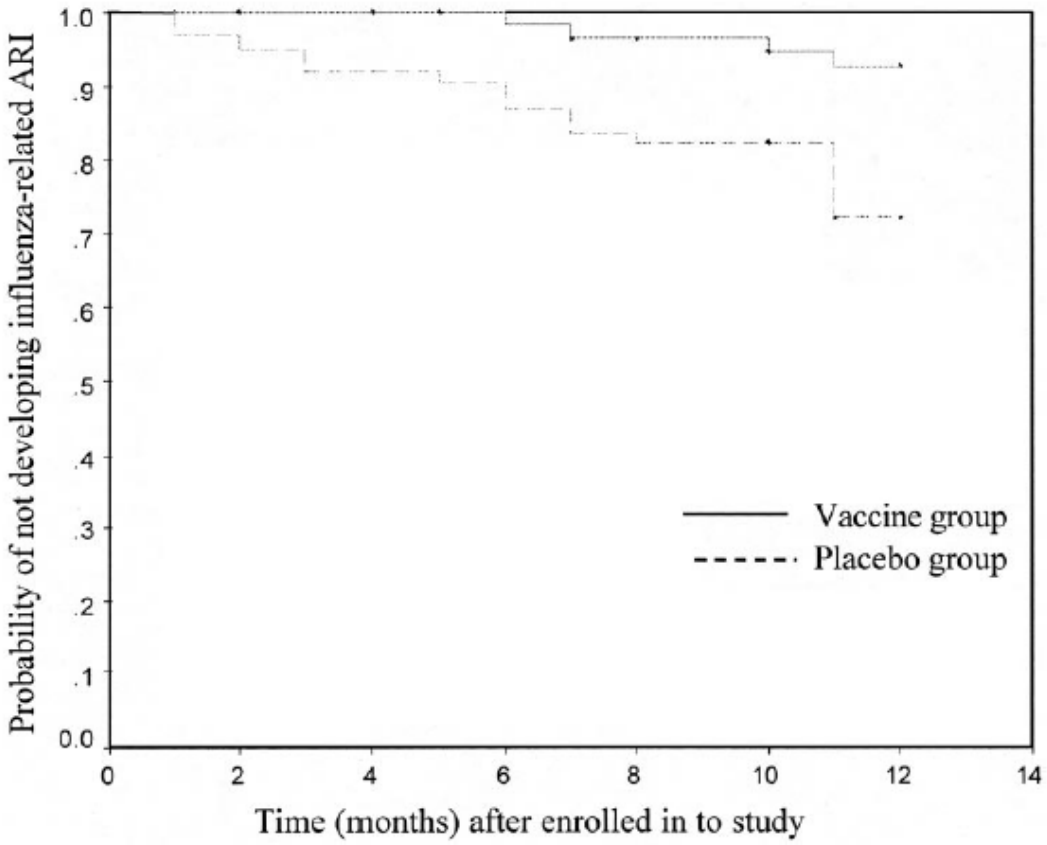
Grippe et BPCO

CHEST
AMERICAN COLLEGE of CHEST PHYSICIANS

Acute Respiratory Illness in Patients With COPD and the Effectiveness of Influenza Vaccination*

A Randomized Controlled Study

Piamsuda Wongsurakiat, MD, FCCP; Khuan Nanta Maranetra, MD



Vacciné n = 62

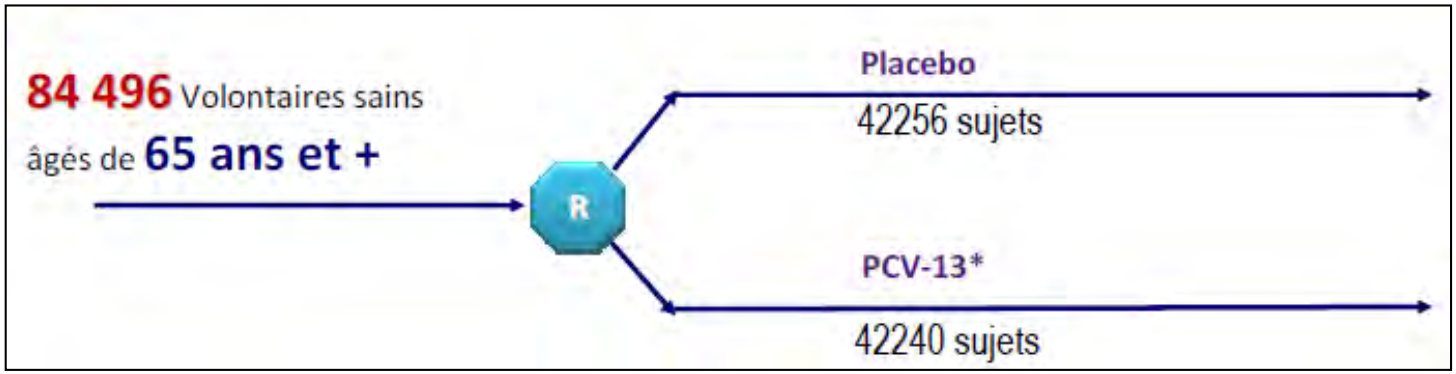
Non vacciné n = 63

Efficacité vaccinale 76%

Wongsurakiat Chest 2004

Efficacité vaccinale anti-pneumococcique

- Etude CAPITA



- Critère de jugement : PAC à pneumocoque de sérotype vaccinal

Bonten NEJM 2015

Efficacité vaccinale anti-pneumococcique

Critère d'efficacité sur les premiers épisodes de	Groupe de vaccination		EV (%)	IC 95,2%	P
	Prevenar 13 (n=42 240)	Placebo (n=42 256)			
PAC-P à sérotype vaccinal confirmée	49	90	45.6	(21.8-62.5)	< 0.001
PAC-P à sérotype vaccinal NB/NI confirmée	33	60	45	(14.2 – 65.3)	0.007
IIP à sérotype vaccinal	7	28	75	(41.4 – 90.8)	<0.001

