

Interactions virus-bactéries dans les infections respiratoires

Impact du vaccin antipneumococcique conjugué

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Inserm 1047



Déclaration d'intérêts de 2014 à 2021

- **Intérêts financiers : Aucun**
- **Liens durables ou permanents : Aucun**
- **Interventions ponctuelles : Astrazeneca, GSK, Janssen, Moderna, MSD, Pfizer, Sanofi**
- **Intérêts indirects : prise en charge congrès (Sanofi, Pfizer)**

Interactions virus-bactéries dans les infections respiratoires

Infection : Action virus infection bactérienne

- **Dysfonction physiologie pulmonaire**
- **Exposition des récepteurs**
- **Inflammation systémique**

Influenza

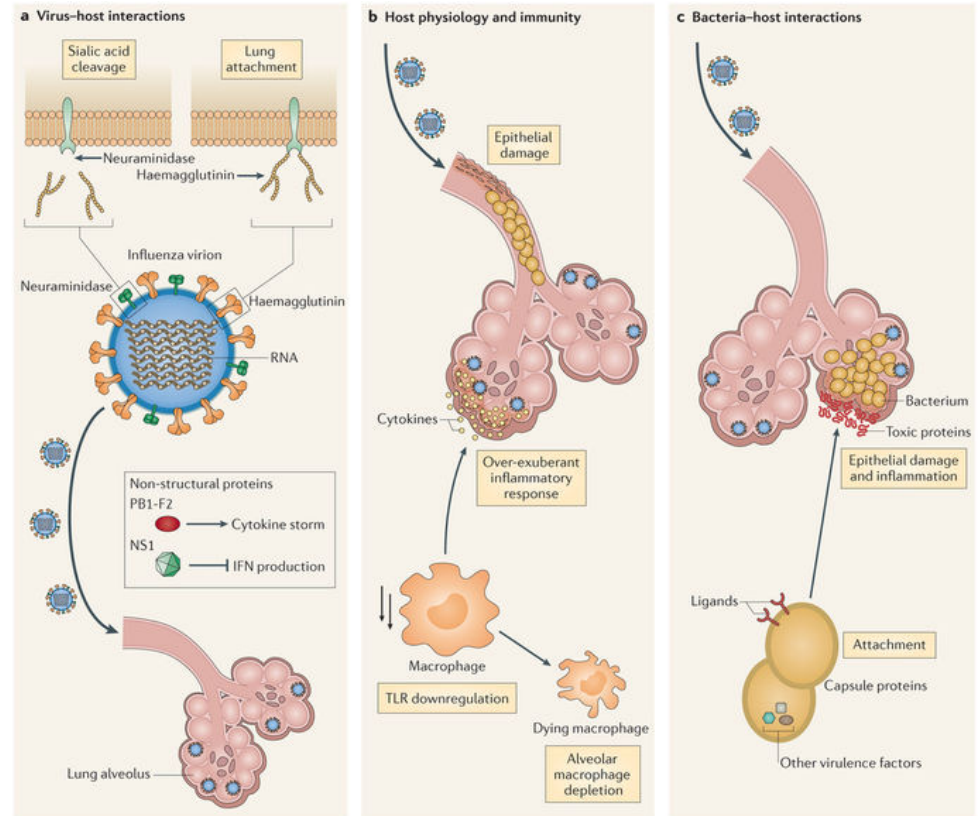
(*Streptocoque pneumoniae*, *Staphylococcus aureus*, *Pseudomonas aeruginosa*)

VRS

(*Streptocoque pneumoniae*)

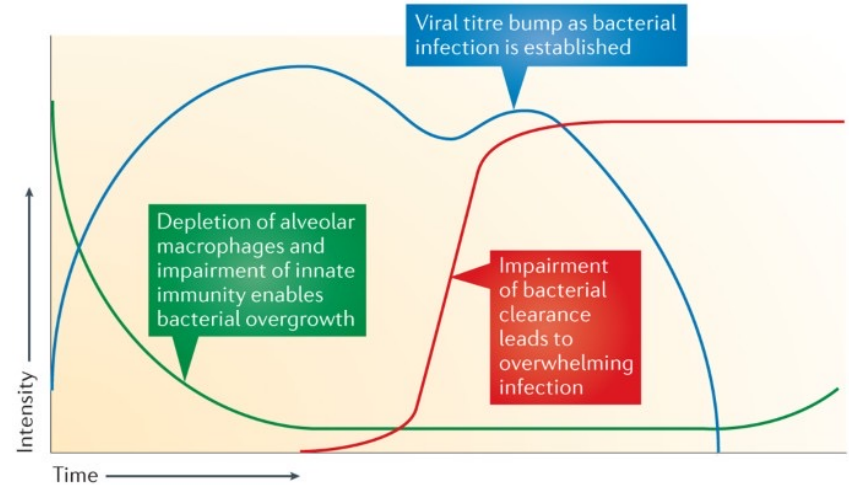
Rhinovirus

(*Streptocoque pneumoniae*)



Infection : Action bactérie sur infection virale

- Interaction directe
- Interférence avec l'immunité antivirale
- Synergie des facteurs de virulence

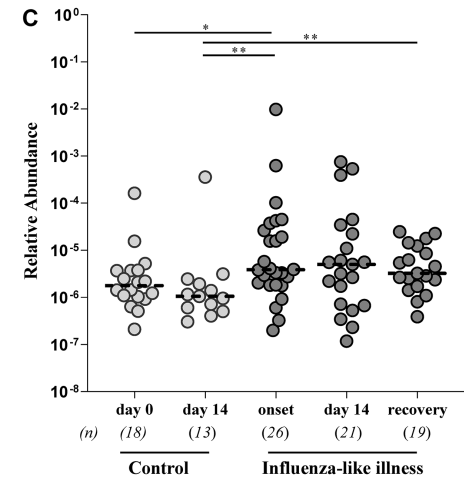
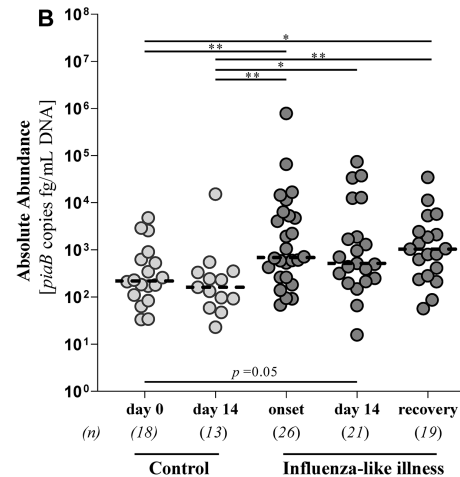


