Antibiorésistance chez nous : Etat des lieux et Conséquences

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Médecine Intensive et Réanimation
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Association Marocaine de Biologie Médicale 02-04 mai 2024, Casablanca

Rationnel

- Antibiorésistance : Connue, chiffrée et régulièrement évaluée à travers le monde

  → Données chez nous ?

- Antibiorésistance en milieu communautaire vs milieu hospitalier ?

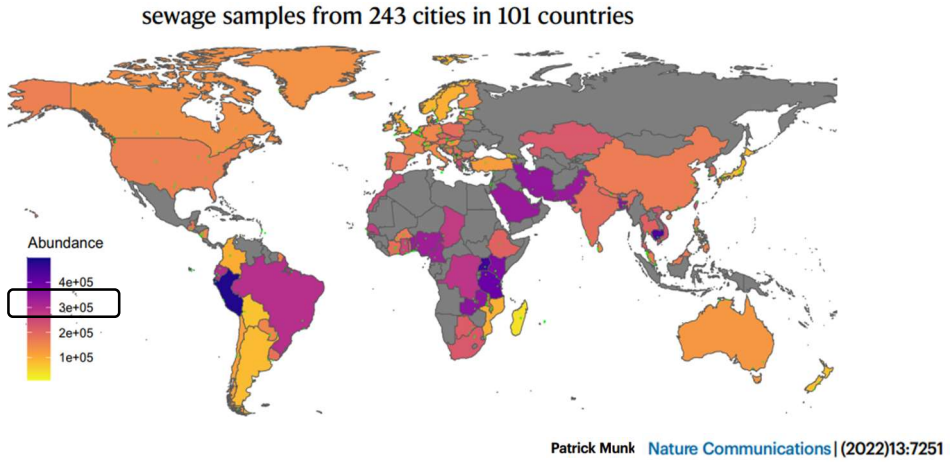
- Conséquences cliniques dans les unités de réanimation sont les plus importants :

  → Malades graves (plus susceptibles d'être infectés, morbi-mortalité)
  → Gestes invasifs : dispositifs (Cathéters, sondes, drains etc.)
  → Utilisation large des antibiotiques (pression de sélection)

Quels sont les messages ?

Quels sont les messages ?

Soyons tous conscient de l'étendu du problème chez nous



Soyons tous conscient de l'étendu du problème chez nous

Les résistances ne concernent pas uniquement les infections hospitalières

Eclairage

Profil de résistance aux antibiotiques des bactéries isolées des infections urinaires au Maroc

Khalid ZEROUALI Revue de Médecine Générale et de Famille / N°18 • Juin-Août 2021

E. coli	%
Amox/clav	44
Ciprofloxacine	42,3
Cotrimoxazole	53,2
Ceftriaxone	19,8
BLSE	18

Que va-t-on pouvoir utiliser en ttt ambulatoire chez ces patients ?

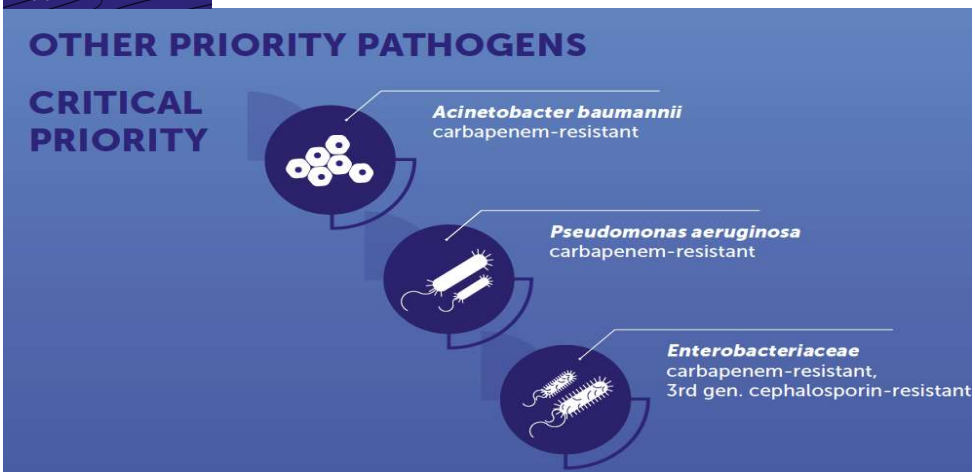
Hospitalisation ?

