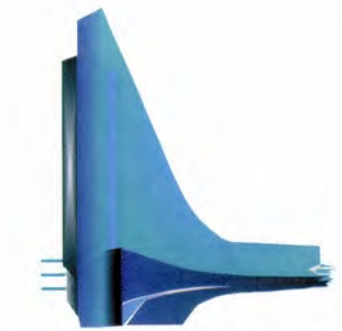
4es JOURNÉES du GREPI

Mycobactéries: les nouveautés de 2016

E. HAUSTRAETE

Service de Pneumologie

CH Robert BISSON - LISIEUX




ABBEVILLE
AMIENS
DIEPPE
CHERBOURG
LE HAVRE
ROUEN
BEAUVAIS
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CAEN
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LES ANDELYS
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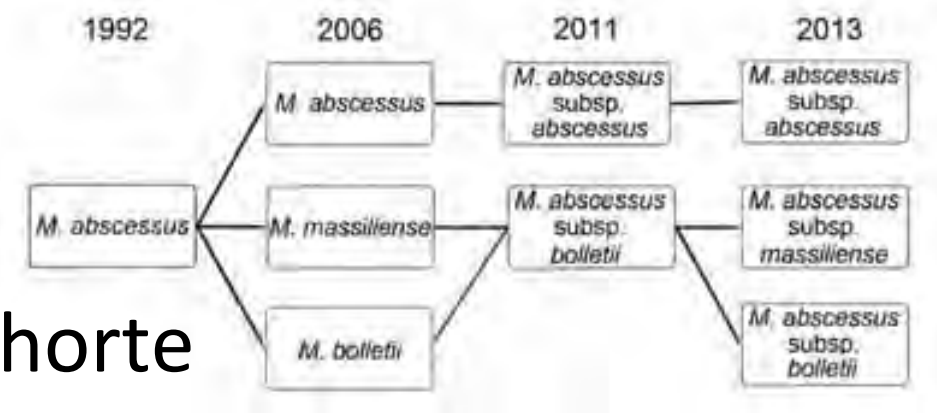
CHARTRES
ÉTAMPLES
FOUGÈRES
MAMERS
MAYENNE
NOGENT-LE-ROTROU
RENNES
PITHIVIERS

Aucun conflit d’intérêt

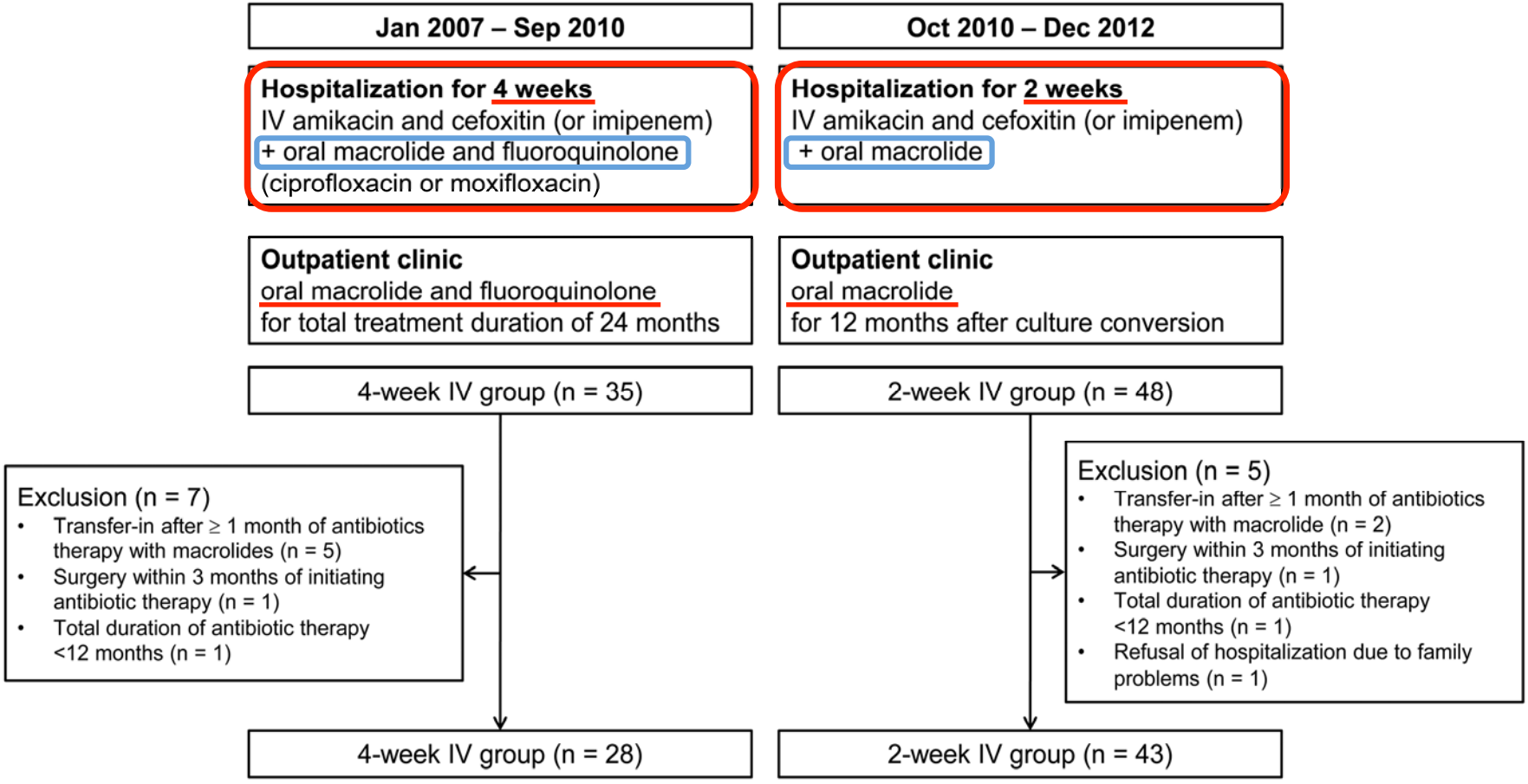
Oral macrolide therapy following short-term combination antibiotic treatment for *Mycobacterium massiliense* lung disease



- Recueil à partir d'une cohorte
- Corée du Sud
- Janv 2007 à Déc 2012
- 71 patients nécessitant une antibiothérapie pour infection pulmonaire à *Mycobacterium massiliense*

Koh WJ. Chest 2016.doi:10.1016/j.chest.2016.05.003.

Oral macrolide therapy following short-term combination antibiotic treatment for *Mycobacterium massiliense* lung disease



Koh WJ. Chest 2016.doi:10.1016/j.chest.2016.05.003.

Oral macrolide therapy following short-term combination antibiotic treatment for *Mycobacterium massiliense* lung disease

TABLE 3] Treatment Outcomes

	4-week IV group (n = 28)	2-week IV group (n = 43)	*P* value
After 12 months of treatment			
Symptomatic improvement	25 (89%)	43 (100%)	.057
HRCT improvement	22 (79%)	39 (91%)	.177
Sputum culture conversion	28 (100%)	39 (91%)	.148
Sputum culture conversion at the end of treatment	28 (100%)	42 (98%)	1.000
Follow-up duration after treatment completion, months	33.8 (12.3-50.3)	14.7 (0.5-29.5)*	.006
Microbiologic recurrence	2/28 (7%)	3/42 (7%)*	1.000

Definition of abbreviations: HRCT = high-resolution computed tomography.

*One patient who did not achieve culture conversion until the end of antibiotic treatment was excluded.