Colonisation : Action virus sur colonisation bactérienne

Multicentrique, prospective, Pays-Bas, 2014-2015
232 adultes > 60 ans avec Syndrome Grippal vs 194 contrôles asymptomatiques
PCR pneumocoque et virus sur échantillons salivaires
Début Syndrome grippal, S2 et S9
Virus respiratoires chez 76% des SG et 15% des contrôles

Pas de différence en terme prévalence
portage pneumocoque
(18% SG vs 13% contrôle)

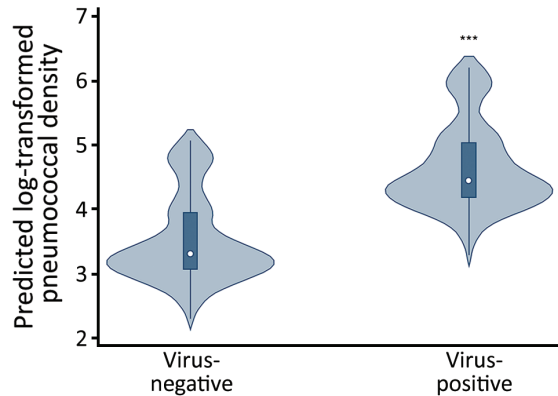
Mais quantité de pneumocoque plus
importante dans le groupe SG avec
persistance à S9



Colonisation : Action colonisation bactérienne sur infection virale

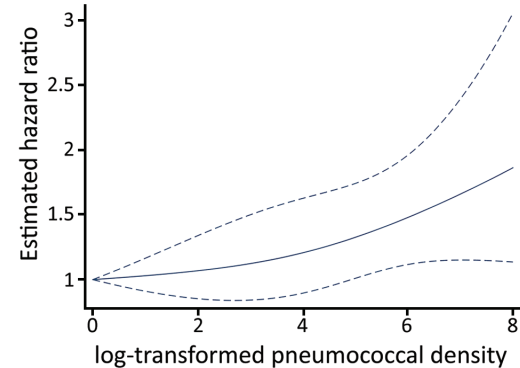
Etude RESPIRA-Peru, Prospective, Pérou, 2009-2011
849 échantillons de 480 enfants asymptomatiques
PCR pneumocoque et virales sur écouvillon NP tous les mois
Surveillance apparition Infections respiratoires aiguës (ARI)

Portage pneumocoque 67% des échantillons
Portage virus respiratoires 42% des échantillons



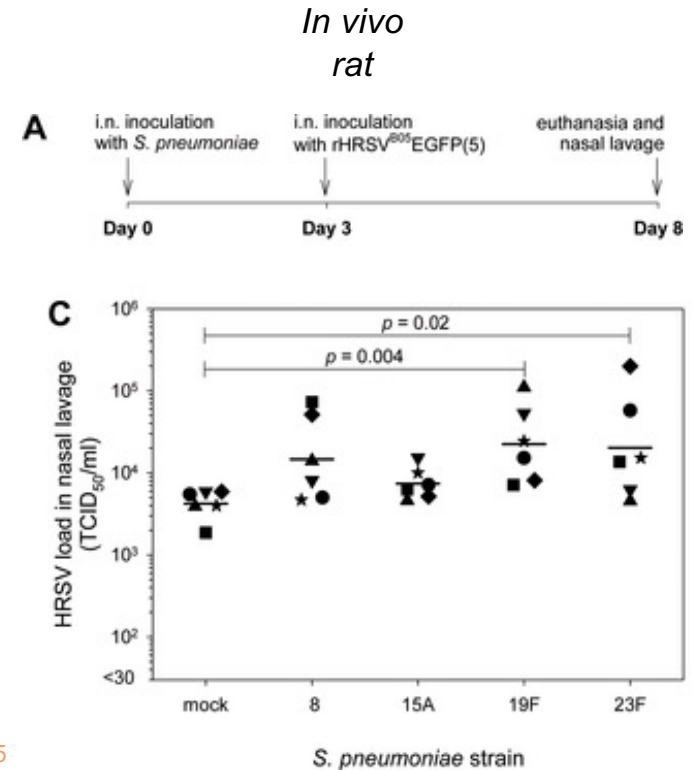
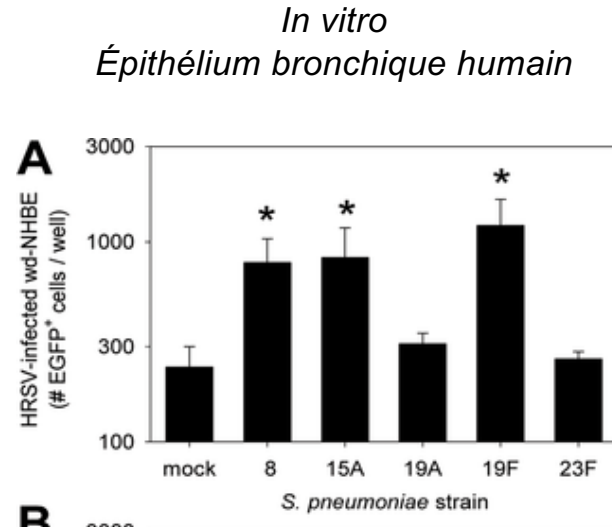
Quantité de pneumocoque plus élevée en présence virus respiratoire

Quantité de pneumocoque associée à survenue ARI



Colonisation : Action colonisation bactérienne sur infection virale

Impact de la colonisation à Pneumocoque sur infection VRS

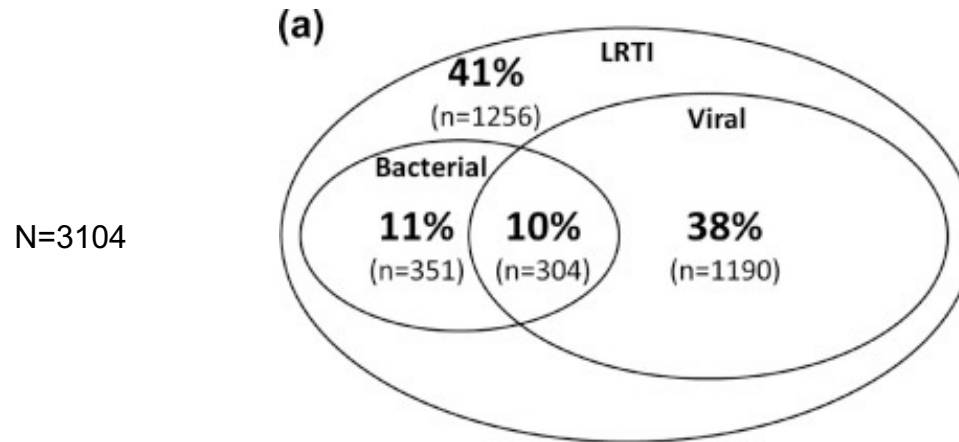


Augmentation nombre cellules infectées par VRS lorsque présence certaines souches Pneumocoque