Soyons tous conscient de l'étendu du problème chez nous

Les résistances en milieu hospitalier sont évidemment pires

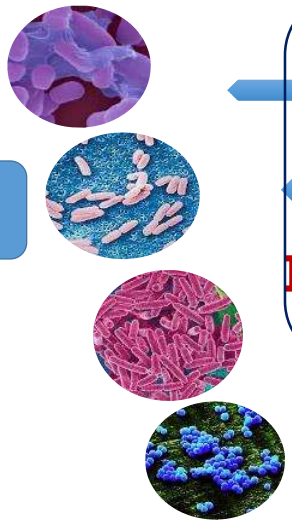
World Health Organization

The critical issue



BMR au CHU Hassan II de Fès : 2019

Idem autres CHU



ABRI 39%

EBC BLSE 36 %

PARC / PARI 19%

SARM 6%

Pr Mahmoud

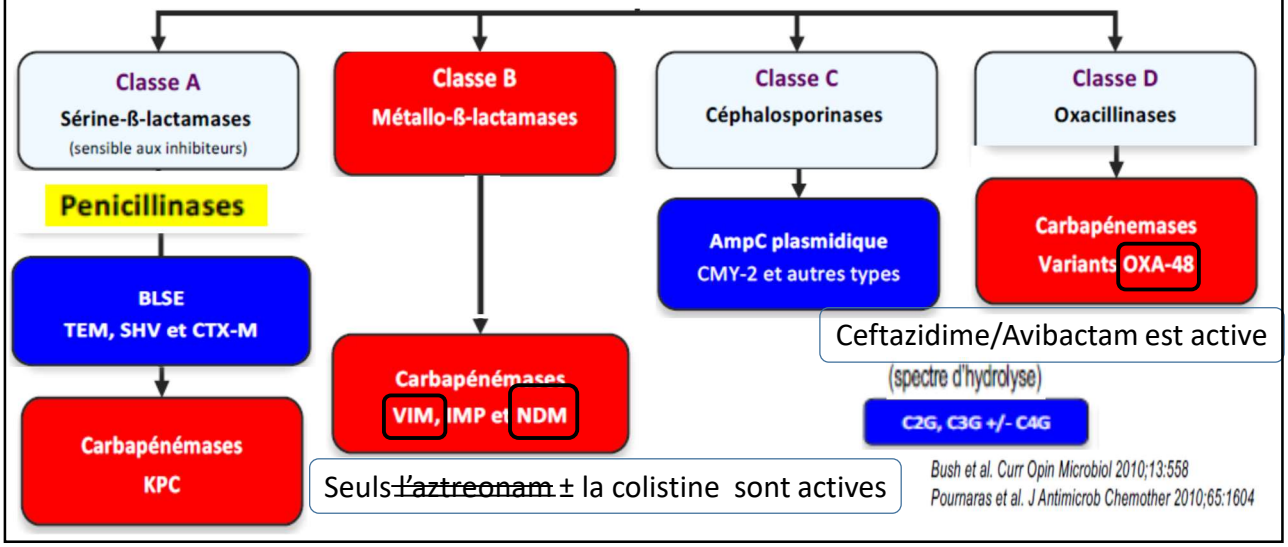
Soyons tous conscient de l'étendu du problème chez nous

Les résistances en milieu hospitalier sont évidemment pires

Dissemination of Carbapenemases (OXA-48, NDM and VIM) Producing *Enterobacteriaceae* Isolated from the Mohamed VI University Hospital in Marrakech, Morocco

Souad Loqman *Antibiotics* **2021**, *10*, 492.

Principales ß-Lactamases chez les Entérobactéries
Classification de Ambler



Ceftazidime/Avibactam est active

Seuls ~~l'aztreonam~~ ± la colistine sont actives

Bush et al. Curr Opin Microbiol 2010;13:558
Pournaras et al. J Antimicrob Chemother 2010;65:1604

Soyons tous conscient de l'étendu du problème chez nous

Les résistances en milieu hospitalier sont évidemment pires

Dissemination of Carbapenemases (OXA-48, NDM and VIM) Producing *Enterobacteriaceae* Isolated from the Mohamed VI University Hospital in Marrakech, Morocco

Antibiotics *	All (*n* = 131)	*K. pneumoniae* (*n* = 77)	*E. cloacae* (*n* = 31)	*E. coli* (*n* = 13)
ETP	100% (*n* = 131)	98.7% (*n* = 76)	100% (*n* = 31)	100% (*n* = 13)
IMP	83.21% (*n* = 109)	80.5% (*n* = 62)	84% (*n* = 26)	76.92% (*n* = 10)
GEN	100% (*n* = 131)	100% (*n* = 77)	100% (*n* = 31)	100% (*n* = 13)
CIP	87.02%(*n* = 114)	84.42% (*n* = 65)	93.55% (*n* = 29)	84.61% (*n* = 11)
SXT	87.79% (*n* = 115)	88.30 (*n* = 68)	93.55% (*n* = 29)	76.92% (*n* = 10)
PTZ	100% (*n* = 131)	100% (*n* = 77)	100% (*n* = 31)	100% (*n* = 13)
CS	34.35% (*n* = 45)	27.27% (*n* = 21)	48.39% (*n* = 15)	38.46% (*n* = 5)

Souad Loqman *Antibiotics* **2021**, *10*, 492.

Soyons clairs : Pour une partie de nos malades, nous sommes déjà dans une période d'impasse thérapeutique au Maroc +++

Modification du type des carbapénèmases produites par nos entérobactéries

- EPC: Prédominance d'Oxa-48 jusqu'à 2018 : sensibles à la ceftazidime/avibactam
- 10 souches analysées en 2019:

  5 /10 NDM-1; 4 / 10 Oxa-48; 1/10 Oxa- 181

- 14 Souches testées en 2020:
  - 9 NDM-1
  - 5 Oxa-48

Pr K Zerouali

_____1er September 2020 au 29 Février 2020___

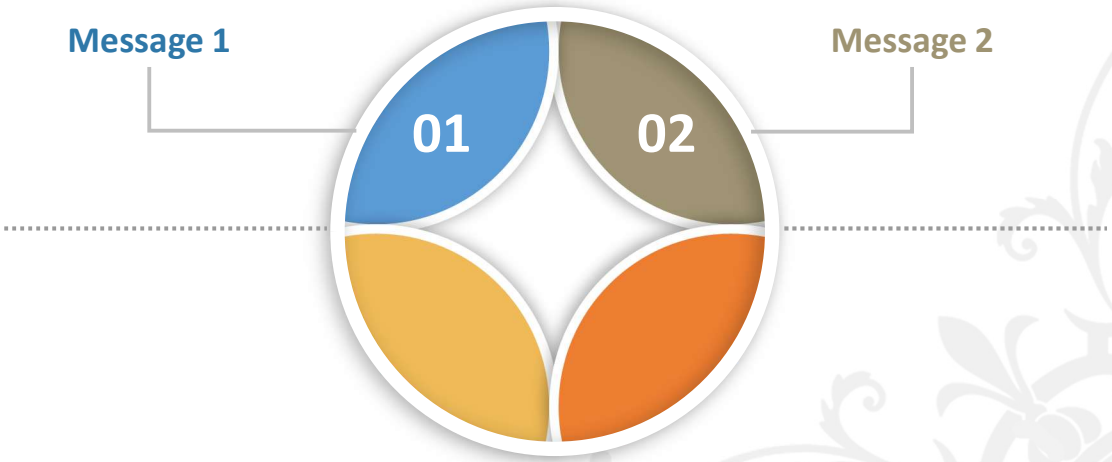
Prévalence d'isolement des ERC par rapport à l'ensemble des entérobactéries CHU- Rabat-2020

Entérobactéries	Nombre total	Phénotype ERC	
		Nombre	%
Escherichia coli	1131	22	1.94%
Klebsiella pneumoniae	487	67	13.75%
Klebsiella oxytoca	53	0	0%
Enterobacter cloacae	167	29	17.36%
Citrobacter freundii	29	01	3.44%
Proteus mirabilis	101	02	1.98%
Proteus vulgaris	15	0	0%
Providencia spp	40	08	20%
Morganella morgannii	28	03	10.71%
Serratia spp	33	05	15.15%

Germes naturellement résistants à la colistine

Pr Souly, Pr Zouhdi

Quels sont les messages ?