Koh WJ. Chest 2016.doi:10.1016/j.chest.2016.05.003.

Lung fonction decline according to clinical course in non-tuberculous mycobacterial lung disease

- Recueil à partir d'un registre de cohorte, Corée du Sud
- 358 patients avec MNT
- EFR au diagnostic et ≥ 3 ans plus tard (méd 5,6 ans)
- 3 groupes:
  - 118 = « observation »: a/paucisymptomatique = pas de traitement
  - 68 = « échec » du traitement: pas de conversion à 12 mois
  - 172 = « succès »: 3 cultures nég dans les 12 mois

Park HY Chest 2016. doi:10.1016/j.chest.2016.06.005

Lung fonction decline according to clinical course in non-tuberculous mycobacterial lung disease

Table 2] Comparison of Lung Function According to Clinical Course of Nontuberculous Mycobacterial Lung Disease

	Total (n = 358)	Observation (n = 118)	Treatment success (n = 172)	Treatment failure (n = 68)	*P* value
Interval between baseline and last spirometry, years	5.6 (4.4-7.4)	5.1 (3.8-6.5)	6.1 (4.8-7.7)	5.6 (4.3-7.6)	.001[a]
Baseline spirometry					
FEV_1, L	2.16 (1.73-2.59)	2.33 (1.78-2.72)	2.10 (1.68-2.51)	2.11 (1.77-2.77)	.078
FEV_1, % predicted	78 (67-89)	83 (70-92)	77 (65-88)	77 (67-87)	.012[a,b]
FVC, L	2.91 (2.45-3.43)	3.07 (2.55-3.64)	2.81 (2.43-3.25)	3.01 (2.43-3.56)	.016[a]
FVC, % predicted	83 (73-92)	85 (78-94)	83 (73-92)	80 (70-87)	.015[b]
FEV_1/FVC	75 (68-82)	75 (67-81)	75 (68-83)	76 (68-82)	.778
Changes in lung function					
FEV_1 decline, mL/yr	-31.6 (-61.0 to -10.3)	-30.8 (-55.4 to -9.4)	-28.2 (-55.9 to -10.9)	-52.2 (-101.4 to -9.3)	.023[c]
FEV_1 decline ≤ -40 mL/yr	150 (41.9)	45 (38.1)	65 (37.8)	40 (58.8)	.007[b,c]
FVC decline, mL/yr	-32.3 (-67.4 to 4.1)	-28.8 (-61.1 to 2.4)	-26.0 (-62.8 to 4.8)	-50.4 (-147.2 to -3.3)	.002[b,c]
FVC decline ≤ -40 mL/yr	163 (45.5)	50 (42.4)	69 (40.1)	44 (64.7)	.002[b,c]
Use of bronchodilator during the follow-up period	31 (8.7)	6 (5.1)	14 (8.1)	11 (16.2)	.033[b,c]

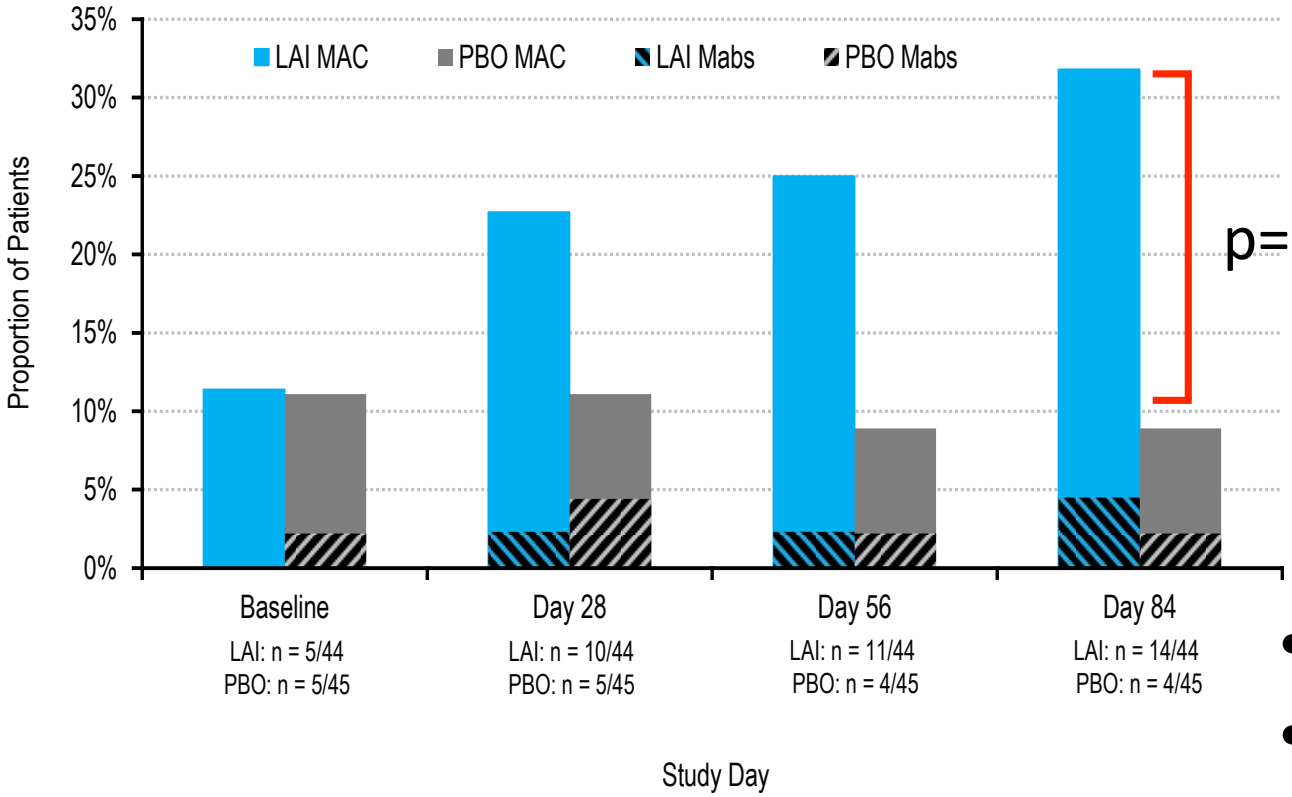
Park HY Chest 2016. doi:10.1016/j.chest.2016.06.005

Randomized trial of liposomal amikacin for inhalation in nontuberculous mycobacterial lung disease.

- Etude de phase II, randomisée, extension en ouvert. 19 centres USA
- 44 LAI nébuliseur eFlow® 590 mg vs 45 pcb (84j)
- ATB préalable ≥ 6 mois, cultures +
- Stratification:
  - Muco/non muco
  - *M. avium* complex (64%)/ *M abscessus* (36%)
- Suivi J84, J168; J28 et 1 an post traitement

Olivier KN. AJRCCM Oct 2016. DOI 10.1164/rccm.201604-0700OC

Randomized trial of liposomal amikacin for inhalation in nontuberculous mycobacterial lung disease.



p=0,006.

- Récurrences = 4
- 1 seule vraie rechute (MAC)

Figure 2. Proportion of patients with negative sputum cultures for nontuberculous mycobacteria (NTM) in the double-blind phase (LOCF: mITT population).

Olivier KN. AJRCCM Oct 2016. DOI 10.1164/rccm.201604-0700OC

Randomized trial of liposomal amikacin for inhalation in nontuberculous mycobacterial lung disease.

- CMI amikacine > 64 µg/L: 5 patients
- 1 Insuff rénale modérée LAI (réversible)
- EI sévères: 18,2% LAI vs 8,9% PCB
- 1 décès (pneumonie) 1ère phase, 1 décès (sepsis urinaire) 2ème phase.

