

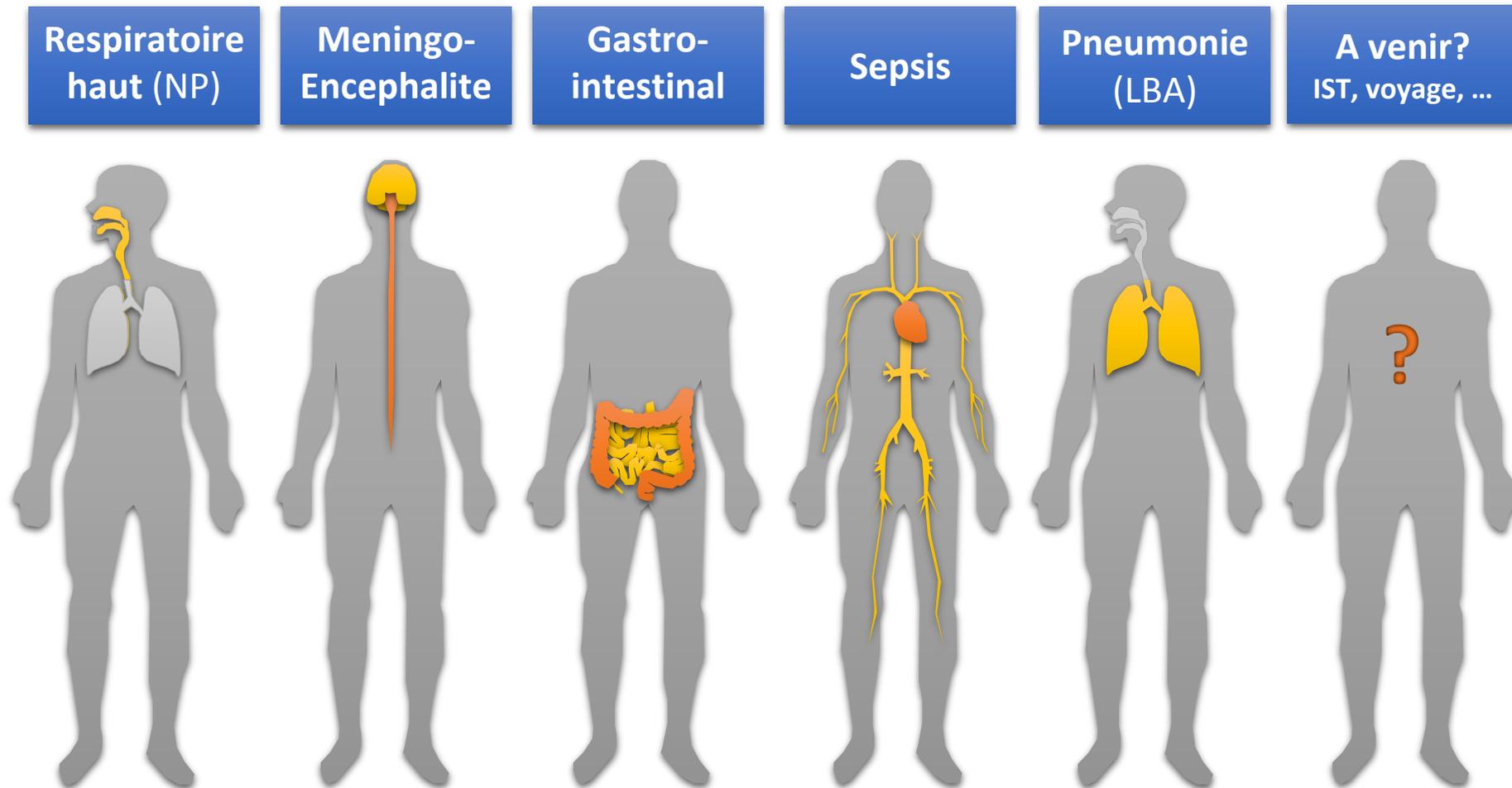


Implémentations des panels syndromiques retour d'expérience de l'hôpital Bichat

Dr Benoit Visseaux
Maitre de Conférence des Université – Praticien Hospitalier
Service de Virologie
Hôpital Bichat Claude Bernard - Paris

- **BioMérieux** : advisory board, congrès et symposium
- **Stat-Diagnostica/QIAGEN** : congrès, symposium et financement d'étude
- **Gilead** : symposium
- **Sanofi** : symposion
- **Hologic** : congrès

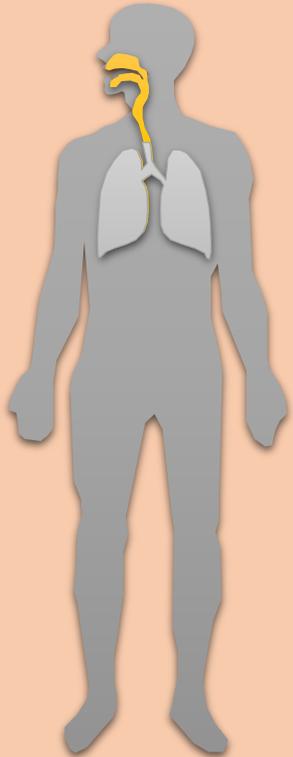
- ... Un nombre de panels en augmentation



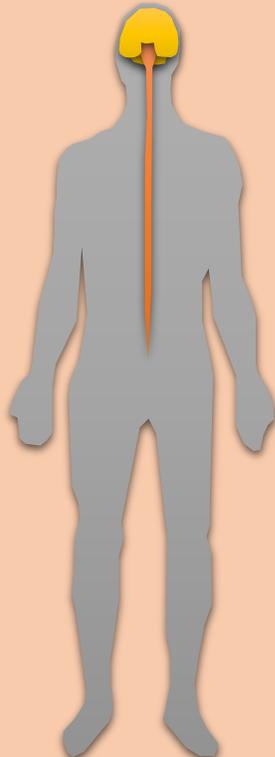
A l'hôpital Bichat...



Virologie



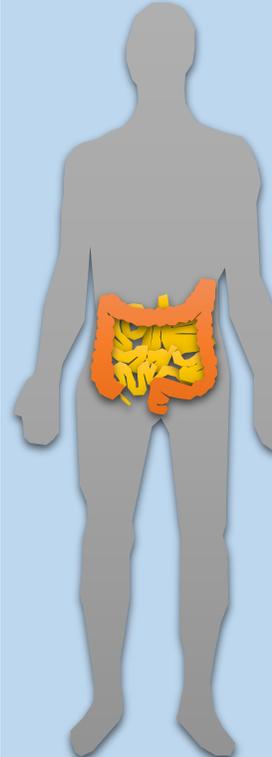
Respiratoire haut (NP)
2009



Méningo-encéphalite
2017



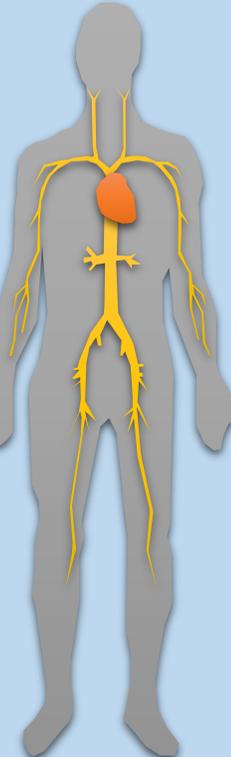
Bacteriologie



Gastro-intestinaux
2019



Respiratoire bas
2018



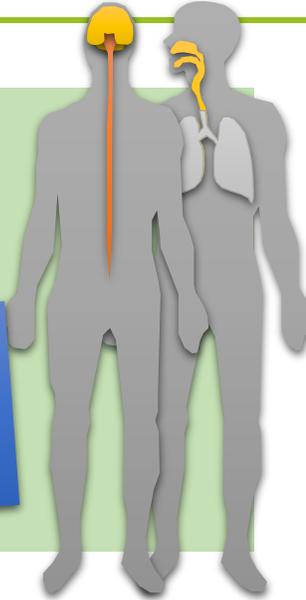
Sepsis
2019



Laboratoire de garde

Méningo-encéphalite
2019

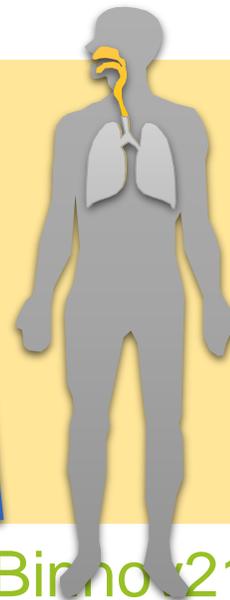
Respiratoire haut (NP)
2020



Urgences

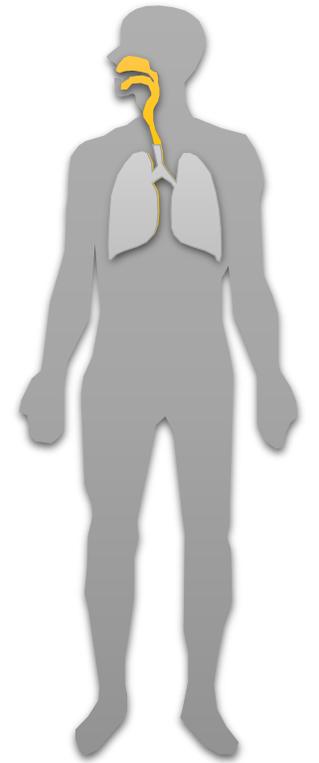
Respiratoire haut (NP)
Essais: 2018

Respiratoire haut (NP)
Prod.: 2020



Les infections respiratoires

Panels « hauts » (virologiques +++)