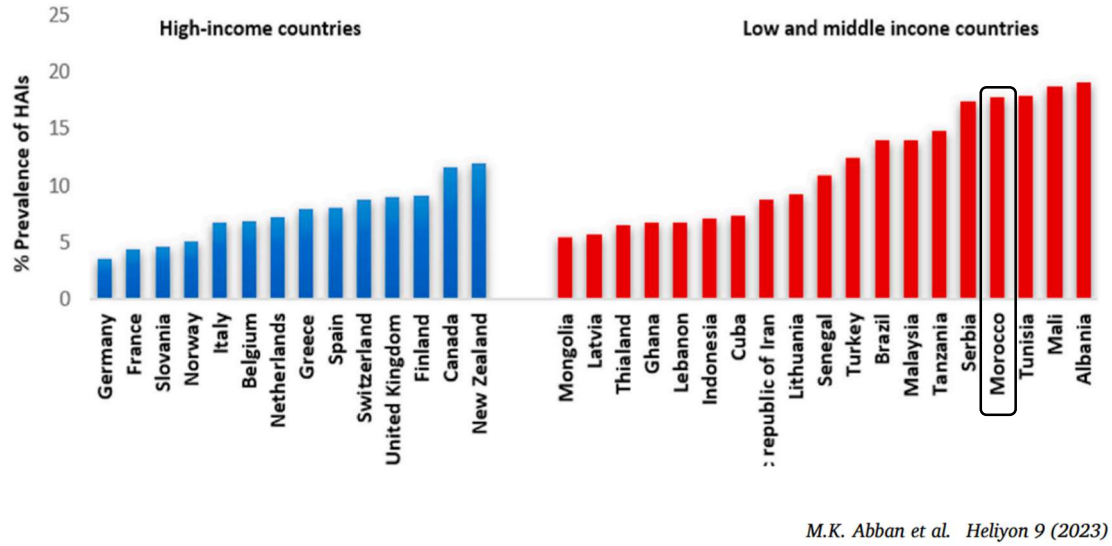


La prévalence et l'incidence des infections hospitalières au

Maroc sont parmi les plus élevées dans le monde !!!

(2e mauvaise nouvelle)

Prévalence des IAS chez nous



M.K. Abban et al. Heliyon 9 (2023)

Incidence IAS en réanimation : Anciennes données

Health-care associated infections rates, length of stay, and bacterial resistance in an intensive care unit of Morocco: Findings of the International Nosocomial Infection Control Consortium (INICC)

Madani et al; *International Archives of Medicine* 2009,

	Studied ICU (Morocco) 2004-2008 Pooled Mean		U.S. NHSN 2005-2006 Pooled Mean (Interquartile range, 25%-75%)
Medical ICU			
CVC-BSI	15.7		2.9 (0.8-4.2)
CAUTI	11.7		4.4 (1.8-5.6)
VAP	43.2		3.1 (0.9-4.6)

Incidence IAS en réanimation marocaine : Données récentes

Réseau Marocain de Recherche en Infectiologie en Réanimation (REMARIR)

Etude multicentrique nationale Services de réanimation 4 CHU

Densité d'incidence	Maroc	Réa-Raisin	US	INICC
PAVM/1000 j ventilation	54,3	15,5	3	14,1
Bactériémies/ 1000 jours CVC	9,9	0,49	0,8	5,05
Infections urinaires/ 1000 jours sondage	29,7	-	1,7	5

33e Congrès de la SMAAR, 9-11 décembre 2021

Incidence très élevée et Résistances bactériennes

Incidence IAS en réanimation marocaine : Données en cours d'analyse

Réseau **A**fricain de **R**echerche en **I**nfectiologie en **R**éanimation (**REARIR**)

Maroc (3 centres), Algérie (2 centres),
Tunisie +++ (15 centres), Sénégal (4 centres),
Mali (6 centres), Congo-Brazaville (1 centre)

Inclusions terminées le 30 avril 2024 (≈ 2000 patients)

Réseaux de recherche en infectiologie et Implications thérapeutiques

Key pathogens and clinical syndromes and/or epidemiological characteristics

Pathogen	Clinical syndromes and/or epidemiological characterictics
Escherichia coli	Number 1 pathogen in most settings; most often urinary tract or abdominal infection as a source; neonatal infections; increasingly resistant to fluoroquinolones and third-generation cephalosporins; common as BSI pathogen during neutropenia
Klebsiella spp.	Second *Enterobacterales* species (after *E. coli*); pneumonia pathogen; also found in intra-abdominal infections; in some regions frequently carbapenem-resistant, sometimes colistin-resistant
Staphylococcus aureus	Number 2 pathogen in most settings; both community-onset (often healthcare-associated) and hospital-onset; high case-fatality, relatively infrequent in children; oxacillin resistance highly variable
Coagulase-negative staphylococci	Almost always healthcare-associated; often device infections; neonatal infections
Pseudomonas aeruginosa	Almost always healthcare-associated; often device infections; intrinsically less susceptible to many antibiotics; high case-fatality; difficult to eradicate
Acinetobacter baumanni	Uncommon BSI pathogen; very often multidrug-resistant
Salmonella enterica	Includes Typhi, Paratyphi and non-typhoidal invasive *Salmonella*; very common BSI pathogen in low resource regions; often paediatric infections; sometimes and increasingly multidrug-resistant
Streptococcus spp.	Less common BSI pathogens; acute and severe infections due to pneumococcus and β-haemolytic streptococci, endocarditis due to non-haemolytic streptococci
Enterococcus spp.	Less common BSI pathogens; *Enterococcus faecium* increasing and often healthcare-associated, in some regions vancomycin-resistant, typically with intra-abdominal focus; endocarditis due to *Enterococcus faecalis*

W.V. Kern, S. Rieg / Clinical Microbiology and Infection 26 (2020)

Réseaux de recherche en infectiologie et Implications thérapeutiques

Frequent resistance mechanisms for selected antibacterial antibiotics in clinically important gram-negative bacteria