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Au total: Pathologies respiratoires chroniques

- Grippe
  - Facteur d'exacerbation
  - Grippe + sévère
  - Données d'efficacité vaccinale dans la BPCO

- Pneumocoque
  - Surrisque largement démontré pour les patients BPCO / asthme / et « chronic lung disease » au sens large

- Cumul des comorbidités = élément fondamental à considérer

Les questions en suspens …

- Quels vaccins pour protéger au mieux nos patients ?
  - Exemple du pneumocoque: vaccin polysaccharidique seul actuellement recommandé mais immunogénicité du vaccin conjugué plus importante …
  - Couverture sérotypique insuffisante du vaccin conjugué ?
- Exacerbation:
  - Peut on vacciner pendant ?
  - Si non, quel délai après l'exacerbation ?
- L'âge est-il un facteur à considérer dans la discussion du meilleur vaccin / schéma vaccinal ?
- Et l'*Haemophilus influenzae* ?

….

NOMBREUSES !!!

Projet de recommandations vaccinales pneumologiques

- Elaborations de recommandations vaccinales propres aux patients de pneumologie
- Collaboration SPLF (GREPI) / SPILF
- Coordonné E.Blanchard/ A.Bergeron

- Questions spécifiques par pathologie respiratoire
  - Asthme
  - BPCO
  - Cancer
  - DDB muco ou non
  - PID sous IS ou non
  - SAOS

- Questions par pathogène

Grippe, pneumocoque, coqueluche, Haemophilus, autres

Projet recommandations vaccinales en pneumologie

- Groupe de travail en cours d'élaboration
- Groupe de relecture en cours d'élaboration
- Appel à candidature !

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Epidémiologie changeante…

Selon les stratégies vaccinales !!!

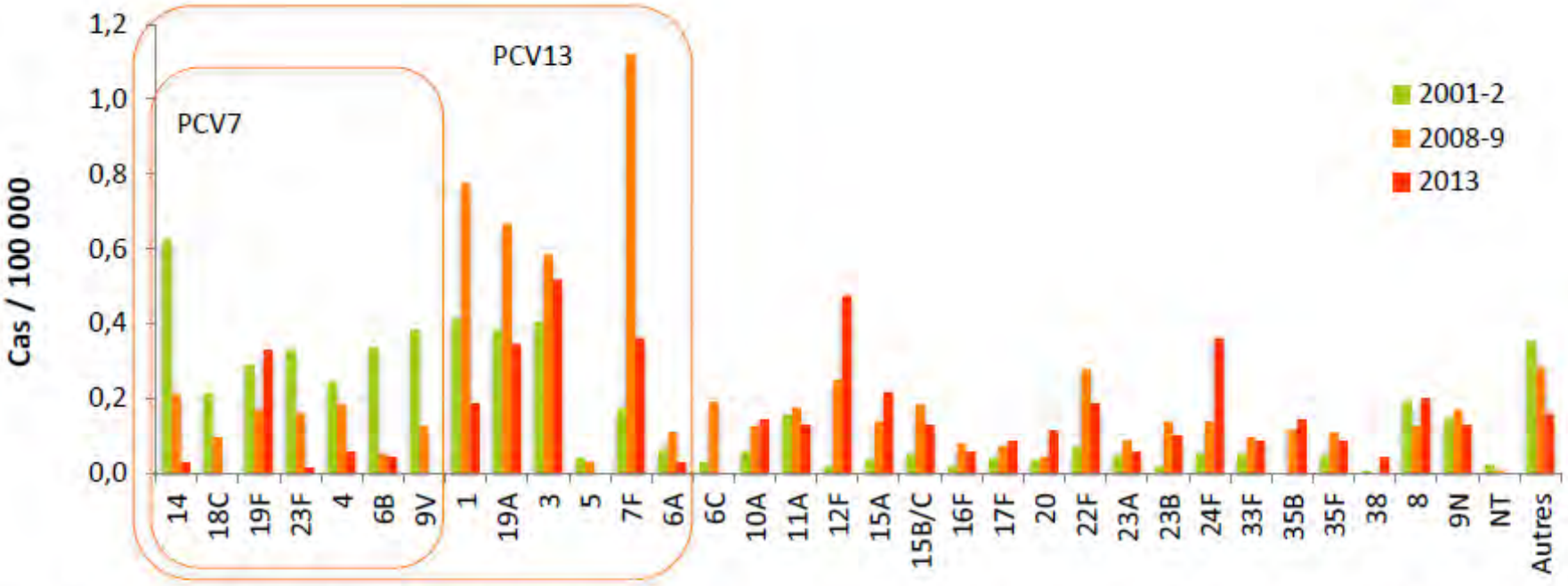

Figure 8 - Évolution de l'incidence des infections invasives à pneumocoque selon le sérotype chez les adultes âgés de 16 à 64 ans entre 2001-2002 et 2013.

Données CNR pneumocoque 2013