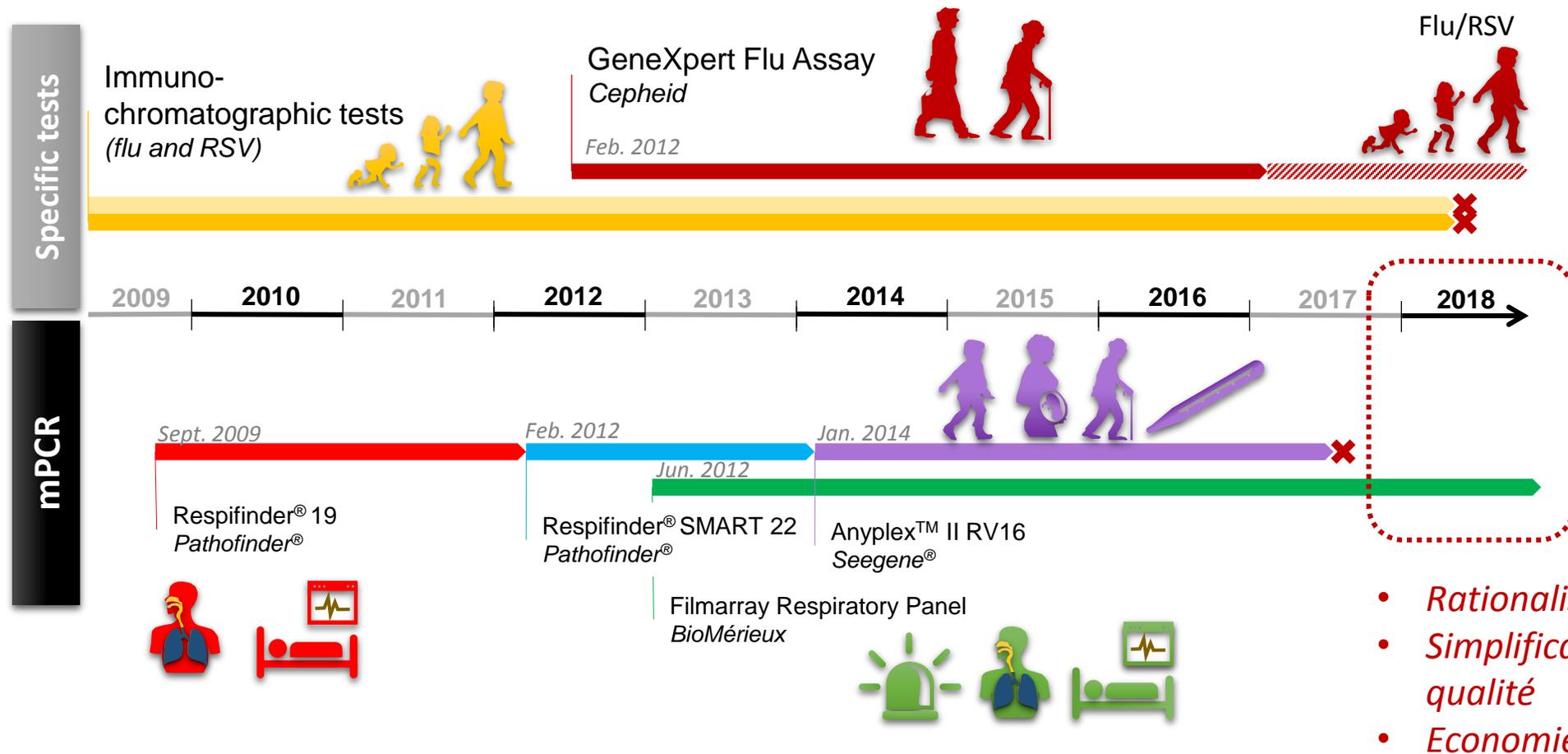
Les panels respiratoires « haut »

- ... Un nombre d'acteurs et de modalités en augmentation !

	<i>Hologic (Panther fusion) Roche (Cobas) Qiagen (NeuMoDx) Beck. Dick. (BDmax) Mobidiag (Amplidiag) ...</i>	<i>Cepheid (Genexpert) Mobidiag (Novodiag) Roche (Liat) ...</i>	<i>Seegene (Anyplex) Pathofinder (Respifinder) ...</i>	<i>BioMérieux (FilmArray) Qiagen (QIAstat-Dx) GenMark Dx (ePlex) ...</i>	<i>Abbott (IDnow) ...</i>
Multiplexing	Faible (Inf./SARS-2/VRS)	Faible (Inf./SARS-2/VRS)	Fort	Fort	Non
Automatisation	Forte	Faible	Intermédiaire	Faible	Nulle
Délai de rendu	4h à 24h	1 à 4h	24h	1 à 4h	0.5 à 2h
Point of care	Non	Possible	Non	Possible à facile	Facile
Coûts	+	++	++	++++	+



Cohabitation des différents tests...

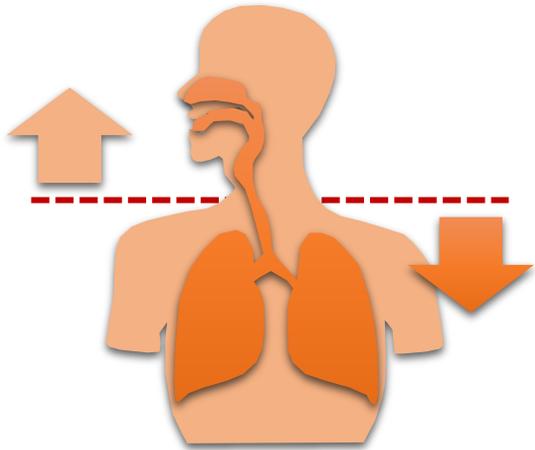


- Rationalisation des circuits
- Simplification de l'assurance qualité
- Economies d'échelles