Bacteria	Cephalosporins	Carbapenems	Aminoglycosides	Quinolones	Polymyxins
Enterobacteriacea (*E. coli, Klebsiellae*)	ESBLs, mainly CTX-M type are major concern. E. coli ST131 with CTX-M-15 has epidemic potential woldwide. Isolates retain sensitivity to carbapenems if not co-produced with carbapenemsases. Many are also resistant to non-beta-lactams for which resistance genes are encoded on the same plasmid.	KPC, OXA-48 and NDM are most important carbapenemases. Isolates only susceptible to colistin, tigecycline and fosfomycin, although not all strains are susceptible. Less frequently, porin loss coupled with ESBL and AmpC beta-lactamase production can lead resistance to carbapenems.	Mainly due to aminoglycoside modifying enzymes or ribosomal (r)RNA methylases that may block aminoglycosides to bind modified bacterial ribosomes. These enzymes are frequently encoded on the same plasmid with ESBLs.	Mutations affecting chromosomal topoisomerase genes *gyrA* and *parC are* main reistance mechanisms.	Chromosomally mediated modificiation of Lipid A component of lipopolysccharide (LPS) leading reduced affinity for polymyxins. Recently described plasmid-mediated colistin resistance through *mcr-1* gene in China, East and South-East Asia and Europe is a big concern.

M. AKOVA VIRULENCE 2016, VOL. 7, NO. 3, 252–266

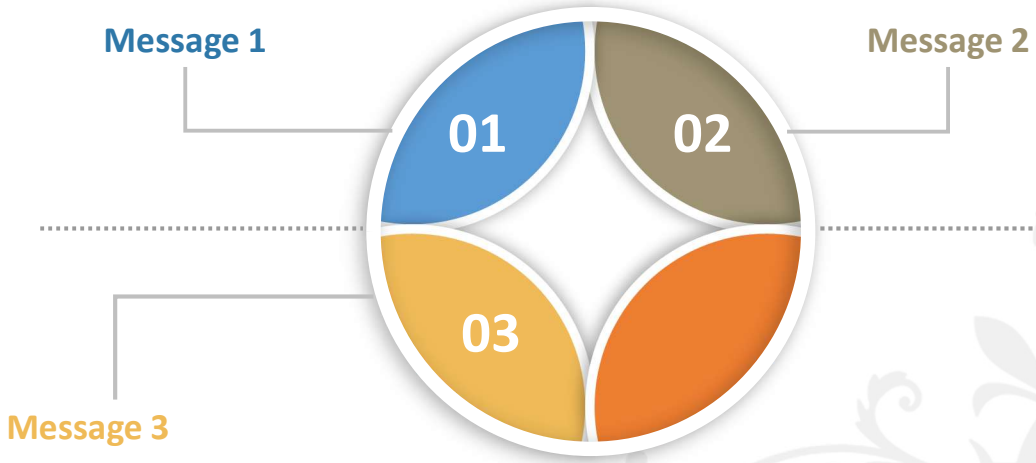
Epidemiology and Transmission of Carbapenemase-Producing *Enterobacteriaceae* in a Health Care Network of an Acute-Care

Aung et al.

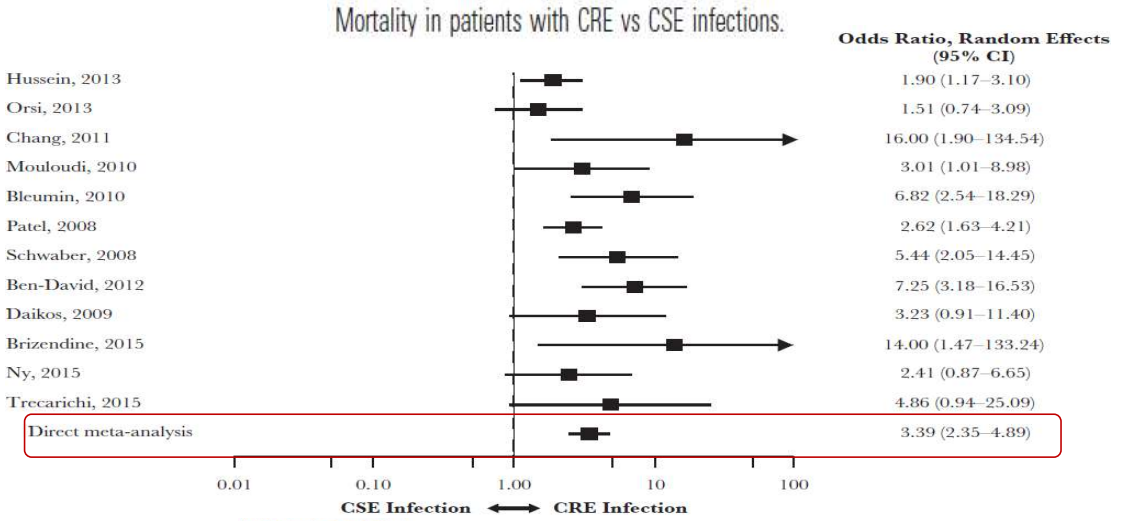
Antimicrobial Agents and Chemotherapy August 2021

Factor[b]	aOR	95% CI	*P*
Current location			
LTCFs	Ref		
ITCFs	4.13	1.08–15.76	**0.038**
ACH	4.57	1.14–18.44	**0.033**
Yr of sample collection			
2014	Ref		
2015	2.61	1.13–6.04	**0.025**
2016	2.98	1.30–6.80	**0.010**
Prior respiratory procedures	4.97	1.09–22.71	**0.038**
Prior gastrointestinal procedures	2.59	0.51–13.05	0.249
Prior urinary procedures	0.33	0.07–1.54	0.157
Prior carriage of:			
CRE	95.86	31.99–287.21	<**0.001**

Quels sont les messages ?



La résistance bactérienne impact clairement le pronostic, mais indirectement



IDSA Infectious Diseases Society of America

Martin et al *Open Forum Infectious Diseases* 2018.

Surmortalité attribuable à quoi ?

The observed differences in mortality may be due to organism-, patient-, and treatment-related factors.

with CRE tend to have a greater disease severity and more comorbid conditions relative to patients with infections due to CSE

Akova M, Clin Microbiol Infect **2012**

studies in which multivariate analyses were used to adjust for baseline characteristics and conditions indicated that the presence of CRE remained a significant predictor of mortality

Ben-David D, Clin Microbiol Infect **2012**
Bleumin D, J Infect **2012**
Brizendine KD, Antimicrob Agents Chemother 2015
Mouloudi E, Infect Control Hosp Epidemiol **2010**

Surmortalité attribuable à quoi ?