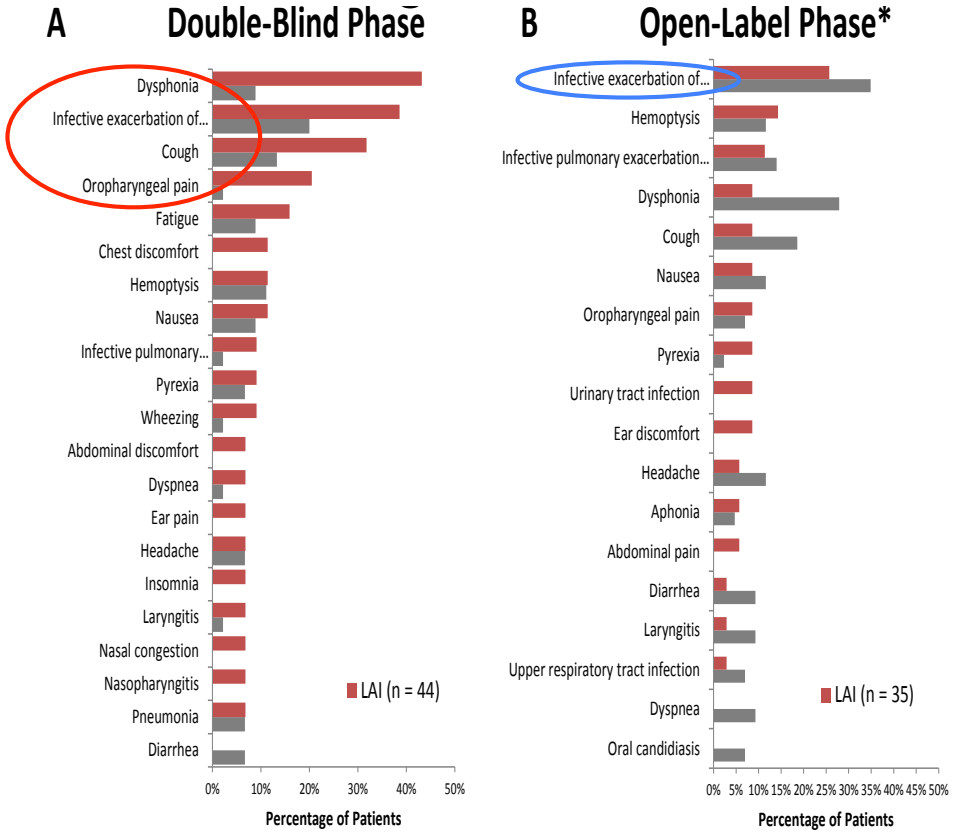


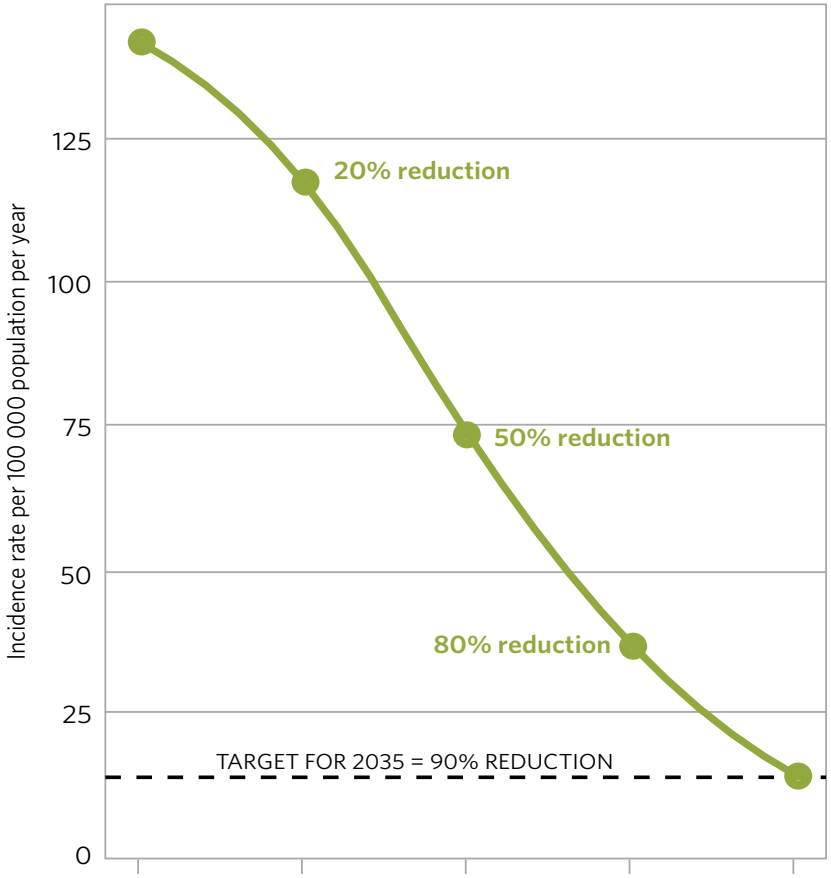
Figure E3. Treatment-emergent adverse events (>5% frequency) during the double-blind phase (*A*) and open-label phase (*B*).*Adverse events during the double-blind phase are those with onset

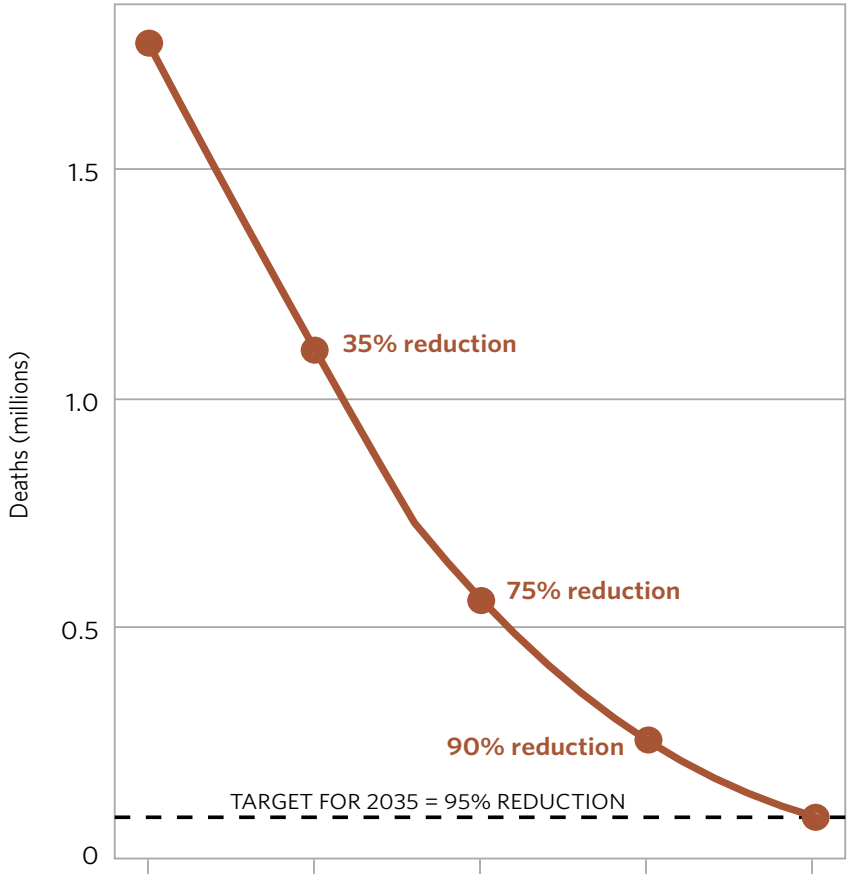
Olivier KN. AJRCCM Oct 2016. DOI 10.1164/rccm.201604-0700OC