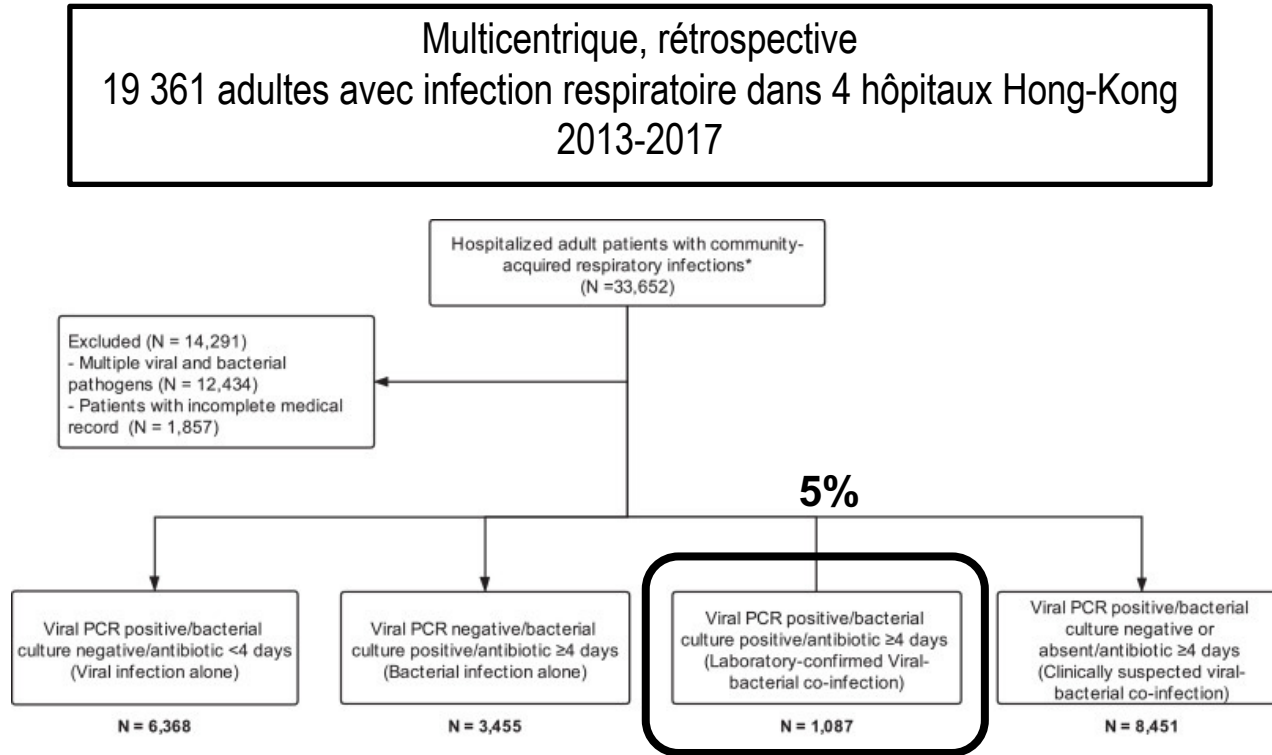
Fréquence et conséquences des co-infections respiratoires virus-bactéries

Prévalence de la co-infection dans les IRB

Multicentrique, prospective
3104 adultes avec IRB confirmée dans 11 pays européens
Soins primaires
2007 - 2010



Prévalence de la co-infection dans les IRB

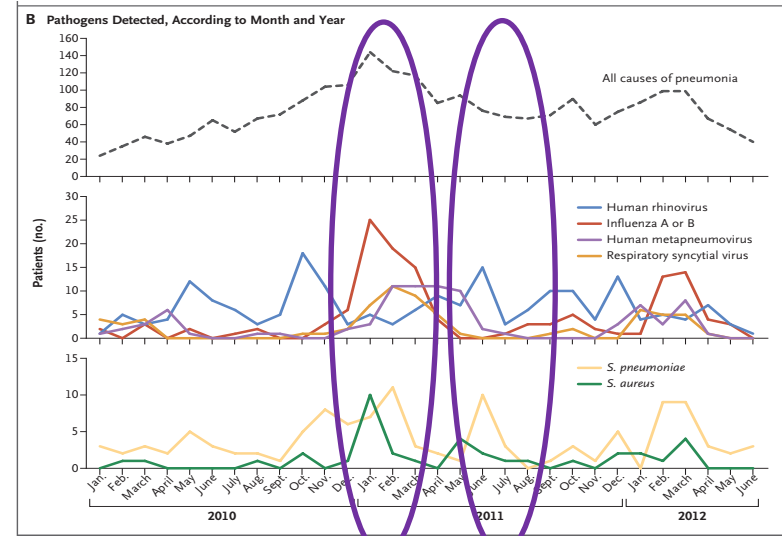
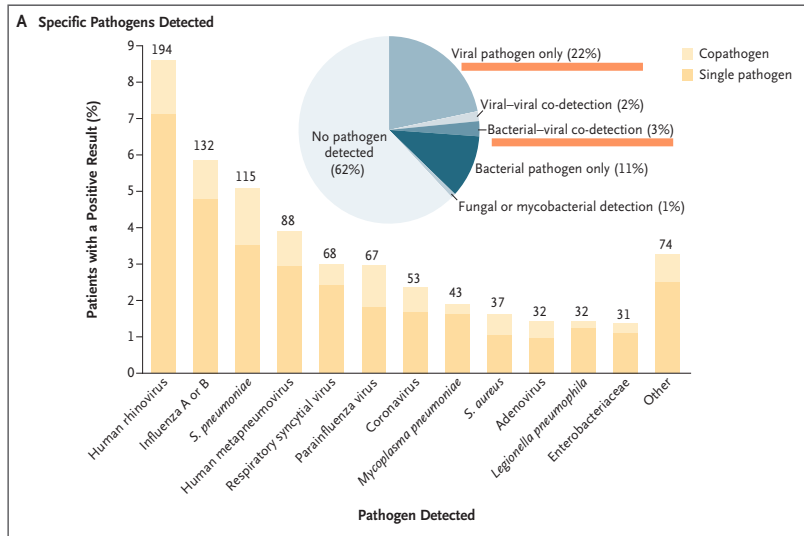