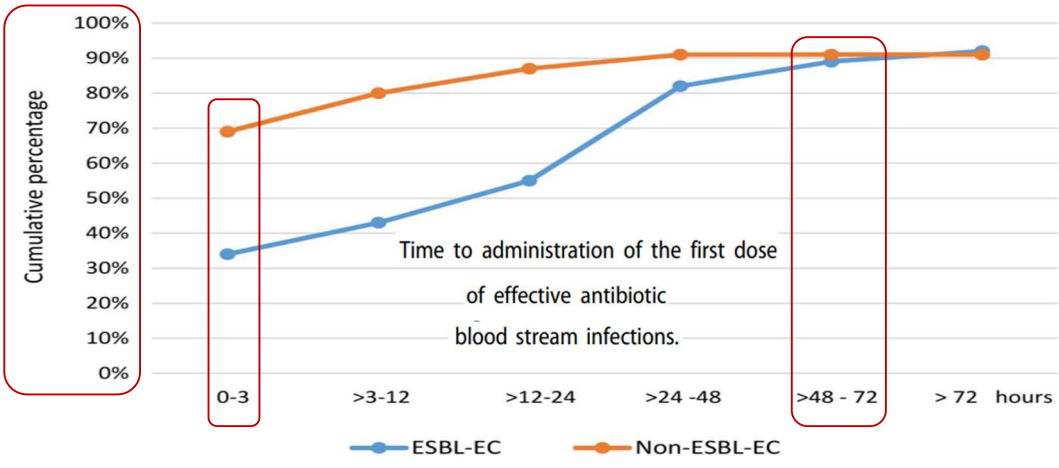
The observed differences in mortality may be due to organism-, patient-, and treatment-related factors.

CRE vs CSE comparative studies included in this meta-analysis that evaluated the effect of timeliness of therapy on mortality, patients who had delays in receipt of microbiologic active therapy had higher mortality, often independent of carbapenem resistance status

IDSA Infectious Diseases Society of America

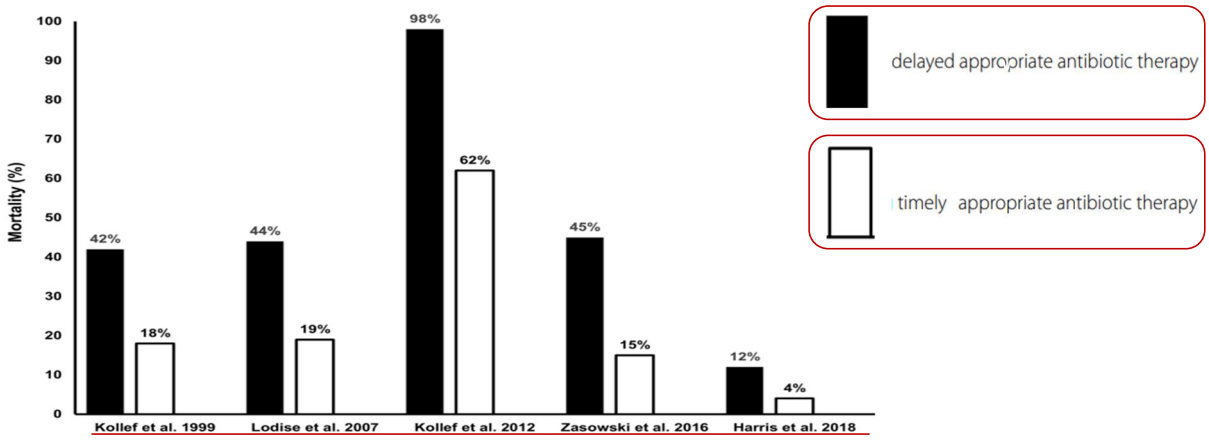
Martin et al *Open Forum Infectious Diseases* 2018.

C'est le délai de l'instauration d'une antibiothérapie appropriée qui impacte le pronostic et non la virulence des germes résistants

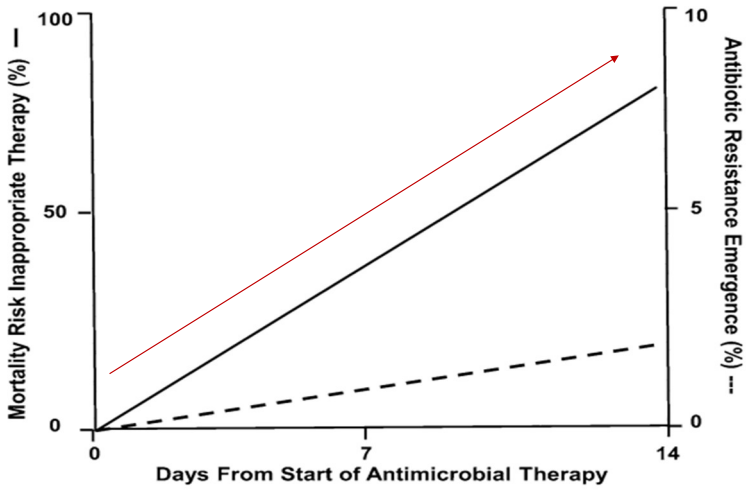


N. HANDAL ET AL. INFECTIOUS DISEASES, 2024; VOL. 56,

Délai d'instauration de l'antibiothérapie appropriée et pronostic



Kollef *et al. Crit Care* *(2021) 25:360*



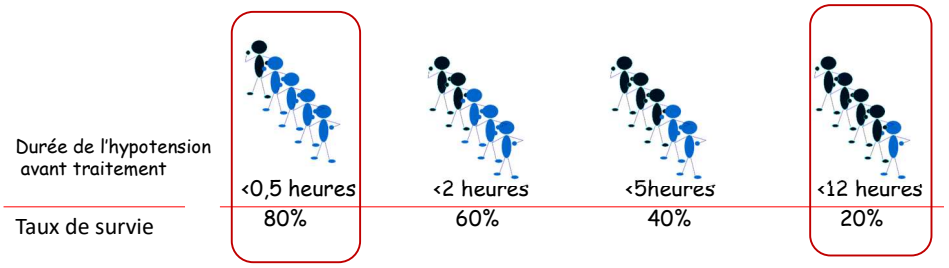
Risque de mortalité augmente avec le délai de manière linéaire