« End TB strategy 2016-2035 »

World Health Organization

Projected incidence and mortality curves that are required to reach End TB Strategy targets and milestones, 2015–2035





Cough aerosols of *Mycobacterium tuberculosis* predict incident tuberculosis disease in household contacts

- Etude rétrospective, USA
- 85 TBM ED+ (Uganda) 2009-2011
  - 3 expectorations pour ED et culture
  - 1 prélèvement d'aérosol lors de la toux (Cough Aerosol Sampling System)

  ➔CFU à 6 sem: Négatif/ Faible (1-9 CFU)/ Fort aérosol (≥ 10 CFU)

Jones-Lopez EC. Clin Infect Dis 2016;63(1):10-20

Cough aerosols of *Mycobacterium tuberculosis* predict incident tuberculosis disease in household contacts

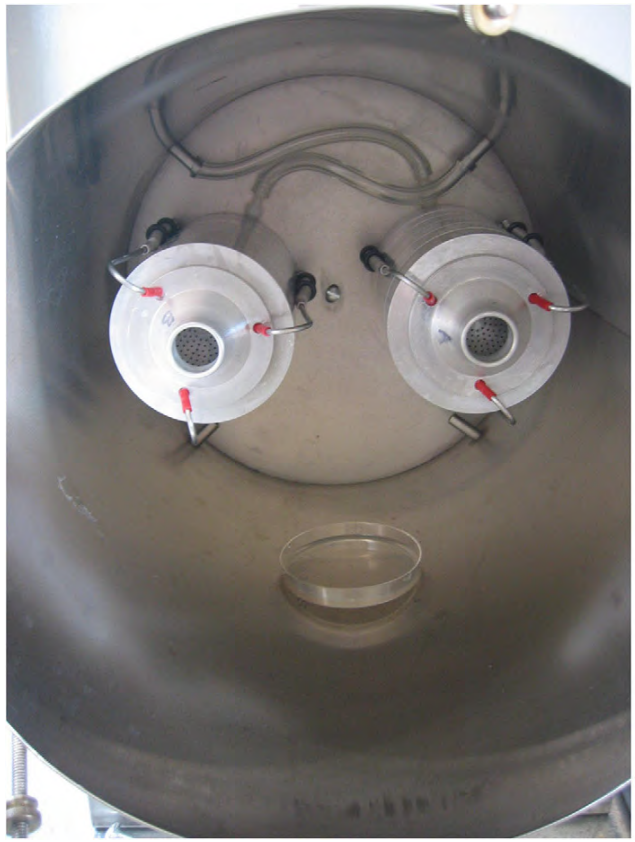
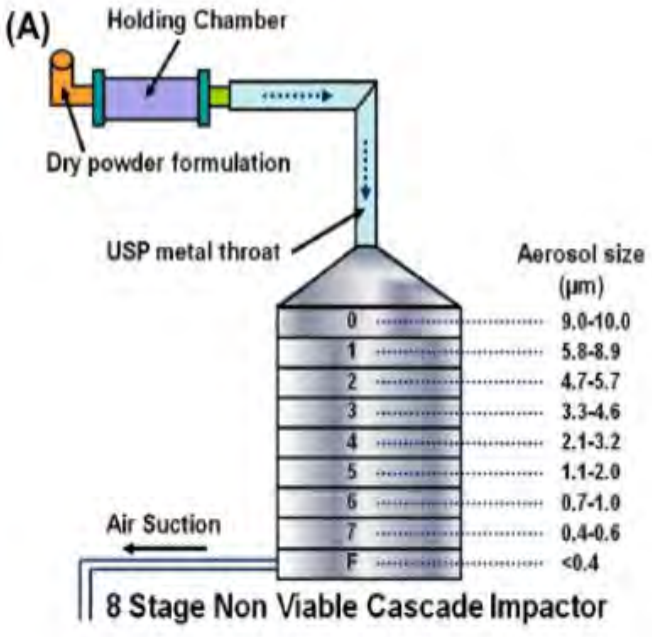
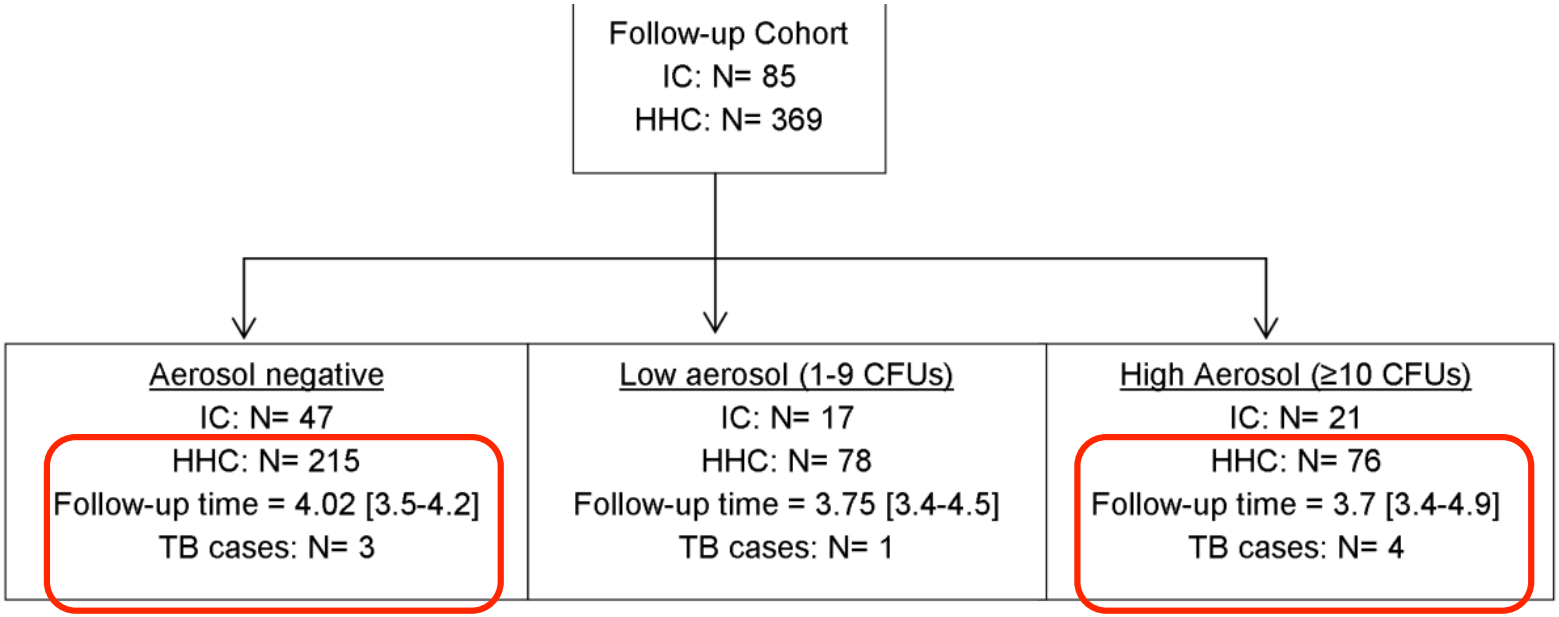


Figure 1. Cough Aerosol Sampling System. View inside of chamber with two Andersen cascade impactors and settle plate (*left*) and set up in procedure room ready for use (*right*).