* All samples were collected within 48 hours of patients' hospital admission and have at least one upper respiratory infection symptoms

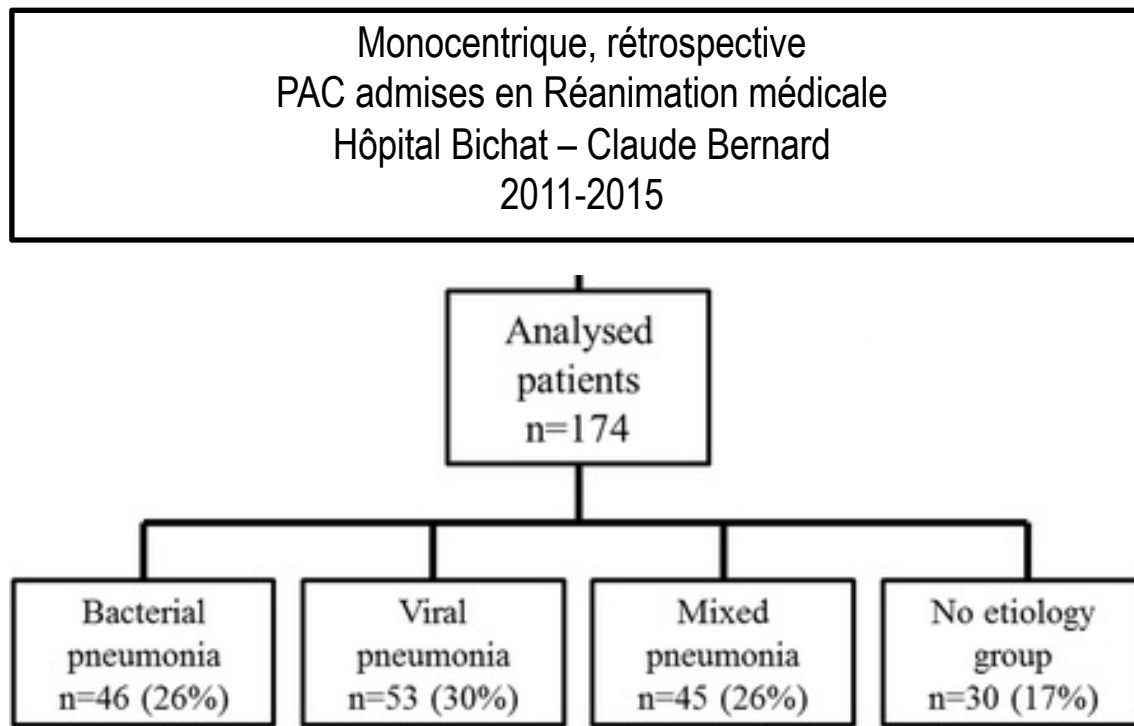
Prévalence de la co-infection dans les PAC

Etude EPIC

Multicentrique, prospective
 2259 adultes avec PAC confirmée dans 5 hôpitaux régions de
 Chicago et Nashville
 janvier 2010 et juin 2012

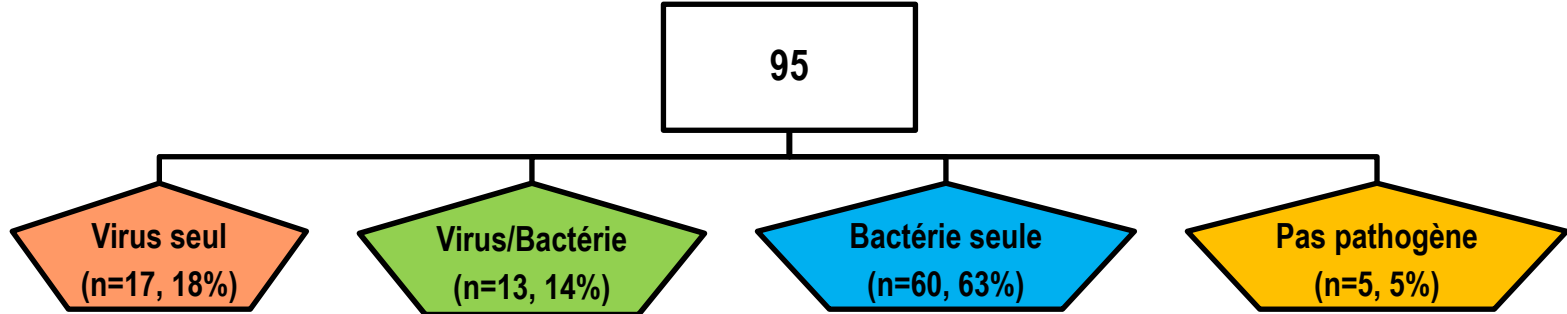


Prévalence de la co-infection dans les PAC admises en réanimation



Prévalence de la co-infection dans les PAH

Monocentrique, rétrospective
95 PAH acquises ou admises en Réanimation médicale
Hôpital Bichat – Claude Bernard
2014-2016

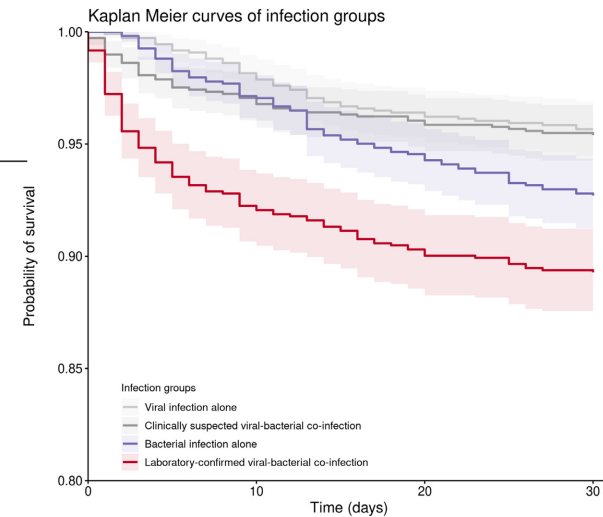


Conséquences de la co-infection dans les PAC

Co-infection associée à mortalité et admission en réanimation

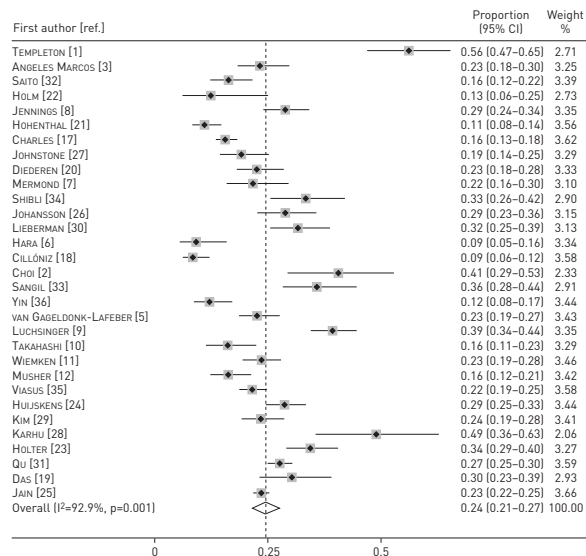
Table 2
Outcomes of patients with different types of infection.