Distribution des virus respiratoires

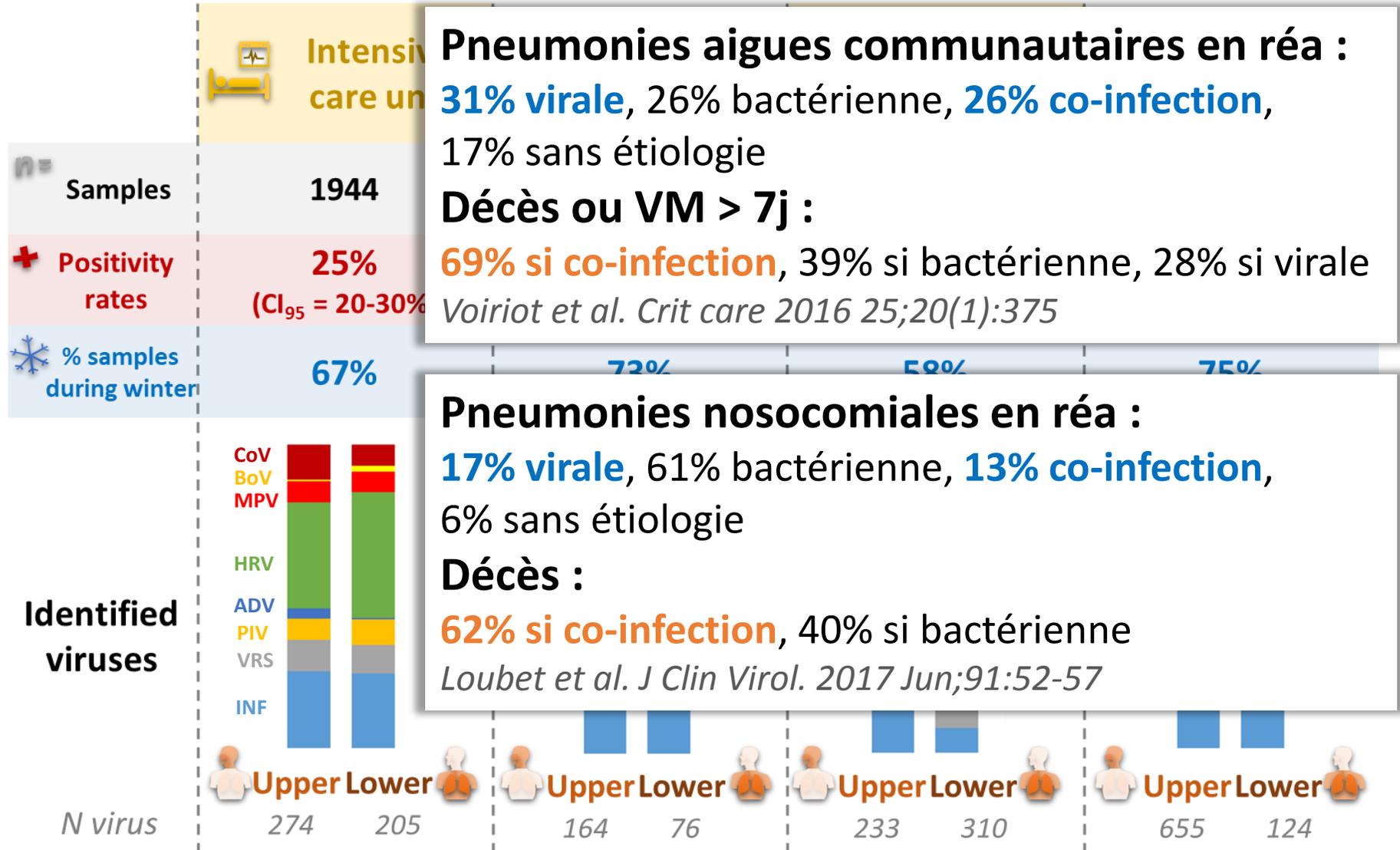
Upper respiratory tract

Nasopharyngeal swabs or aspirates



Broncho-alveolar lavages

Lower respiratory tract



Routine molecular point-of-care testing for respiratory viruses in adults presenting to hospital with acute respiratory illness (ResPOC): a pragmatic, open-label, randomised controlled trial

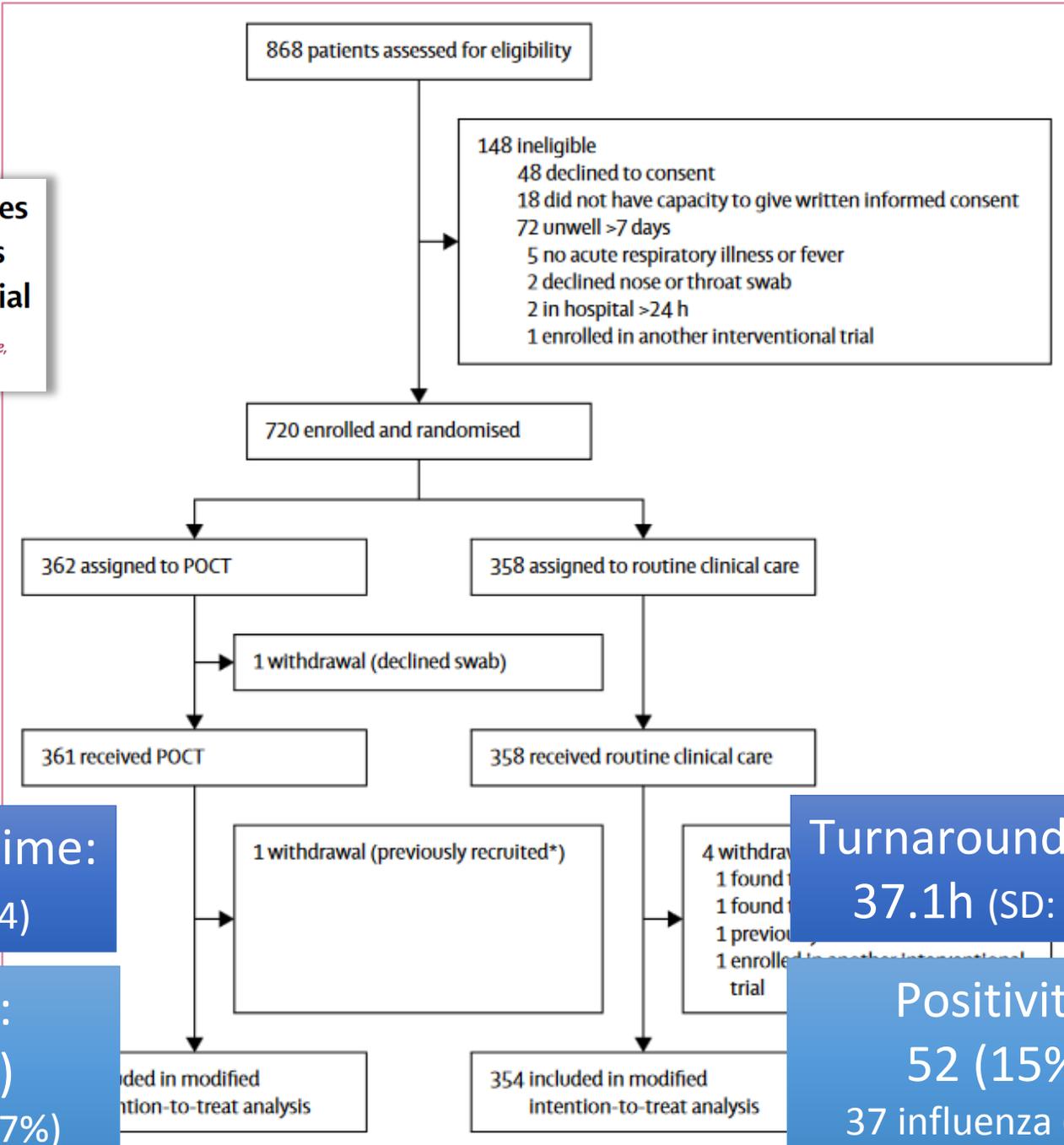
Nathan J Brendish, Ahalya K Malachira, Lawrence Armstrong, Rebecca Houghton, Sandra Aitken, Esther Nyimbili, Sean Ewings, Patrick J Lillie, Tristan W Clark

- mPCR respiratoire aux Urgences**

VS.

Tests usuels au laboratoire

(PCR pour influenza, VRS, hMPV, PIV, ADV)

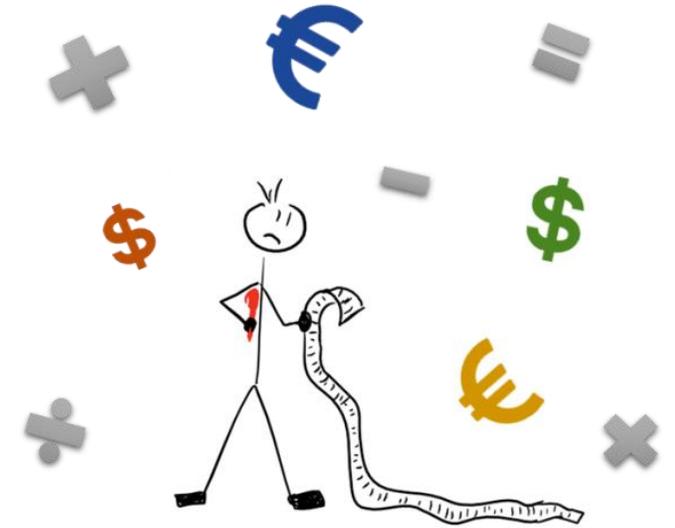


Turnaround time:
2.3h (SD: 1.4)

Positivité:
161 (45%)
61 influenza (17%)

Turnaround time:
37.1h (SD: 21.5)

Positivité:
52 (15%)
37 influenza (10%)



Clinical Practice Guidelines by the Infectious Diseases Society of America: 2018 Update on Diagnosis, Treatment, Chemoprophylaxis, and Institutional Outbreak Management of Seasonal Influenza^a

Timothy M. Uyeki,¹ Henry H. Bernstein,² John S. Bradley,^{3,4} Janet A. Englund,⁵ Thomas M. File Jr,⁶ Alicia M. Fry,¹ Stefan Gravenstein,⁷ Frederick G. Hayden,⁸ Scott A. Harper,⁹ Jon Mark Hirshon,¹⁰ Michael G. Ison,¹¹ B. Lynn Johnston,¹² Shandra L. Knight,¹³ Allison McGeer,¹⁴ Laura E. Riley,¹⁵ Cameron R. Wolfe,¹⁶ Paul E. Alexander,^{17,18} and Andrew T. Pavia¹⁹

12. Clinicians should use multiplex RT-PCR assays targeting a panel of respiratory pathogens, including influenza viruses, in hospitalized immunocompromised patients (A-III).