Cough aerosols of *Mycobacterium tuberculosis* predict incident tuberculosis disease in household contacts

- 369 contacts étroits
  - TST ≥ 10 à S0 ou S6; QFT + à S0 ou S6 (1% INH)
  - suivi méd 3,9 ans: 8 (2%) TBM



Jones-Lopez EC. Clin Infect Dis 2016;63(1):10-20

Cough aerosols of *Mycobacterium tuberculosis* predict incident tuberculosis disease in household contacts

ED	Aérosol
Associé aux marqueurs de la sévérité de la TBM	Pas associé à la sévérité de la TBM
Identifie 68% de contacts comme à haut risque (ED 3+)	Identifie 21% de contacts comme à haut risque (CFU ≥ 10)
80% de TST+, 81% QFT +	94% de TST+ (p=0,02), 87% QFT + (p=0,08)

- Incidence de la TBM chez les contacts:
  - Charge bacillaire chez cas index (culture): OR 8,2 (1,1-59,2), p=0,04
  - **Nb de CFU à 6 sem sur culture aérosol: OR 6 (1,4-25,5), p= 0,01 pour ≥ 10 CFU vs < 10.**
- ED = diagnostic vs Aérosol = contagiosité (inoculum)

Jones-Lopez EC. Clin Infect Dis 2016;63(1):10-20

First evaluation of QuantiFERON-TB Gold Plus performance in contact screening

- TB1 ➔ CD4+
- TB2 ➔ CD4+ et CD8+
- TB2-TB1 ➔ CD8+

- TB1 ou TB2-nul > 0,35 UI/mL = positif
- QFT-plus TB2- QFT-plus TB1 > 0,6 UI/mL = CD8+

Barcellini L. Eur Respir J 2016. DOI:10.1183/13993003.00510-2016.

First evaluation of QuantiFERON-TB Gold Plus performance in contact screening

- Prospective. Milan
- Nov 2014-Juin 2015
- 119 contacts avec TST ≥ 5 mm

107 concordants (89,9%)
K=0,8
(95% CI 0,69-0,91)

TABLE 2 Test results

QFT-GIT results	Subjects	QFT-Plus results		Positive results per tube	
		Negative	Positive	TB1	TB2
Negative	63	51 (80.95)	12 (19.05)	10[#]	10[¶]
Positive	56	0	56 (100)	56	56
Total	119	51 (42.86)	68 (57.14)	66	66

Data are presented as n, n (%) or median (interquartile range). [#]: two were positive to TB1 only; [¶]: two were positive to TB2 only. QFT-GIT: QuantiFERON-TB Gold in Tube; QFT-Plus: QuantiFERON-TB Plus; IFN: interferon.

2 QFT-GIT +
à 10-12 sem

Barcellini L. Eur Respir J 2016. DOI:10.1183/13993003.00510-2016.

First evaluation of QuantiFERON-TB Gold Plus performance in contact screening

Exposition récente?

TABLE 6 Backward stepwise multivariate logistic regression for predicting TB2–TB1 >0.6 IU·mL^{-1}

	OR (95% CI)	p-value
Country of birth		
Non-European	1	
European	3.46 (1.03–11.69)	0.0453
Sleeping proximity to the index case		
Different room	1	
Same room	5.90 (1.83–18.97)	0.0029

Barcellini L. Eur Respir J 2016. DOI:10.1183/13993003.00510-2016.

Added value of molecular assay Xpert MTB/RIF compared to sputum smear microscopy to assess the risk of tuberculosis transmission in a low-prevalence country.

- Etude rétrospective, Lausanne
- Mai 2010 à Décembre 2014
- 242 patients suspects de TB pulmonaire
  - Xpert MTB/RIF,
  - ED et culture (71/242 =29,3% culture +)

Opota O. Clin Microbiol Infect 2016;22(7):613-9

Added value of molecular assay Xpert MTB/RIF compared to sputum smear microscopy to assess the risk of tuberculosis transmission in a low-prevalence country.

	ED	Xpert MTB/RIF
Sen	64,7% (46/71)	91,5% (65/71)
Spé	94,2% (161/171)	99,4% (170/171)
VPP	82,1% (46/56)	98,5% (65/66)
VPN	86,6% (171/186)	96,6% (170/176)

- 20 ED -/Xpert MTB/RIF +:
  - 14/20 symptomatiques
  - 11/20 (55%) excavation
- 46 ED+ ➔ Xpert MTB/RIF +
- 166 Xpert MTB/RIF- ➔ED-

Réduction des mesures d'isolement?

Opota O. Clin Microbiol Infect 2016;22(7):613-9

Added value of molecular assay Xpert MTB/RIF compared to sputum smear microscopy to assess the risk of tuberculosis transmission in a low-prevalence country.