	Before propensity score matching*				After propensity score matching			
	Reference group	Laboratory-confirmed viral-bacterial coinfection group	Risk of the coinfection group [95% CI]	p-value	Reference group	Laboratory-confirmed viral-bacterial coinfection group	Risk of the coinfection group [95% CI]	Adjusted p-value
Laboratory-confirmed viral-bacterial co-infection versus viral infection alone	N = 6368	N = 1087			N = 1083	N = 1083		
30-day mortality N (%)	332 (5.2%)	118 (10.9%)	HR ~2.2 [1.8, 2.7]	<-0.001	47 (4.3%)	117 (10.8%)	HR ~2.6 [1.9, 3.7]	<-0.001
ICU admission N (%)	207 (3.3%)	103 (9.5%)	RR ~2.9 [2.3, 3.7]	<-0.001	35 (3.2%)	102 (9.42%)	RR ~2.9 [2.3, 3.6]	<-0.001
Laboratory-confirmed viral-bacterial co-infection versus bacterial infection alone	N = 3455	N = 1087			N = 1083	N = 1083		
30-day mortality N (%)	310 (9.0%)	118 (10.9%)	HR ~1.3					
[1.01, 1.5]	0.114	79 (7.3%)	116 (10.7%)	HR ~1.4 [1.1, 1.9]	0.028			
ICU admission N (%)	196 (5.7%)	103 (9.5%)	RR ~1.8					
[1.3, 2.1]	<0.001	44 (4.1%)	103 (9.5%)	RR ~1.6 [1.2, 2.1]	<-0.001			
Laboratory-confirmed viral-bacterial co-infection versus clinically suspected viral-bacterial co-infection	N = 8451	N = 1087			N = 1086	N = 1086		
30-day mortality N (%)	400 (4.7%)	118 (10.9%)	HR ~2.4					
[1.9, 2.9]	<0.001	53 (4.9%)	118 (10.9%)	HR ~2.3 [1.7, 3.2]	<-0.001			
ICU admission N (%)	254 (3.0%)	103 (9.5%)	RR ~3.15					
[2.5, 3.9]	<0.001	35 (3.2%)	103 (9.5%)	RR ~3.2 [2.5, 3.9]	<-0.001			



Conséquences de la co-infection dans les PAC

Meta-analyse présence virus dans les PAC (31 études)



25%

Risque de décès augmenté dans les co-infections

(OR 2.1, 95% CI 1.32–3.31)

Co-infection associée à pneumonie complexe (décès ou ventilation mécanique > 7 jours)

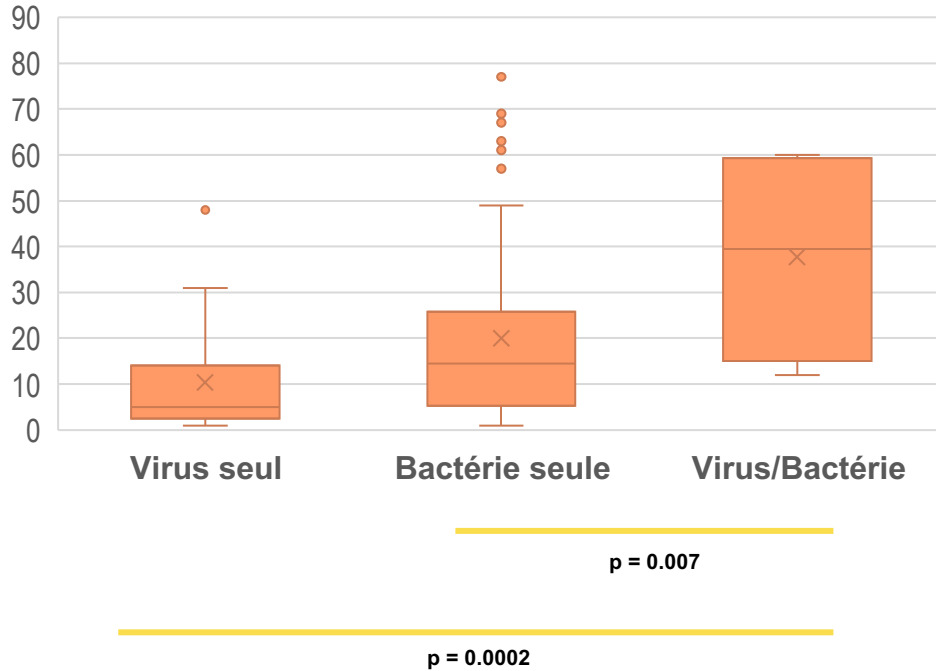
Table 3 Multivariate analysis of the risk factors for complicated course in 174 patients with severe CAP

Variables	OR	95 % CI	p value
Microbiological diagnosis			
Bacterial pneumonia	Ref	...	
Viral pneumonia	0.69	0.24–1.95	0.48
Mixed pneumonia	3.15	1.12–8.83	0.03
No etiology pneumonia	1.29	0.40–4.21	0.67
Coronary artery disease	3.52	1.22–10.15	0.02
Shock on ICU admission	4.63	1.56–13.74	0.006
Lactate dehydrogenase > 245 U/L	4.27	1.55–11.78	0.005
PSI class IV-V at hospital referral	4.67	1.96–11.12	0.0005

CAP community-acquired pneumonia, ICU intensive care unit, OR odds ratio, PSI Pneumonia Severity Index, Ref reference, 95 % CI = 95 % confidence interval