13. Clinicians can consider using multiplex RT-PCR assays targeting a panel of respiratory pathogens, including influenza viruses, in hospitalized patients who are not immunocompromised if it might influence care (eg, aid in cohorting decisions, reduce testing, or decrease antibiotic use) (B-III).

The Brendish study...

Routine molecular point-of-care testing for respiratory viruses in adults presenting to hospital with acute respiratory illness (ResPOC): a pragmatic, open-label, randomised controlled trial

Nathan J Brendish, Ahalya K Malachira, Lawrence Armstrong, Rebecca Houghton, Sandra Aitken, Esther Nyimbili, Sean Ewings, Patrick J Lillie, Tristan W Clark

Brendish *et al.* Lancet Resp Med. 2017

When using mPCR in the ED:

- A (very shy) decrease of antibiotic duration (7.1 vs 7.7 days, $p=0.17$)
- A decreased of length of stay by 1 day (5.7 vs 6.8 days, $p=0.04$)

ECCMID 2019 - O0280 The impact on health care resource utilisation and cost of routine syndromic molecular point-of-care testing for respiratory viruses in adults hospitalised with acute respiratory illness: further analysis from a pragmatic randomised controlled trial (ResPOC).

Nathan Brendish^{*1,2}, Micah Rose³, Jo Lord⁴, Tristan Clark^{2,1}

Brendish *et al.* ECCMID 2019

When using mPCR in the ED:

- Costs were £64 less expensive than with usual cares



The other studies...

RESEARCH ARTICLE

Open Access



Multiplex PCR point of care testing versus routine, laboratory-based testing in the treatment of adults with respiratory tract infections: a quasi-randomised study assessing impact on length of stay and antimicrobial use

Denise Andrews¹, Yumela Chetty¹, Ben S. Cooper^{2,3}, Manjinder Virk⁴, Stephen K Glass⁵, Andrew Letters⁶, Philip A. Kelly¹, Malur Sudhanva⁴ and Dakshika Jeyaratnam^{5*}

Andrews *et al.* BMC Infect Dis. 2017

When using mPCR in the ED (TAT = 19h):

- No decrease of antibiotic duration (6 vs 6 days, $p=0.23$)
- No decrease of length of stay (54 vs 61 hours, $p=0.66$)

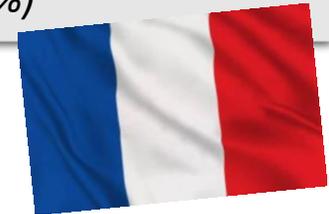


Added value of rapid respiratory syndromic testing at point of care versus central laboratory testing: a controlled clinical trial

Bouzid *et al.* JAC. 2021

When using mPCR in the ED vs mPCR in the lab:

- No decrease of antibiotic duration
- No decrease of length of stay
- **A strong increase of correct isolation** (influenza, RSV, MPV: 74 vs 50%)



Evaluation of a molecular point-of-care testing for viral and atypical pathogens on intravenous antibiotic duration in hospitalized adults with lower respiratory tract infection: a randomized clinical trial

D. Shengchen^{1,2,3,†}, X. Gu^{4,5,6,†}, G. Fan^{4,5,6}, R. Sun^{4,5,6}, Y. Wang², D. Yu⁷, H. Li², F. Zhou², Z. Xiong⁸, B. Lu^{2,8}, G. Zhu³, B. Cao^{2,5,6,8,9,10,*}

Shengchen *et al.* CMI. 2019

When using mPCR in the ED:

- A (very shy) decrease of antibiotic duration (7 vs 8 days, $p<0.001$)
- A decreased of length of stay by 1 day (8 vs 9 days, $p<0.001$)
- About 200\$ less costly



- **Un résultat rapide est nécessaire pour désengorger les urgences...**
- **... et sécuriser les soins !**
- De très nombreux hôpitaux se sont équipés en « point of care »
 - Au SAU
 - En laboratoire de garde
 - En laboratoire à réponse rapide
 - ...

	Point-of-care testing*	Control*	Between-group difference (95% CI)†	p value
Time to results, h	1.7 (1.6 to 1.9)	21.3 (16.0 to 27.9)	-19.6 (-19.0 to -20.3)	<0.0001
COVID-19 positive	197/499 (39%)	155/555 (28%)	11.5% (5.8 to 17.2)	0.0001
Admitted for >24 h	428/499 (86%)	421/555 (76%)	10.0% (5.0 to 14.7)	<0.0001
Transferred from assessment area to correct definitive clinical area on the basis of test result‡	313/428 (73%)	242/421 (57%)	15.7% (9.1 to 22.0)	<0.0001
Time from admission to arrival in a definitive clinical area‡, h	8.0 (6.0 to 15.0)	28.8 (23.5 to 38.9)	-20.8 (-18.4 to -21.2)	<0.0001
Bed moves between admission and arrival in definitive clinical area‡	<0.0001
0	43/313 (14%)	0/236
1	244/313 (78%)	163/236 (67%)
2	26/313 (8%)	56/236 (23%)
3	0/313	12/236 (5%)
4	0/313	4/236 (2%)
5	0/313	1/236 (<1%)
Mean (SD)	0.9 (0.5)	1.4 (0.7)	-0.5 (-0.4 to -0.6)	<0.0001

Respiratory testing timeframe

• **Potential impacts:**



Decrease antibiotics consumption



Complementary exams



Patient's isolation



Hospitalisation duration

The duration of most consultation...

No sensitive technology is able to reach it today

A quite ideal time frame

The ED physician is deciding about patient orientation and all medical decisions



Still an impact... But a lower one...

From there, the result will mostly impact the 48h re-evaluation



¼h

1h

2-4h

24h

48h

The gray zone...

The ED physician is often still deciding, but it is starting to be late for most medical decision

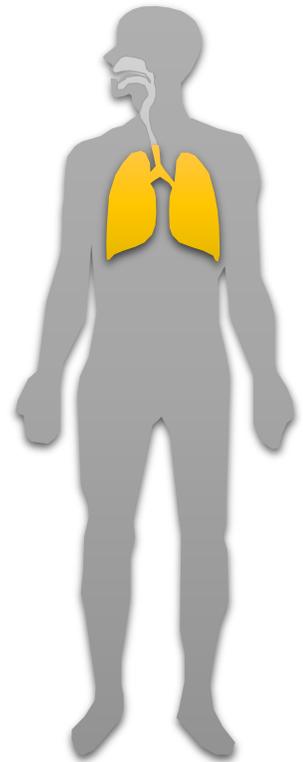


After this point...

... You are mostly documenting
... At a high cost

Les infections respiratoires

Panels « bas » (bactériologiques +++)



Panels « haut » vs « bas »

Prélèvements
naso-pharyngés

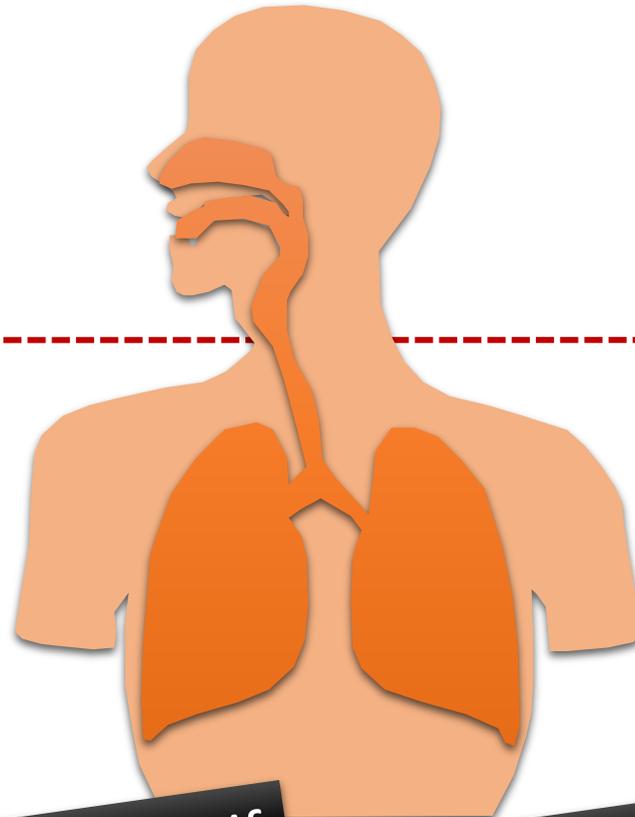


Sphère respiratoire haute

Sphère respiratoire basse



Aspi. trachéales
LBA
PDP
(...)