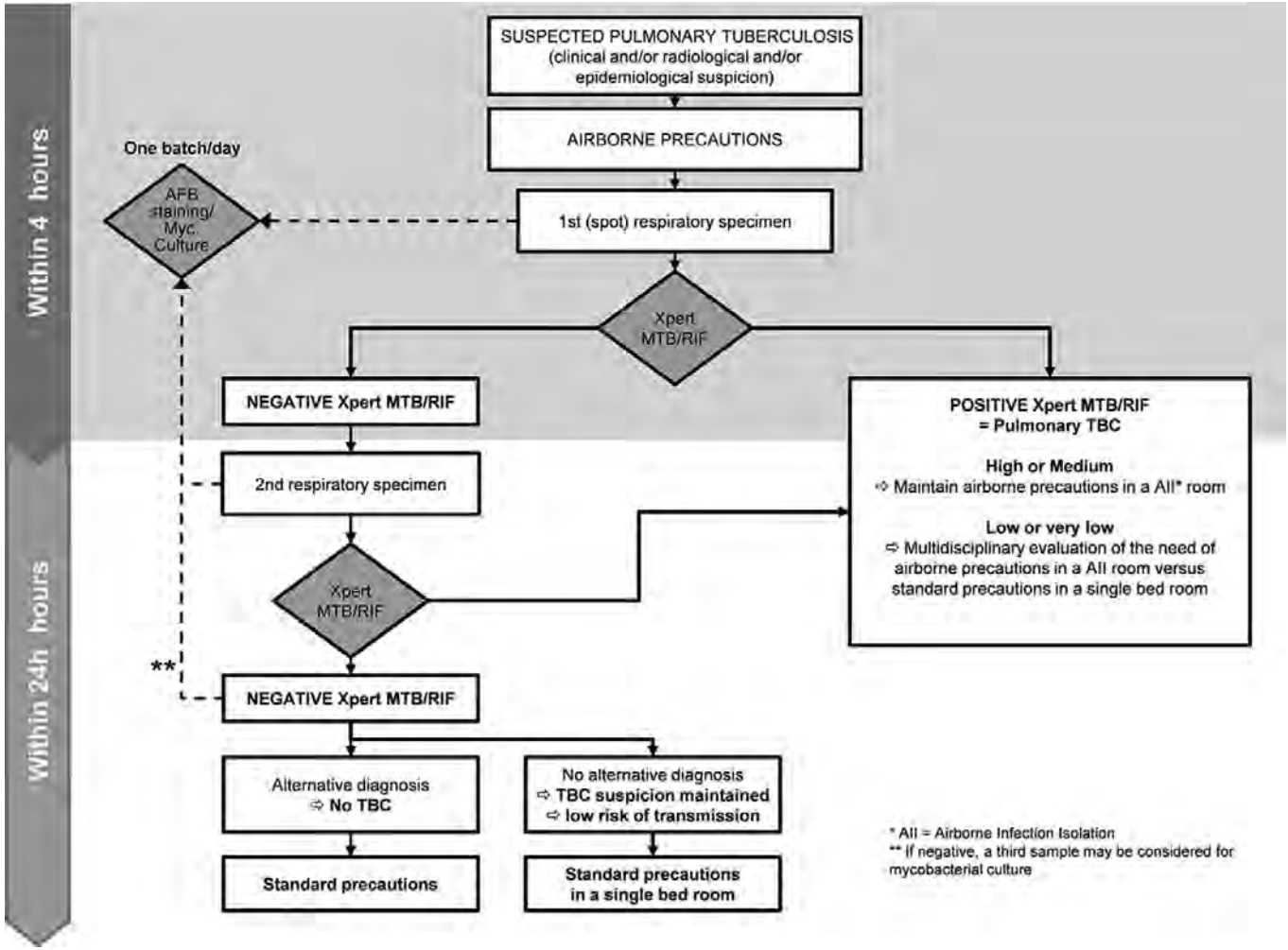


Fig. 2. Proposed work flow for pulmonary tuberculosis diagnosis based on molecular point-of-care test.

Opota O. Clin Microbiol Infect 2016;22(7):613-9

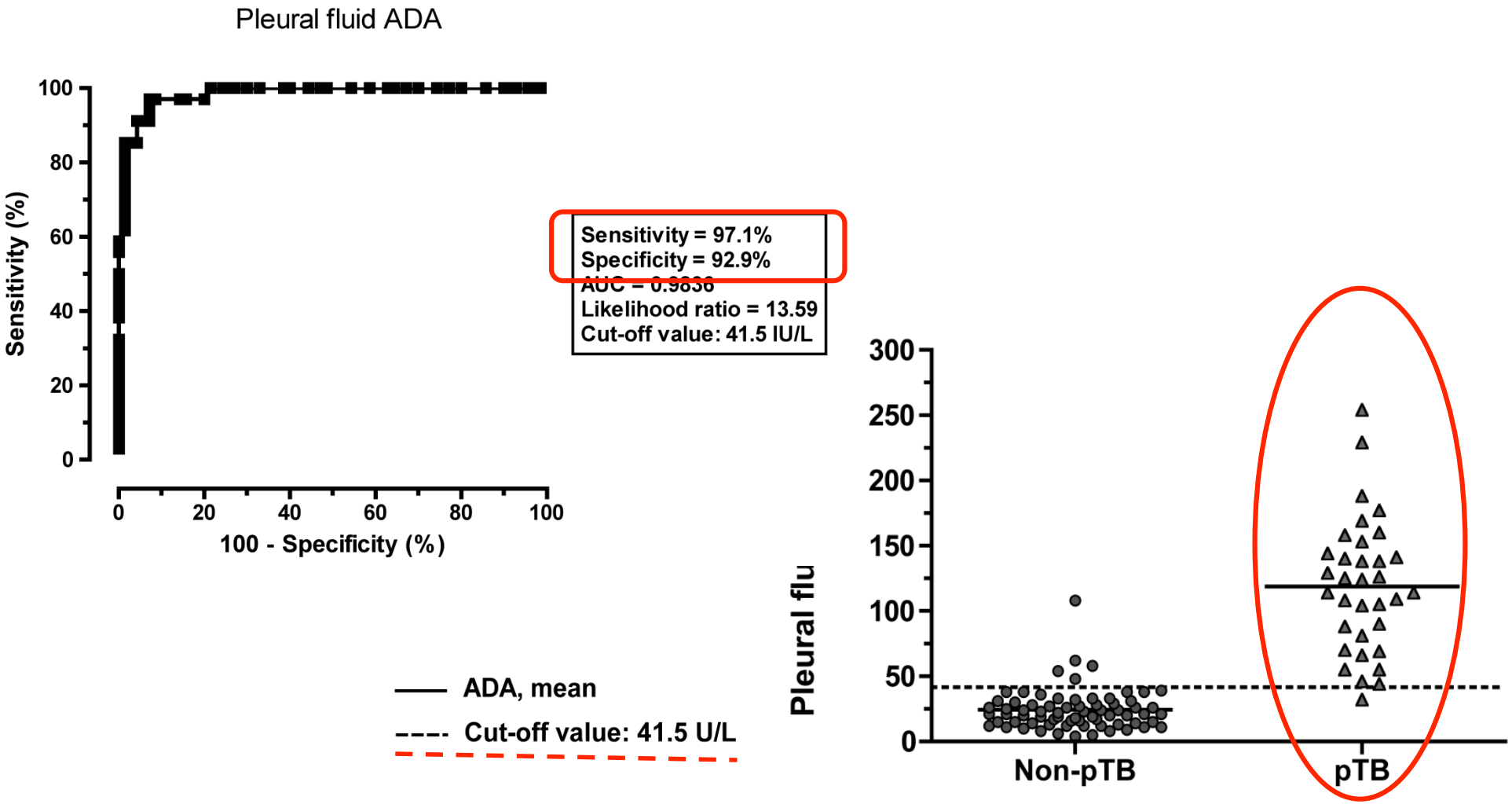
Adenosine deaminase is a useful biomarker to diagnose pleural tuberculosis in low to medium prevalence settings

- Etude rétrospective 2001-2008
- Suivi méd 15,6 mois (IQR 5,9-44,3)

	Total n=104 (100%)	**pTB n=34 (33%)**	**Non-pTB n=70 (67%)**	**p**
Age moy	55 (21)	41 (20)	62 (19)	<0,001
ADA moy U/L [range]	55 [4-254]	119 [32-254]	24 [4-108]	< 0,001

Michot JM. *Diagnostic Microbiol Infect Dis* 2015, doi: 10.1016/j.diagmicrobio.2015.11.007

Adenosine deaminase is a useful biomarker to diagnose pleural tuberculosis in low to medium prevalence settings



Michot JM. *Diagnostic Microbiol Infect Dis* 2015, doi: 10.1016/j.diagmicrobio.2015.11.007

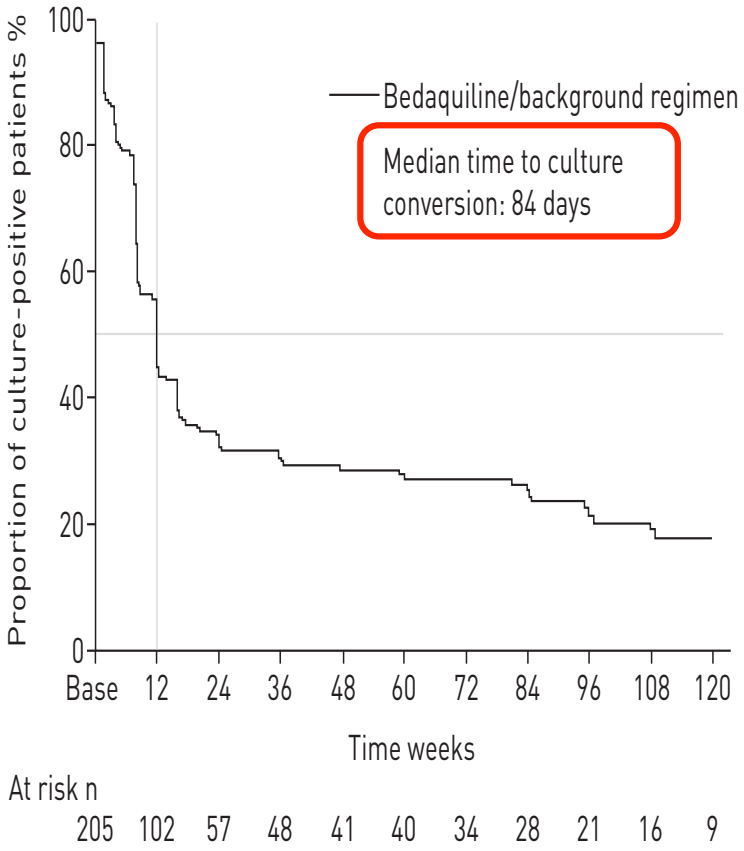
Bedaquiline in the treatment of multidrug- and extensively drug- resistant tuberculosis