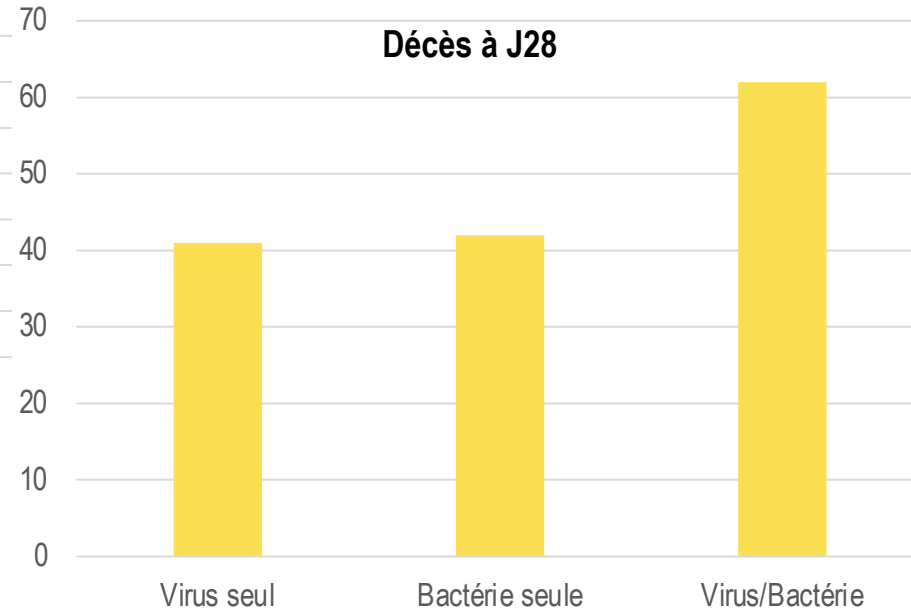
Conséquences de la co-infection dans les PAH

Durée médiane de séjour (jours)



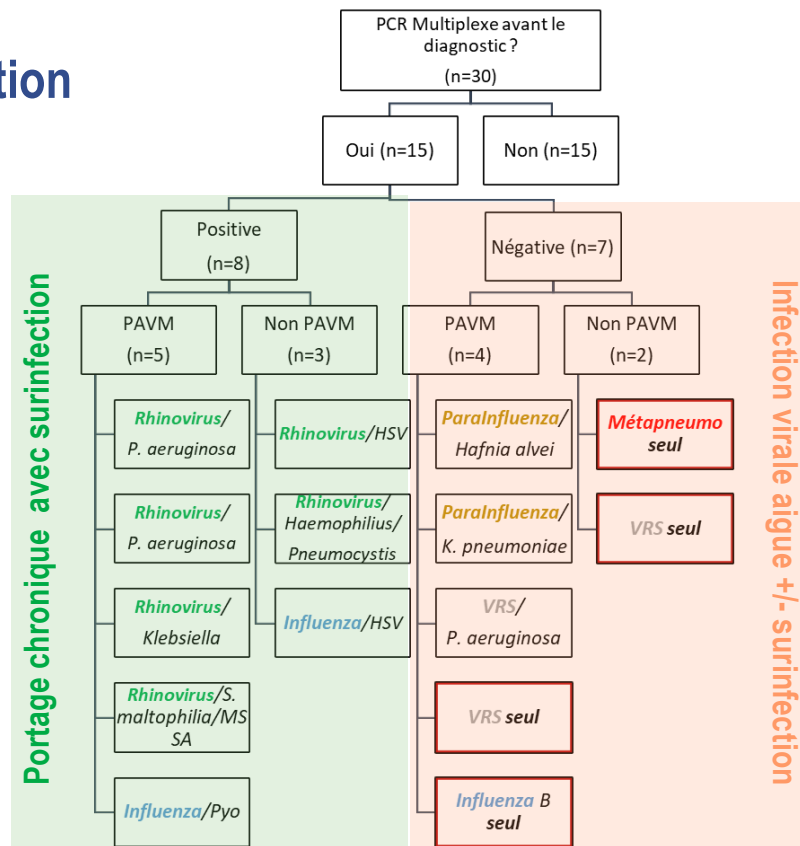
Co-infection associée à plus longue durée de séjour

Décès à J28



Conséquences de la co-infection dans les PAH

Timing de la co-infection



Impact du vaccin pneumococcique conjugué sur les infections respiratoires virales ?

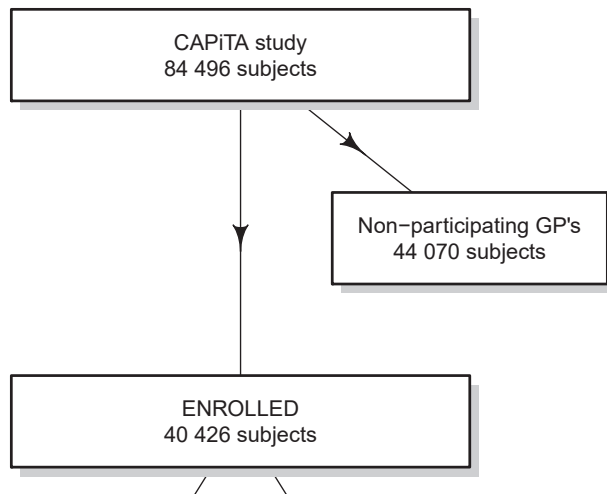
PCV9 et pneumonies virales chez l'enfant

RCT, Afrique du Sud
38 900 enfants VIH+/-
PCV9 vs Placebo

Diagnostic	Vaccin (n=18 245)	Placebo (n= 18 245)	Efficacité (IC95%)	p-value
Pneumonie virale toute cause	160	231	31% (15-43)	0.0004
Grippe A	31	56	45% (14-64)	0.01
VRS	90	115	22% (-3-41)	0.08
Para Influenza	24	43	44% (8-66)	0.02
Adenovirus	14	15	7% (-94-55)	0.9
Coronavirus (hors SARS-CoV-2)	41	62	34% (2-55)	0.038

PCV13 et IRB toutes causes chez l'adulte > 65 ans

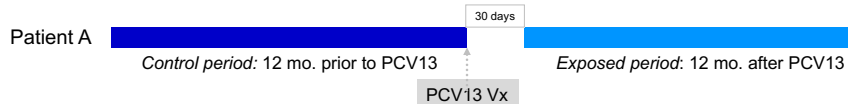
EtioCAP = Sous étude, Essai CAPiTA, Pays-Bas
RCT PCV13 vs Placebo
Données soins primaires



Diagnostic	Efficacité vaccinale (IC95%)
Hospitalisées	-
IIP sérotype vaccinal	76 % (48-89)
PAC sérotype vaccinal	38% (14-55)
PAC clinique	8% (-1-16)
Ambulatoires + Hospitalisées	-
PAC clinique	7% (0-14)
IRB	4% (0-9)

PCV13 et IRB toutes causes chez l'adulte > 65 ans

Cohorte rétrospective, USA
 Kaiser Permanente South California
 42 700 adultes > 65 ans
 Incidence IRB toute cause avant/après PCV13
 2016-2019