Kollef *et al. Crit Care* *(2021) 25:360*

Feature Articles

Duration of hypotension before initiation of effective antimicrobial therapy is the critical determinant of survival in human septic shock*

Anand Kumar, MD; Daniel Roberts, MD; Kenneth E. Wood, DO; Bruce Light, MD; Joseph E. Parrillo, MD; Satendra Sharma, MD; Robert Suppes, BSc; Daniel Feinstein, MD; Sergio Zanotti, MD; Leo Taiberg, MD; David Gurka, MD; Aseem Kumar, PhD; Mary Cheang, MSc



Lila Bouadma

Surviving Sepsis Campaign: International Guidelines for Management of Sepsis and Septic Shock 2021

Evans et al *Critical Care Medicine* November 2021

ONLINE SPECIAL ARTICLE

Delayed Second Dose Antibiotics for Patients Admitted From the Emergency Department With Sepsis: Prevalence, Risk Factors, and Outcomes

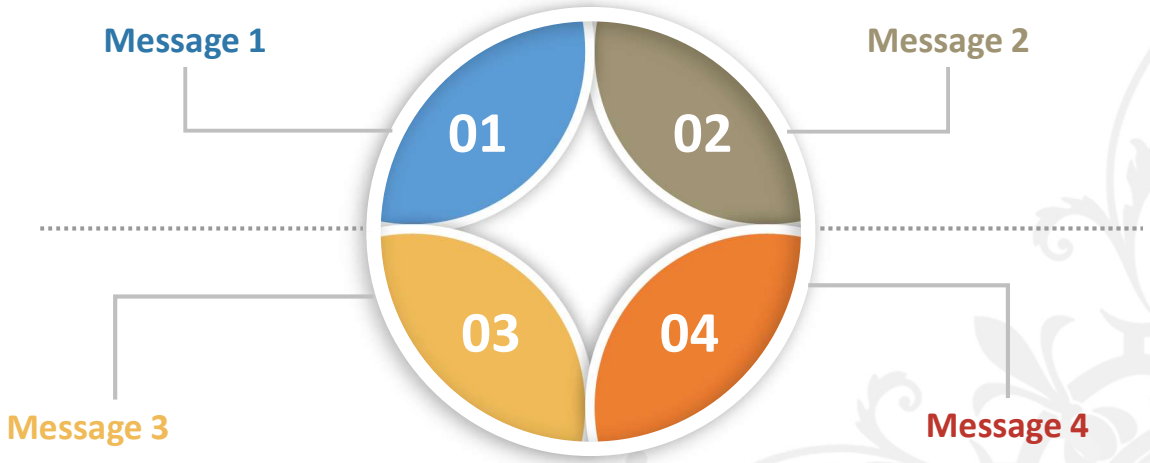
Leisman et al *Crit Care Med* 2017

Et chez nous ?

Main Results: Of 828 sepsis cases, 272 (33%) had delay greater than or equal to 25%. Delay frequency increased dose dependently

Parameter	Regression Type	Model Fit	Model Output	Effect Size	95% CI	p
Primary outcome						
Mortality[a]	Logistic	$\chi^2 = 5.9; p = 0.65$	OR	1.61	1.01–2.57	0.046
Secondary outcomes						
Hospital length of stay[b]	Cox	–	Inverse hazard ratio	1.16	0.97–1.39	0.11
ICU admission[c]	Logistic	$\chi^2 = 5.9; p = 0.66$	OR	1.49	0.92–2.40	0.103
Mechanical ventilation after second antibiotic dose[d]	Logistic	$\chi^2 = 4.2; p = 0.84$	OR	2.44	1.27–4.69	0.007

Quels sont les messages ?

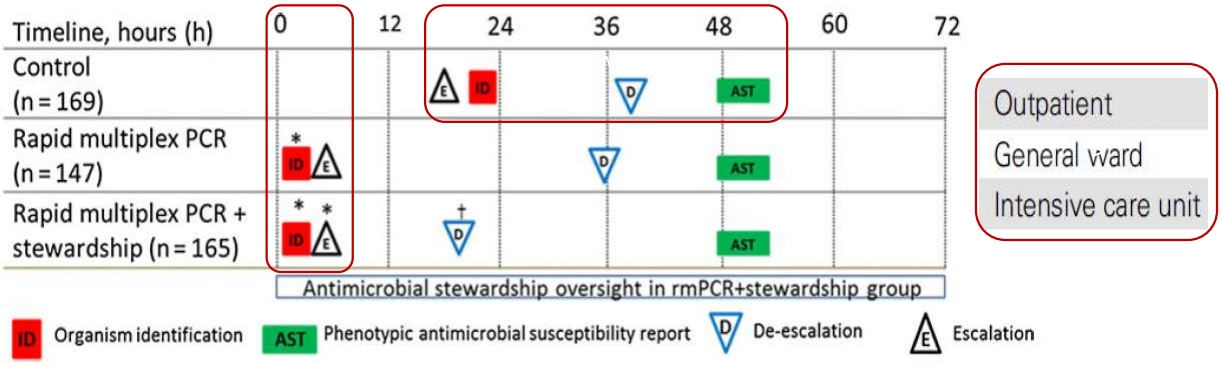


Quels sont les moyens pour raccourcir

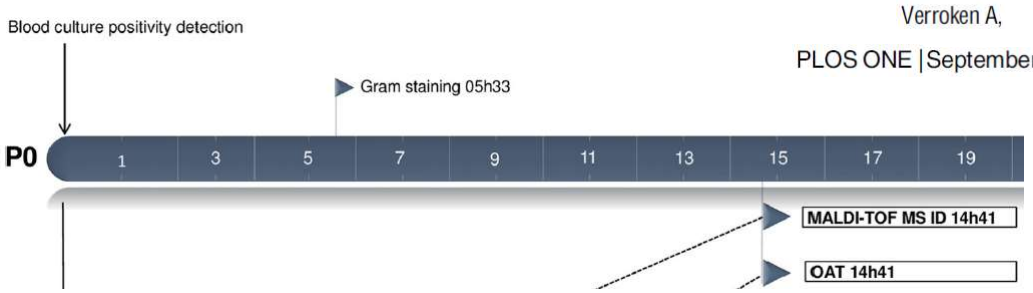
le délai d'une antibiothérapie précoce appropriée ?