- Etude multicentrique de phase II
- 20/08/2009-27/09/2010
- 233 patients (63,5% MDR, 18,9% pré XDR, 16,3% XDR)
- 400 mg bedaquiline/j 2 sem puis 200 mg x3/ sem pendant 22 sem en association
- Suivi 96 sem après fin du traitement bédaquiline (17,9% tjrs sous autres ATB)= S120

Pym AS. Eur Respir J 2016;47(2):564-74

Bedaquiline in the treatment of multidrug- and extensively drug- resistant tuberculosis

- 47/233 (20,2% SAE)
- 20/233 (8,6%) arrêt avant S24
- 16/233 (6,9%) décès



- Taux de conversion S120:
  - 73,1% (62,9-81,8%) MDR
  - 70,7% (54,8-83,3%) pré-XDR
  - 62,2% (44,8-77,6%) XDR

FIGURE 3 Kaplan–Meier plot for time to confirmed culture conversion (efficacy (modified intent-to-treat) population). The vertical line represents the median time to culture conversion. Base: baseline.

Pym AS. Eur Respir J 2016;47(2):564-74

Effect of drug resistance on negative conversion of sputum culture in patients with pulmonary tuberculosis

- Etude rétrospective
- 01/2009 - 12/2012
- Corée du Sud
- 535 TBM; 3 groupes:
  - 448 (83,7%) « DS » sensible aux ATB de 1ère ligne
  - 52 (9,7%) «ODR » mono-poly ou résistance mais pas multiR
  - 35 (6,%) « MDR »: MDR/XDR

Table 1
Demographic and baseline characteristics of the three groups of patients

	All drug-sensitive	Other drug-resistant	MDR or XDR	*p*-Value
Number (total = 535)	448	52	35	
Age, years, median (IQR)	56 (39, 70)	55 (37, 69)	41 (33, 55)	0.002
Male, *n* (%)	264 (58.9)	30 (57.7)	24 (68.6)	0.52
Body weight, kg, median (IQR)	55 (49, 64.2)	56.3 (50, 62.2)	56.8 (49, 67)	0.28
Sputum studies				
Positive acid-fast staining, *n* (%)	140 (31.3)	19 (36.5)	17 (48.6)	0.008
Time to culture of *M. tuberculosis*, days, median (IQR)	16 (12, 20)	14 (10.5, 19)	15 (11, 20)	0.39
History of tuberculosis, *n* (%)	67 (15.2)	11 (22.0)	19 (55.9)	<0.001
Comorbidities				
Diabetes, *n* (%)	81 (18.1)	11 (21.2)	3 (8.6)	0.29
Malignancy, *n* (%)	54 (12.1)	7 (13.5)	1 (2.9)	0.24
Immunosuppressants, *n* (%)	22 (4.9)	1 (1.9)	2 (2.9)	0.55
HIV/AIDS, *n* (%)	1 (0.2)	1 (1.9)	2 (5.7)	0.001
Chronic liver disease, *n* (%)	34 (7.6)	4 (7.7)	1 (2.9)	0.58
Chronic kidney disease, *n* (%)	21 (4.7)	2 (3.9)	1 (2.9)	0.86
Smoking status				
Current smoker, *n* (%)	81 (18.1)	6 (11.5)	8 (8.4)	0.82
Pack-years, median (IQR)	30 (15, 50)	40 (30, 40)	20 (15, 40)	0.36
Radiographic characteristics				
Presence of a cavity, *n* (%)	100 (26.1)	10 (25.6)	11 (34.4)	0.59
Bilateral involvement, *n* (%)	194 (50.7)	27 (69.2)	19 (59.4)	0.001

MDR, multidrug-resistant; XDR, extensively drug-resistant; IQR, interquartile range.

Joohae K. Intern J Infect Dis 2016(42):64-8

Effect of drug resistance on negative conversion of sputum culture in patients with pulmonary tuberculosis

Table 3

Conversion rate of patients with negative culture conversion at 4, 8, and 12 weeks[a]

	All drug-sensitive	Other drug-resistant	MDR or XDR	*p*-Value
Number (total = 535)	448	52	35	
4 weeks	236 (52.7)	16 (30.8)	16 (45.7)	0.010
8 weeks	342 (76.3)	33 (63.5)	21 (60.0)	0.020
12 weeks	385 (85.9)	44 (84.6)	26 (74.3)	0.176
Time to negative culture conversion				
Mean ± SD	53.1 ± 68.1	59.3 ± 36.9	109.2 ± 175.1	<0.001
Median (IQR)	39 (16, 67)	56 (28, 80)	56 (0, 92)	

MDR, multidrug-resistant; XDR, extensively drug-resistant.

[a] Values are *n* (%).

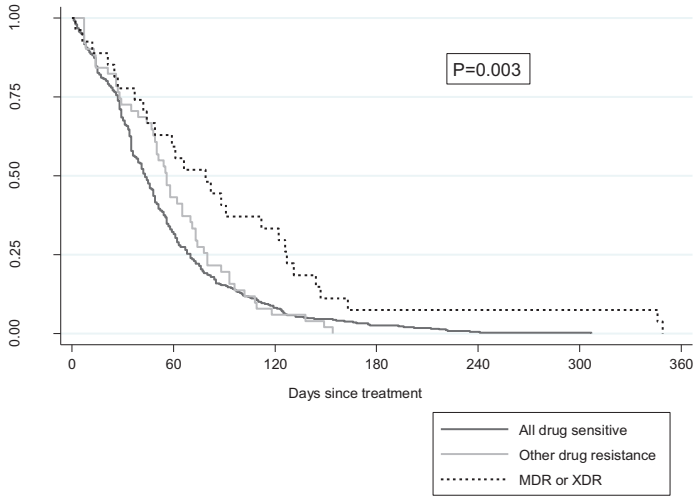
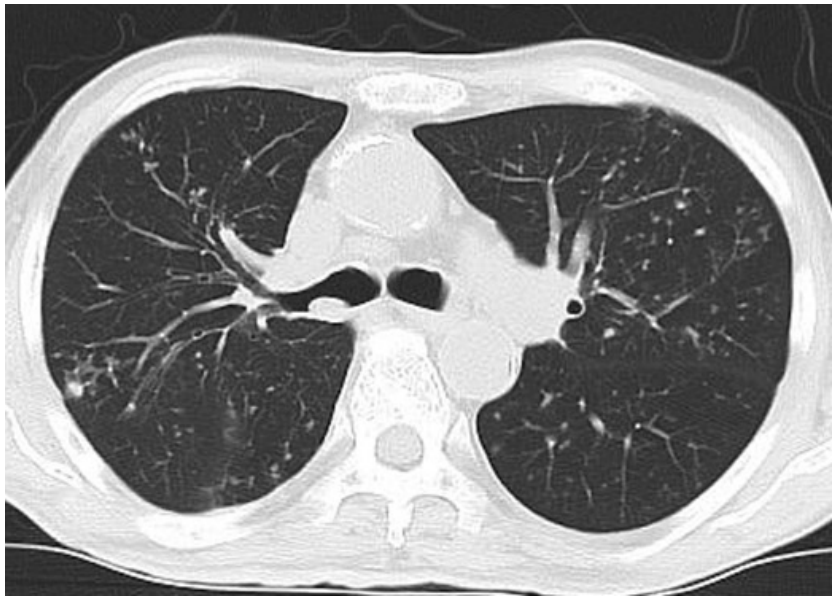


Figure 1. Comparison of time to culture conversion in TB patients grouped by different drug sensitivities.