Outcome	Exposure	Vaccine Effectiveness (95% CI)	Rate Difference per 100,000 PY (VPDI)	Number needed to vaccinate (NNV)
Medically-attended all-cause CAP	PCV13	8.8% (-0.2, 17.0)	500 (0 to 1100)	40 (-91 to 252)
	PPV23	3.9 (-9.4, 15.6)		
	Zoster Vx	-2.6 (-19.8, 12.1)		
Medically-attended LRTI	PCV13	9.9% (1.1, 17.9)	800 (200 to 1400)	26 (14 to 113)
	PPV23	1.0 (-18.0, 17.0)		
	Zoster Vx	-1.7 (-15.3, 10.3)		

PCV13 et Pneumonies virales chez l'adulte > 65 ans

Sous-analyse, Essai CAPiTA, Pays-Bas
 RCT PCV13 vs Placebo
 800 PAC confirmées et 1500 PAC suspectées
 Prélèvements bactério-viro
 7% co-infection bactéries-virus

First episode of virus-associated 'confirmed CAP' and 'suspected pneumonia'

First episode	Confirmed CAP (n = 1653)						Suspected pneumonia (n = 2917)					
	PCV13	Placebo	VE	99.3%CI	p-value	VE ^a	PCV13	Placebo	VE	99.3% CI	p-value	VE ^a
Influenza virus (either A or B)	23	35	34.4%	-35.4%	68.2%	0.117	61 ^c	71 ^c	14.2%	-37.4%	46.4%	0.381
Influenza virus A	18 ^b	28 ^b	35.8%	-45.0%	71.6%	0.143	48 ^c	57 ^c	15.9%	-42.7%	50.4%	0.377
Influenza virus B	4 ^b	3 ^b	-33.2%	-100.0%	83.0%	0.707	10	9	-11.0%	-283.2%	67.9%	0.821
Detection of any virus	163	169	3.6%	-29.6%	28.3%	0.736	313	324	3.5%	-19.5%	22.0%	0.656
Para-influenza virus (1, 2, 3 or 4)	18	8	-124.8%	-607.2%	28.5%	0.057	34	22	-54.5%	-223.1%	26.1%	0.112
Human adenovirus	4	2	-99.9%	-1966%	80.7%	0.424	6	6	0.1%	-374.0%	78.9%	0.999
Human bocavirus	2	2	0.0%	-1383%	93.3%	1.000	2	3	33.4%	-681.6%	94.3%	0.657
Human coronavirus	26	34	23.6%	-54.3%	62.2%	0.302	50	72	30.6%	-14.0%	57.8%	0.047
Human metapneumovirus	17	19	10.6%	-120.0%	63.7%	0.737	37	36	-2.7%	-93.1%	45.4%	0.910
Respiratory syncytial virus	20	15	-33.2%	-234.6%	47.0%	0.401	51	40	-27.4%	-125.2%	27.9%	0.251
Human rhinovirus	63	62	-1.5%	-64.5%	37.3%	0.932	98	101	3.1%	-42.1%	33.9%	0.827

PCV13 et Pneumonies et IRB virales chez l'adulte > 18 ans

Etude cas-contrôles, USA
 Kaiser Permanente South California
 13 856 cas = IRB avec virus +
 227 887 témoins
 Exposition = Atcd vaccination PCV 13
 2015-2019

Efficacité significative tous
 virus confondus PAC et IRB
 Pas sur VRS ni Adenovirus

	Nonpneumonia LRTI ^a					Matched, Adjusted VE (95% CI), % ^b	Pneumonia				
	PCV13 Receipt				Matched, Adjusted VE (95% CI), % ^b		PCV13 Receipt				Matched, Adjusted VE (95% CI), % ^b
	Case Patients		Controls				Case Patients		Controls		
Respiratory Virus Detected	%	No./Total No.	%	No./Total No.		%	No./Total No.	%	No./Total No.		
Any virus detected	56.6	2434/4297	58.5	51 315/87 726	21.5 (10.9–30.9)	72.1	6890/9559	73.6	103 094/140 161	24.9 (18.4–30.9)	
Any virus detected, by specific virus identified											
Influenza A	56.5	1115/1974	57.8	25 171/43 530	13.3 (–5.3 to 28.7)	70.6	1400/1982	71.0	18 920/26 648	17.9 (2.3–31.1)	
Influenza B	47.1	286/607	58.1	5331/9173	52.6 (34.6–65.6)	67.2	359/534	70.9	3034/4282	22.3 (–13.0 to 46.6)	
RSV	70.6	226/320	72.2	4549/6297	11.9 (–38.0 to 43.8)	77.9	890/1142	80.1	13 875/17 325	–1.8 (–30.7 to 20.7)	
HCoVs (229E, HKU1, OC43, NL63)	45.1	92/204	47.2	1684/3571	51.4 (6.0–74.9)	73.9	570/771	77.4	7999/10 331	23.5 (–4.1 to 43.8)	
Parainfluenza viruses (1–4)	70.4	231/328	66.0	5251/7958	–1.5 (–65.9 to 37.8)	77.7	723/931	78.9	13 145/16 658	24.2 (–6 to 42.9)	
Adenoviruses ^c	48.6	18/37	29.9	254/850	...	48.1	65/135	43.5	841/1935	6.0 (–114.6 to 58.8)	
HMPV	65.2	120/184	59.4	2013/3389	–25.2 (–131.6 to 32.3)	69.7	890/1276	70.6	13 027/18 445	28.1 (9.8–42.7)	
Enteroviruses	53.8	346/643	54.5	7062/12958	31.8 (3.2–52.0)	71.5	1993/2788	72.4	32 253/44 537	28.6 (16.7–38.8)	
Single virus detected											
Influenza A	56.1	1043/1859	57.6	23 582/40 962	13.8 (–5.6 to 29.5)	70.0	1284/1834	70.9	17 589/24 792	21.0 (5.4–34.1)	
Influenza B	45.8	255/557	57.3	4814/8400	52.1 (33.3–65.6)	67.4	319/473	71.8	2585/3598	17.7 (–23.1 to 45.0)	
RSV	70.1	199/284	73.2	3887/5313	29.1 (–14.0 to 55.9)	77.8	777/999	79.7	11 885/14 917	5.5 (–23.3 to 27.6)	
HCoVs (229E, HKU1, OC43, NL63)	44.0	55/125	45.9	906/1975	55.3 (–12.9 to 82.3)	73.8	456/618	78.7	6571/8350	32.7 (4.8–52.5)	
Parainfluenza viruses (1–4)	68.9	210/305	66.9	4859/7258	22.0 (–27.7 to 52.4)	77.8	676/869	79.3	12 404/15 635	27.5 (2.8–45.9)	
Adenoviruses ^c	33.3	8/24	22.3	143/642	...	48.1	50/104	42.4	639/1506	...	
HMPV	65.6	112/171	61.5	1962/3189	–19.6 (–123.5 to 35.9)	69.5	821/1182	70.1	12 163/17 347	26.5 (6.8–42.1)	
Enteroviruses	53.1	304/572	53.8	6186/11 489	41.6 (15.4–59.7)	71.1	1832/2577	72.1	29 734/41 243	30.4 (18.3–40.7)	
No virus detected (negative for all) ^d	47.6	165/347	44.5	2468/5544	–18.0 (–106.0 to 32.4)	69.3	2226/3213	71.1	32 935/46 341	31.8 (21.7–40.4)	