Randomized Trial of Rapid Multiplex Polymerase Chain Reaction–Based Blood Culture

antimicrobial de-escalation or escalation was shortest in the rmPCR/AS group



Banerjee et al **CID 2015:61**



Verroken A,

PLOS ONE | September 26, 2019

FilmArray®
Pneumonia Panel *plus* - IVD

BIOFIRE
A BIOMÉRIEUX COMPANY
www.BioFireDx.com

Run Information

Sample ID		Run Date	
Protocol		Serial No.	
Pouch Type	Pneumo*plus* v2.0	Lot No.	
Controls	Passed	Operator	
Run Status	Completed	Instrument	

Result Summary

Bacteria

	Bin (copies/mL)		Bin (copies/mL)			
			10^4	10^5	10^6	≥10^7
Not Detected		*Acinetobacter calcoaceticus-baumannii* complex				
Not Detected		*Enterobacter cloacae* complex				
Not Detected		*Escherichia coli*				
Not Detected		*Haemophilus influenzae*				
Not Detected		*Klebsiella aerogenes*				
Not Detected		*Klebsiella oxytoca*				
Not Detected		*Klebsiella pneumoniae* group				
Not Detected		*Moraxella catarrhalis*				
Not Detected		*Proteus* spp.				
✓ Detected	10^6	*Pseudomonas aeruginosa*				
Not Detected		*Serratia marcescens*				
✓ Detected	≥10^7	*Staphylococcus aureus*				
Not Detected		*Streptococcus agalactiae*				
Not Detected		*Streptococcus pneumoniae*				
Not Detected		*Streptococcus pyogenes*				

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 *plus* 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.

Antimicrobial Resistance Genes

Not Detected	CTX-M
Not Detected	IMP
Not Detected	KPC
Not Detected	*mecA/C* and MREJ
Not Detected	NDM
N/A	OXA-48-like
✓ Detected	VIM

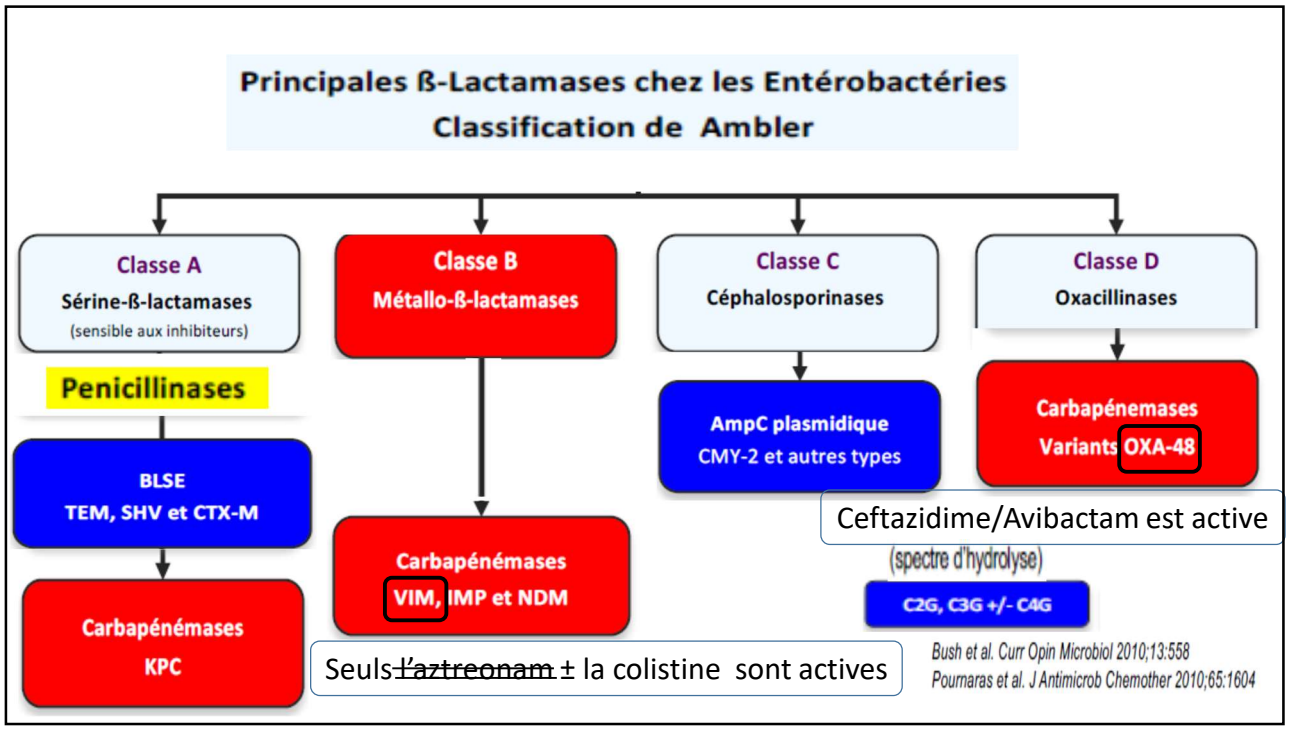
Note: Antimicrobial resistance can occur via multiple mechanisms. A Not Detected result for a genetic marker of antimicrobial resistance does not indicate susceptibility to associated antimicrobial drugs or drug classes. A Detected result for a genetic marker of antimicrobial resistance cannot be definitively linked to the microorganism(s) detected. Culture is required to obtain isolates for antimicrobial susceptibility testing and FilmArray Pneumonia Panel *plus* results should be used in conjunction with culture results for the determination of susceptibility or resistance.