Semi-quantitatif

Résistance

Virus

Adénovirus
Coronavirus
Rhino./Entero.
Métagpneumo.
Influenza
Parainfluenza
V.R.S.

Atypiques

L. pneumophila
C. pneumophila
M. pneumoniae

Virus

Adénovirus
Coronavirus
Rhino./Entero.
Métagpneumo.
Influenza
Parainfluenza
V.R.S.

Bactéries

A. baumannii
E. cloacae
E. coli
H.influenzae
Klebsiella
M.catharralis
Proteus
P.aeruginosa
Serratia
S.aureus
Streptococcus
(...)

Atypiques

L. pneumophila
C. pneumophila
M. pneumoniae

Test Unyvero HPN (Curetis)

GROUP	PATHOGEN	GENE	RESISTANCE AGAINST	
Gram-positive bacteria	<i>Staphylococcus aureus</i>	<i>ermB</i>	Macrolide/Lincosamide	
	<i>Streptococcus pneumoniae</i>	<i>mecA</i>	Oxacillin	
Enterobacteriaceae	<i>Citrobacter freundii</i>	<i>mecC</i> (LGA251)	Oxacillin	
	<i>Escherichia coli</i>	<i>tem</i>	Penicillin	
	<i>Enterobacter cloacae</i> complex	<i>shv</i>	Penicillin	
	<i>Enterobacter aerogenes</i>	<i>ctx-M</i>	3rd generation Cephalosporins	
	<i>Proteus</i> spp.	<i>kpc</i>	Carbapenem	
	<i>Klebsiella pneumoniae</i>	<i>imp</i>	Carbapenem	
	<i>Klebsiella oxytoca</i>	<i>ndm</i>	Carbapenem	
	<i>Klebsiella varicola</i>	<i>oxa-23</i>	Carbapenem	
	<i>Serratia marcescens</i>	<i>oxa-24/40</i>	Carbapenem	
	<i>Morganella morganii</i>	<i>oxa-48</i>	Carbapenem	
	Non-fermenting bacteria	<i>Moraxella catarrhalis</i>	<i>oxa-58</i>	Carbapenem
		<i>Pseudomonas aeruginosa</i>	<i>vim</i>	Carbapenem
<i>Acinetobacter baumannii</i> complex		<i>sul1</i>	Sulfonamide	
<i>Stenotrophomonas maltophilia</i>		<i>gyrA83</i>	Fluoroquinolone	
<i>Legionella pneumophila</i>		<i>gyrA87</i>	Fluoroquinolone	
Others / Fungi	<i>Pneumocystis jirovecii</i>			
	<i>Haemophilus influenzae</i>			
	<i>Mycoplasma pneumoniae</i>			
	<i>Chlamydophila pneumoniae</i>			



 curetis

Temps rendu :
4/5h
Cout : +/- 200 €

- Performances cliniques sur 95 épisodes de pneumopathies (72 LBA et 23 PDP) chez 85 patients (vs culture utilisant les seuils cliniques + bactérie non détectées par le panel)

Table 2 Performance of multiplex PCR (M-PCR) for the identification of micro-organisms isolated at clinical thresholds

Organism	True positive (culture = M-PCR)	False positive (M-PCR+/culture -)	False negative (culture+/M-PCR-)	Se (%) [95% CI]	Sp (%) [95% CI]	PPV (%) [95% CI]	NPV (%) [95% CI]
Gram-positive bacteria							
<i>Staphylococcus aureus</i>	8	0	3	73	100	100	97
<i>Streptococcus pneumoniae</i>	0	0	2	0	100	-	98
Enterobacteriaceae							
<i>Citrobacter freundii</i>	0	0	0	-	100	-	100
<i>Escherichia coli</i>	12	3	1	92	96	80	99
<i>Enterobacter cloacae</i> complex	4	2	2	67	98	67	98
<i>Enterobacter aerogenes</i>	1	0	0	100	100	100	100
<i>Proteus</i> spp.	7	0	0	100	100	100	100
<i>Klebsiella pneumoniae</i>	9	0	3	75	100	100	97
<i>Klebsiella oxytoca</i>	2	2	0	100	98	50	100
<i>Klebsiella varicola</i>	0	1	0	-	99	0	100
<i>Serratia marcescens</i>	5	0	0	100	100	100	100
<i>Morganella morganii</i>	1	1	2	33	99	50	98
<i>Hafnia alvei</i> *	0	0	5	0	100	-	95
<i>Citrobacter koseri</i> *	0	0	2	0	100	-	98
<i>Serratia rubidaea</i> *	0	0	1	0	100	-	99
Non-fermenting bacteria							
<i>Moraxella catarrhalis</i>	1	1	0	100	99	50	100
<i>Pseudomonas aeruginosa</i>	31	2	0	100	97	94	100
<i>Acinetobacter baumannii</i> complex	3	0	0	100	100	100	100
<i>Stenotrophomonas maltophilia</i>	1	2	0	100	98	33	100
<i>Legionella pneumophila</i>	2	0	0	100	100	100	100
Others							
<i>Pneumocystis jirovecii</i>	0	0	0	-	100	-	100
<i>Haemophilus influenzae</i>	3	0	1	75	100	100	99
<i>Mycoplasma pneumoniae</i>	0	0	0	-	100	-	100
<i>Chlamydia pneumoniae</i>	0	0	0	-	100	-	100
Total	90	14	22	80 [73-88]	99 [99-100]	87 [80-93]	99 [99-99]

For culture, only bacteria that were superior to diagnostic thresholds (10^4 CFU/ml for BAL and 10^3 CFU/ml for PTC) were considered
*Organisms not screened on the multiplex PCR system

- Sensibilité 80% [73–88]
 - Gram-negative bacteria 90%
 - Gram-positive cocci 62%
- Spécificité 99% [99–100]
- VPP 87%[80-93]
- VPN 99% [99-99]

Test FilmArray® Pneumonia plus



BACTÉRIES

(Résultats semi-quantitatifs)

Acinetobacter calcoaceticus-baumannii complexe
Enterobacter cloacae complexe
Escherichia coli
Haemophilus influenzae
Klebsiella aerogenes
Klebsiella oxytoca
Groupe *Klebsiella pneumoniae*
Moraxella catarrhalis
Proteus spp.
Pseudomonas aeruginosa
Serratia marcescens
Staphylococcus aureus
Streptococcus agalactiae
Streptococcus pneumoniae
Streptococcus pyogenes

BACTÉRIES ATYPIQUES

(Résultats qualitatifs)

Chlamydia pneumoniae
Legionella pneumophila
Mycoplasma pneumoniae

VIRUS

Adénovirus
Coronavirus
Métagenomevirus humain
Entérovirus/rhinovirus humains
Virus de la grippe A
Virus de la grippe B
Coronavirus du syndrome respiratoire du Moyen-Orient (MERS CoV)
Virus parainfluenza
Virus respiratoire syncytial