Lewnard et al. J Infect Dis 2022

PCV13 et Covid-19 chez l'adulte > 65 ans

Etude cas-contrôles, USA
 Kaiser Permanente South California
 3677 cas = Covid-19 (1075 Hospit, 344 décès)
 530 000 témoins
 Exposition = Atcd vaccination PCV 13 et/ou PPSV23
 2020

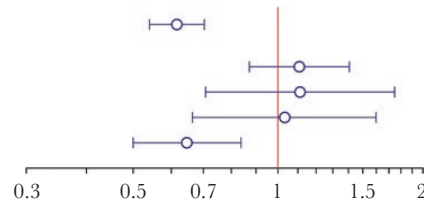
Efficacité PCV13 sur Covid,
 hospitalisation et décès
 Pas efficacité du PPSV23

Disparition efficacité PCV13 si
 utilisation ATB récente

-> argument action probable sur le
 portage pneumocoque

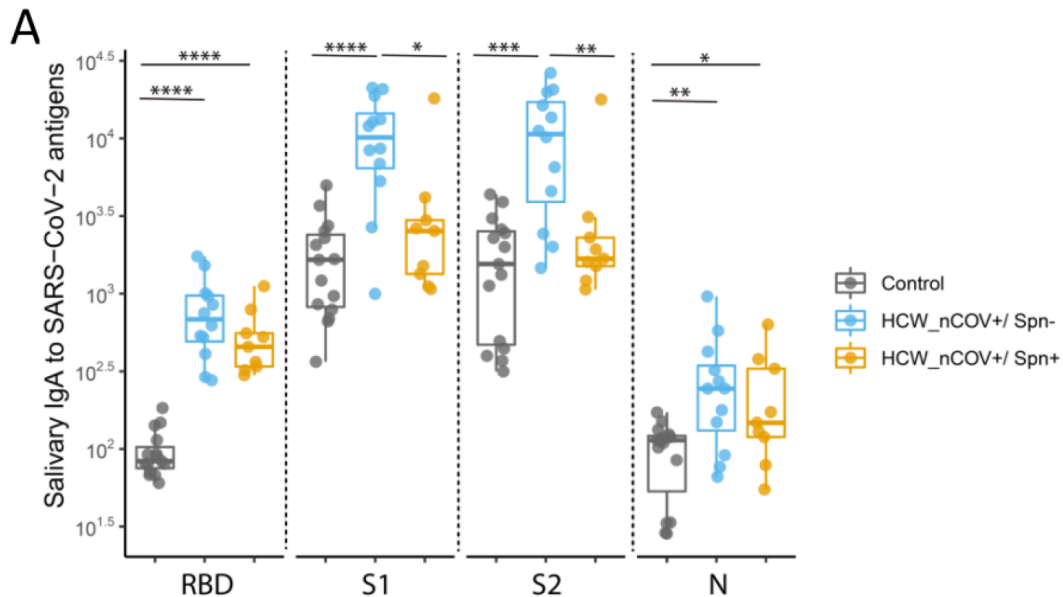
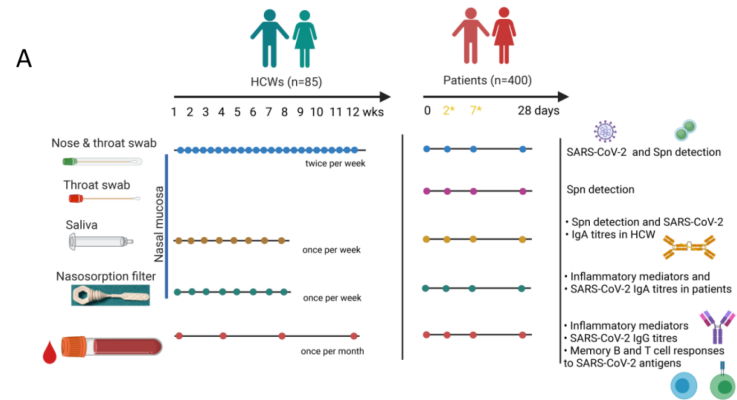
aOR (95% CI)

No antibiotics in study period 0.62 (.54-.70)
 Antibiotics 1-30 days previously 1.12 (.87-1.41)
 Antibiotics 31-60 days previously 1.14 (.71-1.75)
 Antibiotics 61-90 days previously 1.06 (.66-1.60)
 Antibiotics >90 days previously 0.65 (.50-.84)



Outcome	Exposure	Adjusted HR (95% CI)	Vx Effectiveness (95% CI)
Any COVID-19 diagnosis	PCV13	0.65 (0.59 – 0.72)	35% (28%, 41%)
	PCV13 + PPV23	0.66 (0.56 – 0.76)	34% (24%, 44%)
COVID-19 hospitalization	PCV13	0.68 (0.57 - 0.83)	32% (17%, 43%)
	PCV13 + PPV23	0.54 (0.41 – 0.73)	46% (27%, 59%)
Fatal COVID-19 hospitalization	PCV13	0.68 (0.49 – 0.95)	32% (5%, 51%)
	PCV13 + PPV23	0.57 (0.33 – 0.97)	43% (3%, 67%)
Any COVID-19 diagnosis	PPV23	1.19 (1.05 – 1.36)	-19% (-36%, -5%)
COVID-19 hospitalization	PPV23	1.02 (0.78 – 1.29)	-2% (-29, 22%)

Hypothèse : action sur le portage ?



**Plus bas niveau d'IgA chez les PS
avec portage Pneumocoque que chez ceux sans portage Pneumocoque**

Conclusions

- **Synergie virus/bactéries :**
 - Colonisation
 - Infection
- **Co/super infections virus-bactéries peu fréquentes mais plus graves**
- **Possible effet préventif des vaccins anti-pneumocociques conjugués sur les infections à certains virus respiratoires (action sur portage)**
- **Intérêt de la vaccination grippe + pneumocoque**