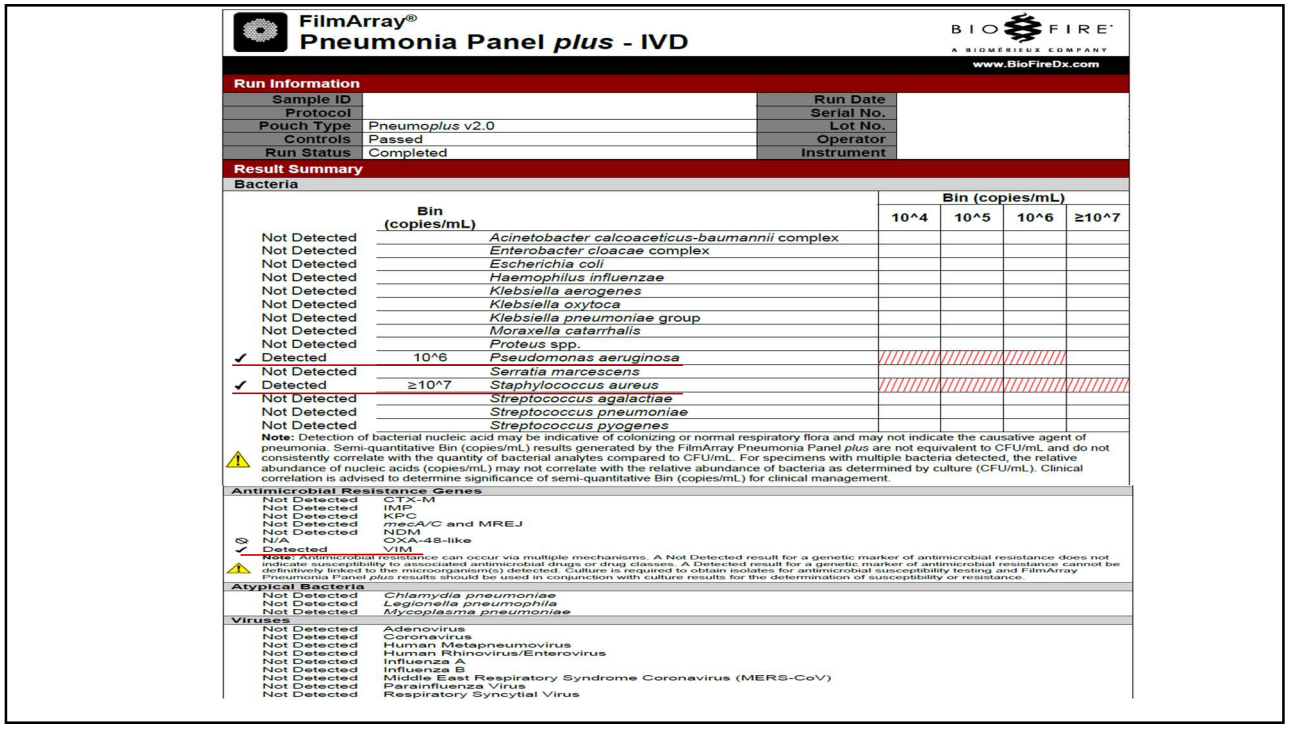
Atypical Bacteria

Not Detected	*Chlamydia pneumoniae*
Not Detected	*Legionella pneumophila*
Not Detected	*Mycoplasma pneumoniae*

Viruses

Not Detected	Adenovirus
Not Detected	Coronavirus
Not Detected	Human Metapneumovirus
Not Detected	Human Rhinovirus/Enterovirus
Not Detected	Influenza A
Not Detected	Influenza B
Not Detected	Middle East Respiratory Syndrome Coronavirus (MERS-CoV)
Not Detected	Parainfluenza Virus
Not Detected	Respiratory Syncytial Virus





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Not Detected		*Klebsiella pneumoniae* group				
Not Detected		*Moraxella catarrhalis*				
Not Detected		*Proteus* spp.				
✓ Detected	10^6	*Pseudomonas aeruginosa*				
Not Detected		*Serratia marcescens*				
✓ Detected	≥10^7	*Staphylococcus aureus*				
Not Detected		*Streptococcus agalactiae*				
Not Detected		*Streptococcus pneumoniae*				
Not Detected		*Streptococcus pyogenes*				

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⊘ N/A	OXA-48-like
✓ Detected	VIM

⚠ **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 *plus* results should be used in conjunction with culture results for the determination of susceptibility or resistance.

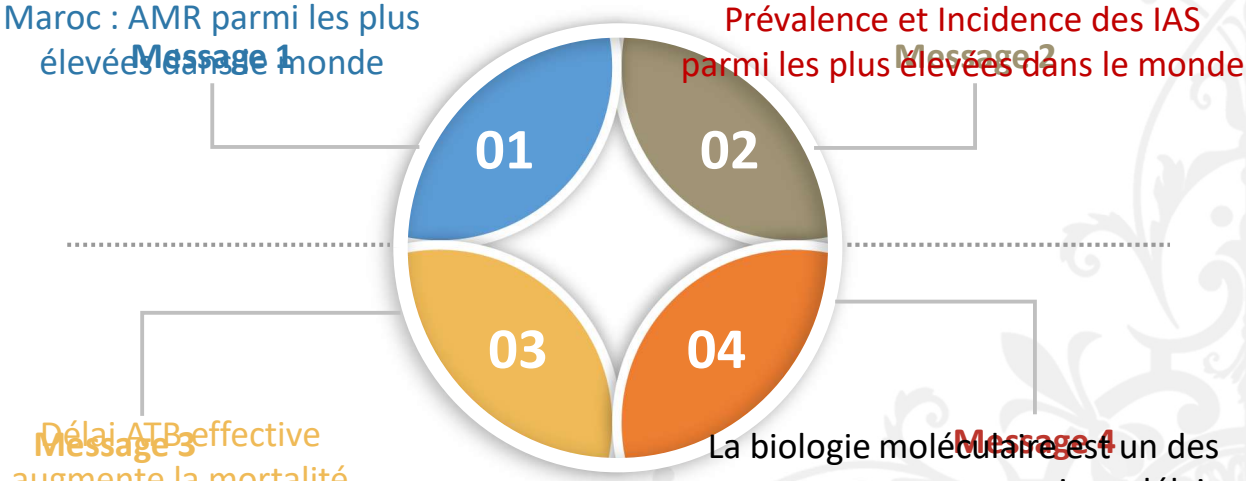
Atypical Bacteria

Not Detected	*Chlamydia pneumoniae*
Not Detected	*Legionella pneumophila*
Not Detected	*Mycoplasma pneumoniae*

Viruses

Not Detected	Adenovirus
Not Detected	Coronavirus
Not Detected	Human Metapneumovirus
Not Detected	Human Rhinovirus/Enterovirus
Not Detected	Influenza A
Not Detected	Influenza B
Not Detected	Middle East Respiratory Syndrome Coronavirus (MERS-CoV)
Not Detected	Parainfluenza Virus
Not Detected	Respiratory Syncytial Virus

Quels sont les messages ?



Merci de votre attention

Des questions