GÈNES DE RÉSISTANCE AUX ANTIBIOTIQUES

Résistance à la méticilline
mecA/C et MREJ

Carbapénémases

IMP
KPC
NDM
OXA-48-like
VIM

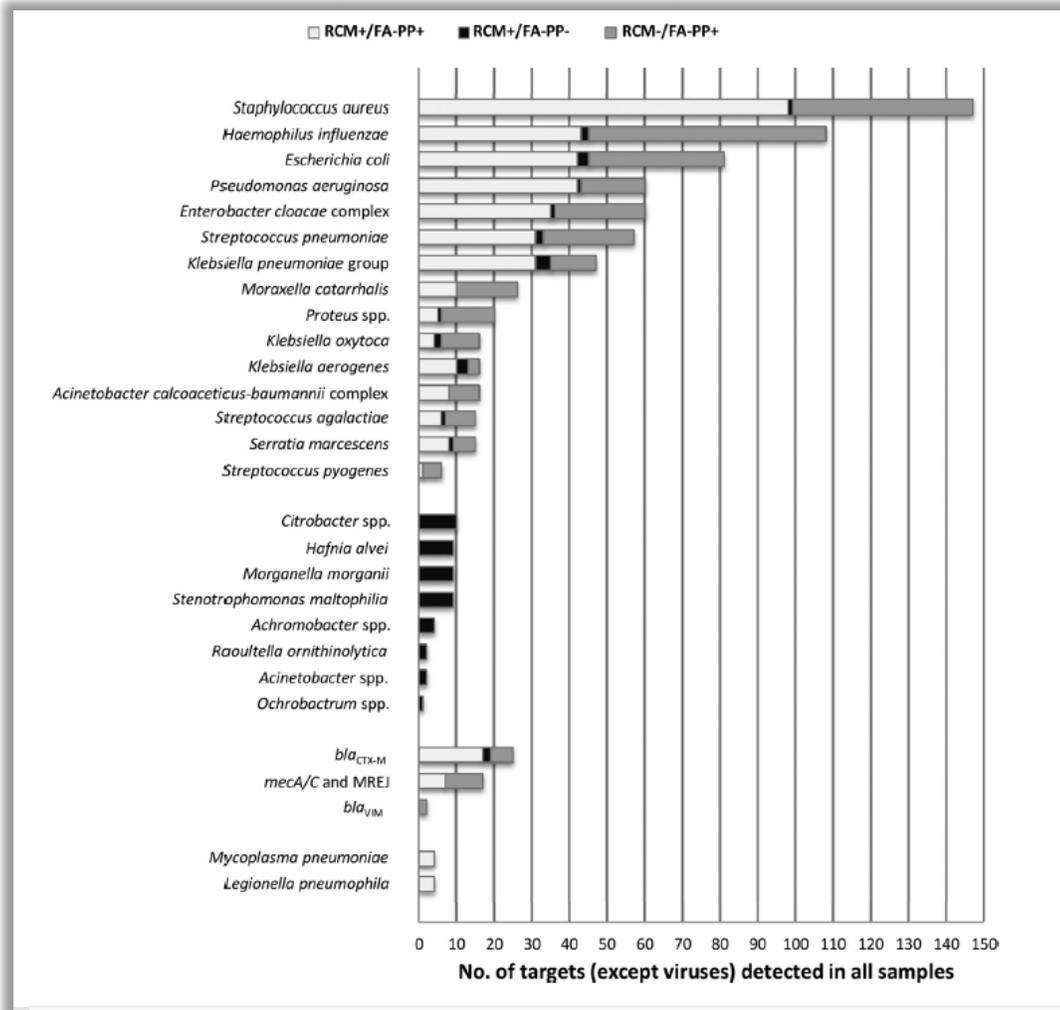
BLSE
CTX-M

Temps rendu : 1h30
Cout : +/- 200 €

ATTENTION
Panel non exhaustif

Par exemple, pas de détection de :
***Morganella morganii*,**
***Hafnia alvei*,**
Stenotrophomonas maltophilia (...)
et
pas tous les gènes de résistance ...

515 prélèvements respiratoires



Sensibilité : 94.4% (95% CI 91.7%-96.5%)
Spécificité : 96.0% (95% CI 95.5%-96.4%)

68 pathogènes non détectés :
- 46/68, 68% bactéries absentes du panel
- 22/68, 32% faux négatifs (++) entérobactéries)

Résultats semi-quantitatifs

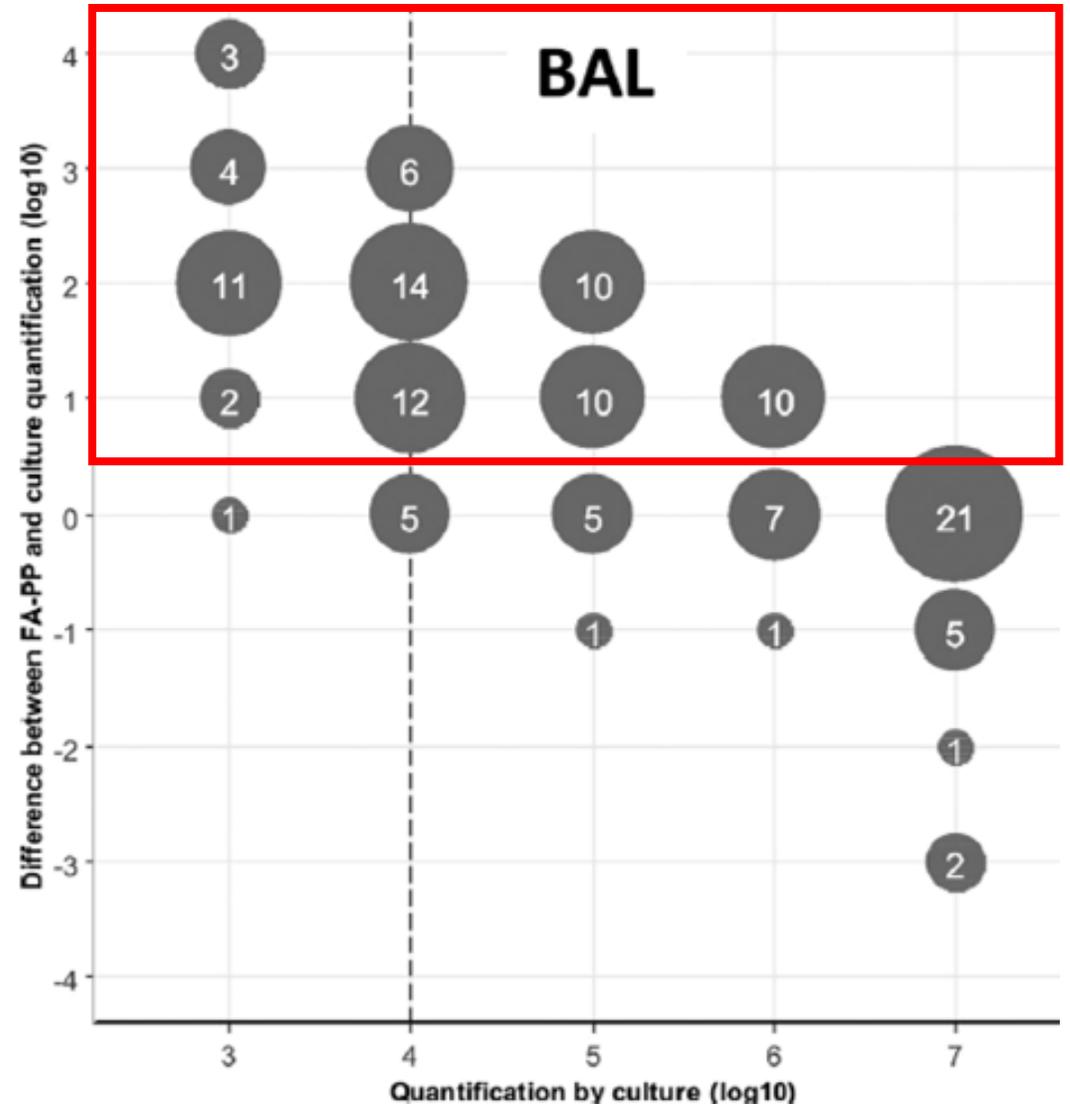
 FilmArray® Pneumonia Panel <i>plus</i> - IVD		 A BIOMÉRIEUX COMPANY www.BioFireDx.com	
Run Information			
Sample ID	2001029	Run Date	10 Jan 2020 3:31 PM
Protocol	BAL v3.3	Serial No.	20998316
Pouch Type	Pneumoplus v2.0	Lot No.	509019
Controls	Passed	Operator	signara gueye (signara)
Run Status	Completed	Instrument	FA2741
Detection Summary			
Bacteria			
	Bin (copies/mL)	Bin (copies/mL)	
		10 ⁴	10 ⁵
		10 ⁶	≥10 ⁷
Detected: ✓	10 ⁶ <i>Staphylococcus aureus</i>		
<p>Note: Detection of bacterial nucleic acid may be indicative of colonizing or normal respiratory flora and may not indicate the causative agent of pneumonia. Semi-quantitative Bin (copies/mL) results generated by the FilmArray Pneumonia Panel <i>plus</i> are not equivalent to CFU/mL and do not consistently correlate with the quantity of bacterial analytes compared to CFU/mL. For specimens with multiple bacteria detected, the relative abundance of nucleic acids (copies/mL) may not correlate with the relative abundance of bacteria as determined by culture (CFU/mL). Clinical correlation is advised to determine significance of semi-quantitative Bin (copies/mL) for clinical management.</p>			
Antimicrobial Resistance Genes			
Detected:	None		
<p>Note: Antimicrobial resistance can occur via multiple mechanisms. A Not Detected result for a genetic marker of antimicrobial resistance does not indicate susceptibility to associated antimicrobial drugs or drug classes. A Detected result for a genetic marker of antimicrobial resistance cannot be definitively linked to the microorganism(s) detected. Culture is required to obtain isolates for antimicrobial susceptibility testing and FilmArray Pneumonia Panel <i>plus</i> results should be used in conjunction with culture results for the determination of susceptibility or resistance.</p>			
Atypical Bacteria			
Detected:	None		
Viruses			
Detected:	None		

Résultats semi-quantitatifs

Taux de concordance : **43.3%**
(142/327)

Quantité en copie d'ADN/mL surestimé
par rapport aux UFC/mL de la culture.
≥1 log₁₀ dans **48.6%** des cas(159/327)

90.1% des bacteries avec ≥10⁶ DNA copies/mL
→ taux significatifs en culture.



- **Évaluation multicentrique d'un test PCR multiplex rapide, (FilmArray pneumonia) pour l'adaptation précoce de l'antibiothérapie chez des patients adultes atteints de pneumonie**
 - 159 épisodes de pneumonies (Bichat-Paris, Cochin-Paris, Rennes, Lyon)
 - 81% de patients en réanimation
 - Types de pneumonie : 43% HAP, 34% CAP et 23% PAVM
 - Prélèvements : 45% AT, 21% ECBC, 21% LBA, 13% PDP.
- Adjudication par un comité multi-disciplinaire (infectiologues, réanimateurs, microbiologistes)
- **Modification de l'antibiothérapie dans 77% (123/159)**
 - **Désescalade dans 51% (63/123)**
 - **Escalade/adéquation dans 28% (35/123)**
 - Pas de changement dans 21% (25/123)

Qu'est ce que le SARS-CoV-2 a changé
à notre vision des infections respiratoires virales ?

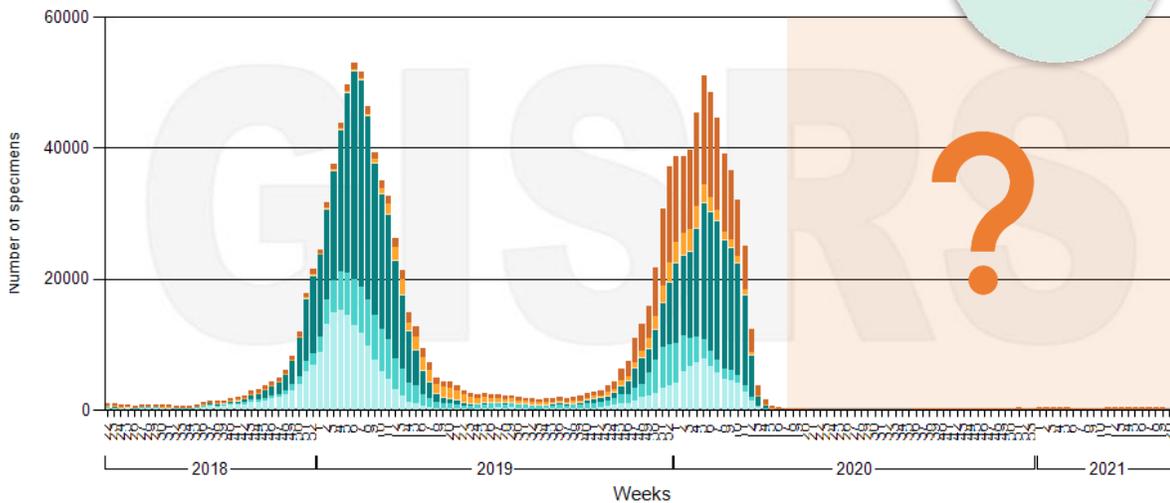
La disparition...

- Un phénomène mondial !

Influenza Laboratory Surveillance Information
by the Global Influenza Surveillance and Response System (GISRS)
generated on 25/05/2021 14:04:53 UTC

Northern hemisphere

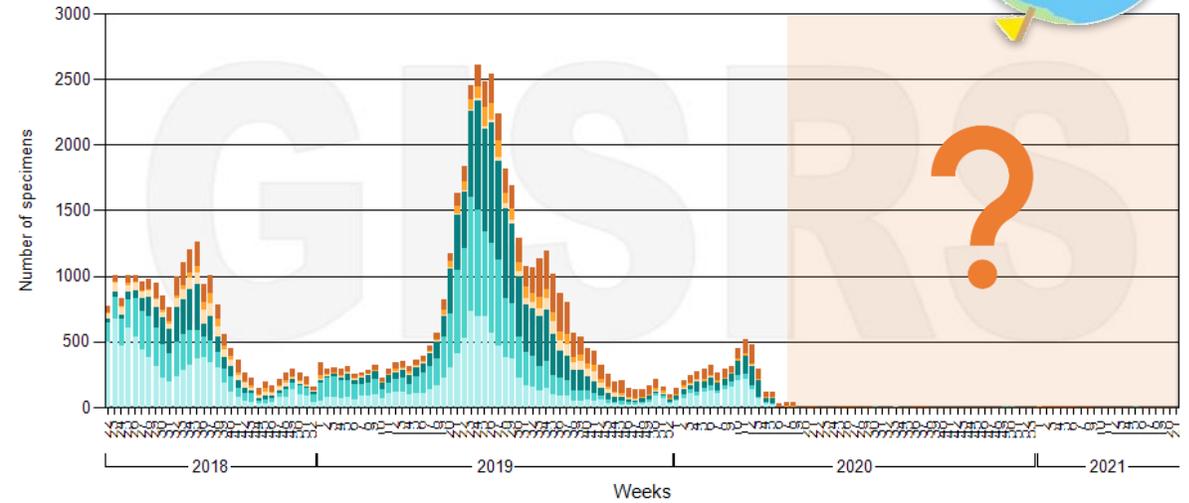
Number of specimens positive for influenza by subtype



Data from: All sites

Southern hemisphere

Number of specimens positive for influenza by subtype



Et la suite ???

- Les deux leviers pour lutter contre une épidémie virale :

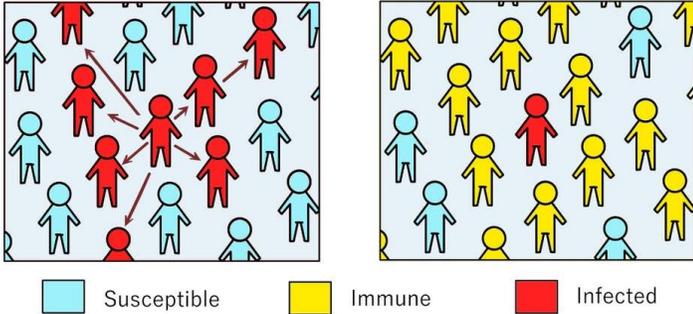
Très efficace contre la grippe

R_0 influenza $\approx 1,5$
 R_0 SARS-CoV-2 $\approx 2,5$
 ≈ 8 pour le δ



Limitera l'impact de la COVID-19... Mais pas les autres pathogènes !

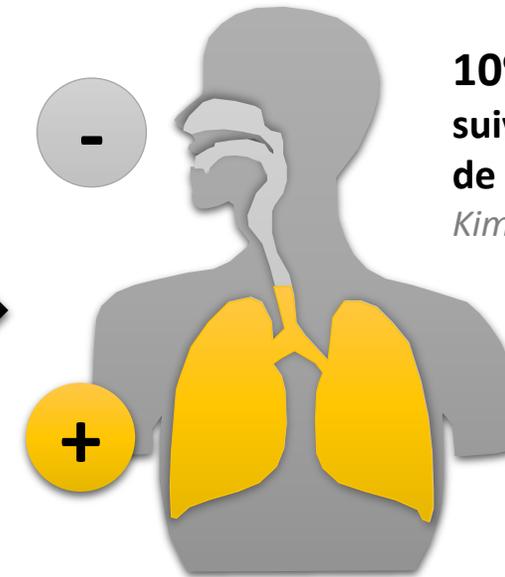
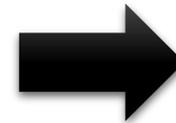
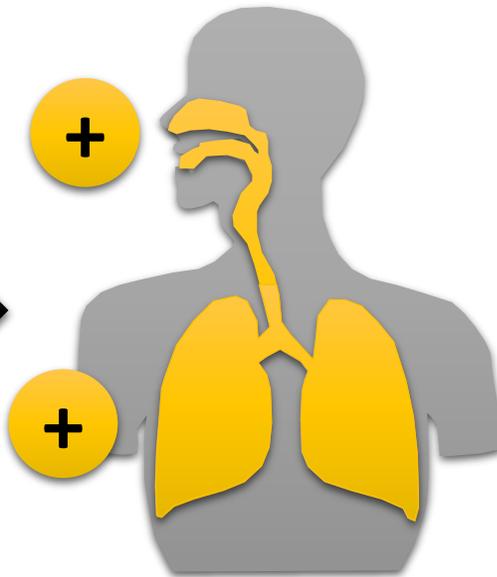
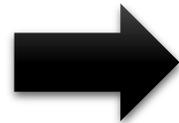
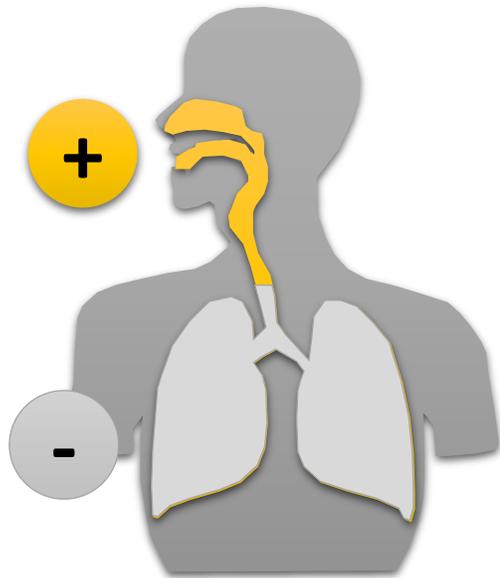
Un besoin de suivre une épidémie probablement mixte



Pneumonies et LBA

Infection débutante

Pneumonie établie



10% (mais variable
suivant la typologie
de patients)

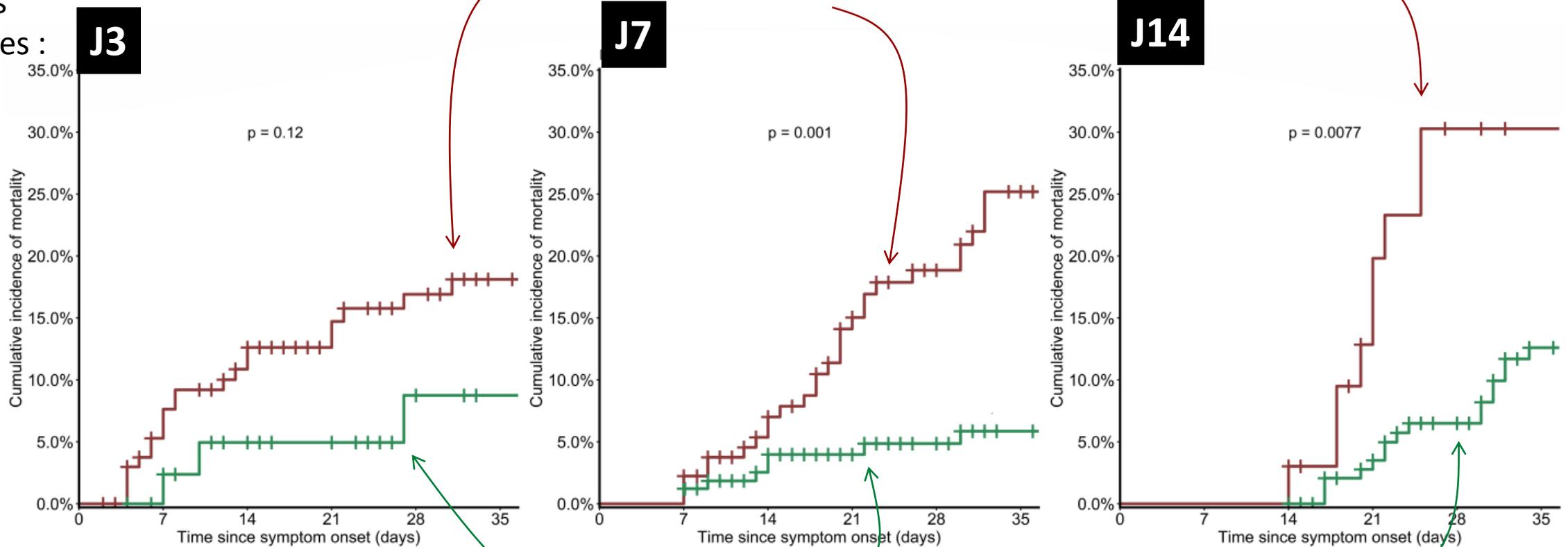
Kim et al. Radiology 2020

Systematisation des tests à visée virologique dans les prélèvements profonds ?

L'importance des Ct

- **Un indice pronostic (imparfait) :**

Délai depuis de
début des
symptômes :



Charge virale initiale
 $< 6 \text{ log/mL}$

Charge virale initiale
 $\geq 6 \text{ log/mL}$

L'importance des Ct

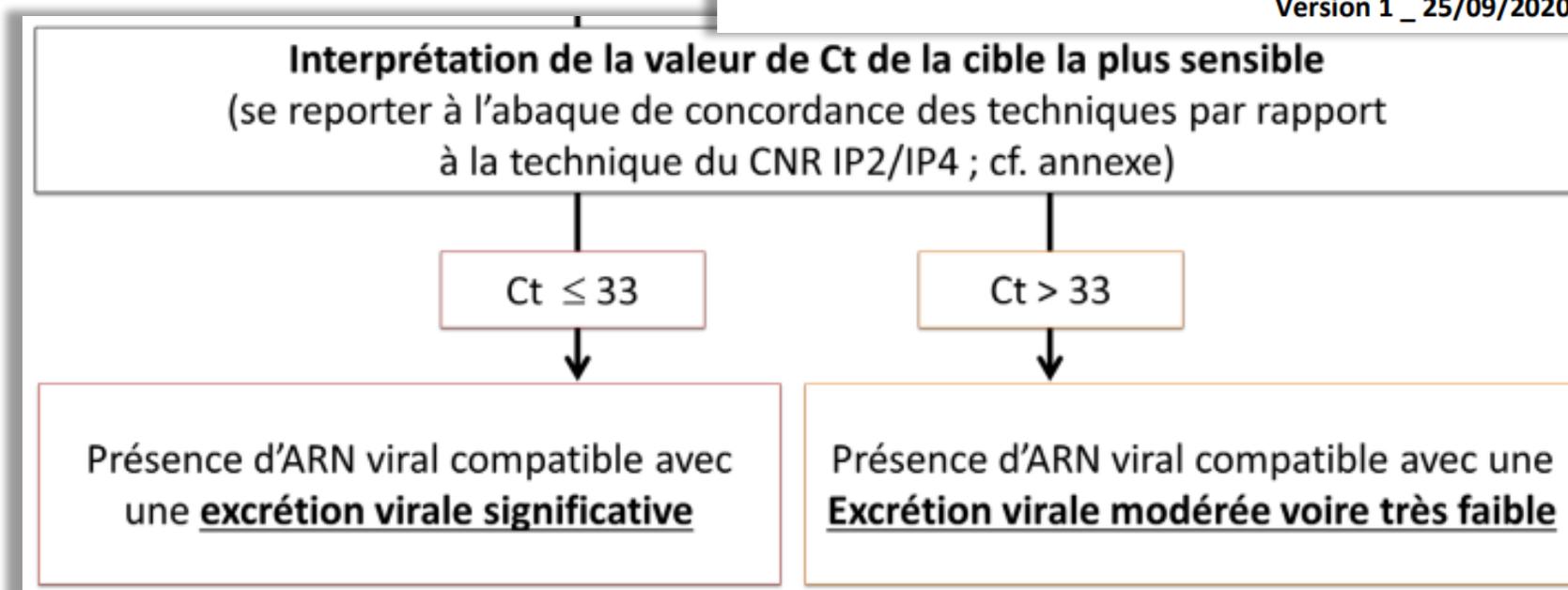
- **Un indice sur le timing...**

- PCR positive sans symptôme avec Ct fort (>30) : plutôt un COVID ancien...
- ... A vérifier à 24h en cas de tout début d'infection

- **Un indicateur de l'infectiosité...**



Avis du 25 septembre 2020 de la Société Française de Microbiologie (SFM)
relatif à l'interprétation de la valeur de Ct (estimation de la charge virale)
obtenue en cas de RT-PCR SARS-CoV-2 positive sur les prélèvements cliniques
réalisés à des fins diagnostiques ou de dépistage
Version 1 _ 25/09/2020



Les besoins futurs du syndromique ?

- Attention... Ca n'est que ma propre liste de souhait très personnelle...
- **Un besoin de rendu rapide...** Toujours plus rapide 😊
 - Un besoin de recommandations pour accompagner leurs déploiements.
- **Un positionnement en cohérence avec le parcours des patients**
 - Adaptés aux laboratoires centraux et à réponse rapide... Voir délocalisé dans certains services...
 - Concertations en amont et régulière avec les services cliniques concernés.
- **Une interprétation mieux maîtrisée**
 - Importance des prélèvements profonds, Ct, ...
 - Vérifier que les limites d'interprétation soient bien connues de tous (formations, comptes rendus, reco...)
- **Un accompagnement (déjà actif) des industriels toujours plus appuyé**
 - Aide à l'accréditation, systèmes experts, connexions à distance
- **Des coûts en baisse ???**

Merci pour votre attention



2019



2020

2021

2022