Joohae K. Intern J Infect Dis 2016(42):64-8

Anti-PD1 antibody treatment and the development of acute pulmonary tuberculosis



- Homme de 72 ans, QFT -
- Cancer épidermoïde du poumon,
- 2ème ligne par Nivolumab
- Apparition de nodules centro-lobulaires après 8 injections.
- QFT +, culture LBA + *Mycobacterium tuberculosis*.
- Biopsies transbronchiques: infiltrat lymphocytaire

Fujita K. J Thorac Oncol 2016

Anti-PD1 antibody treatment and the development of acute pulmonary tuberculosis

- Inhibition PD1-PDL1 → « uprégulation » de la production d'IFN-γ.
- « IRIS »?

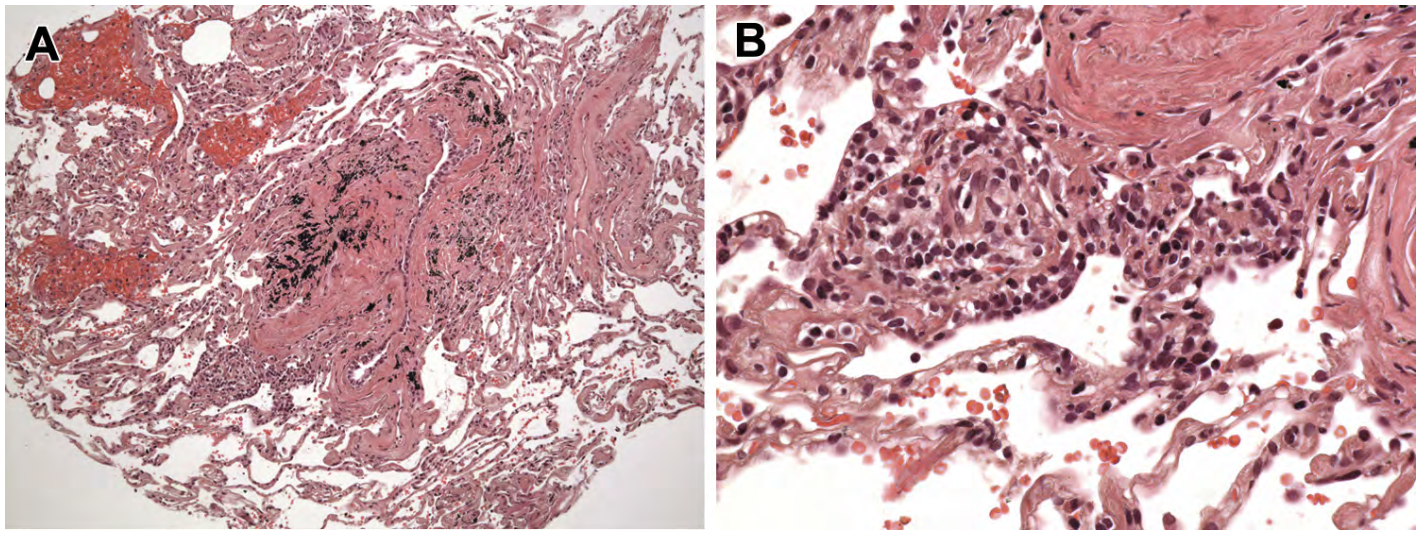
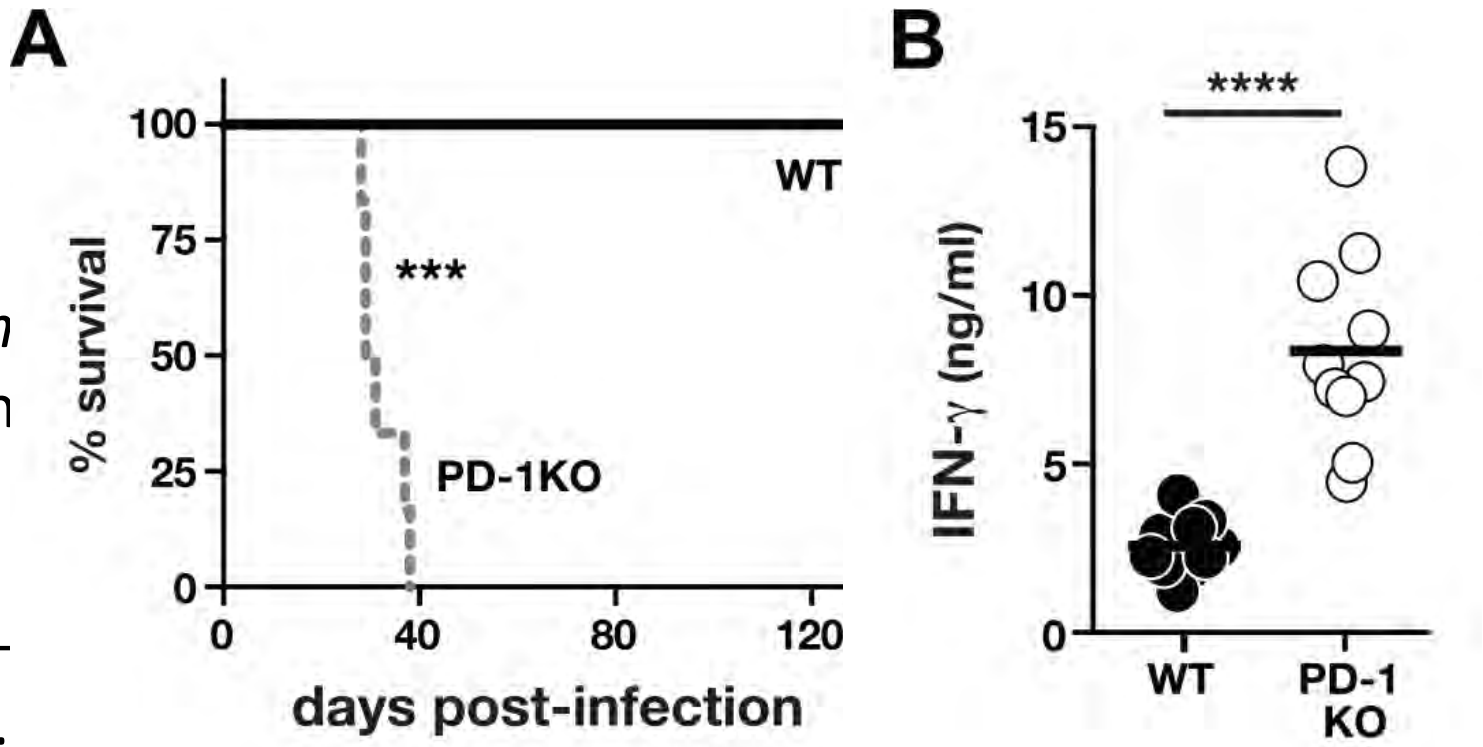


Figure 2. Histopathological findings of examination of the lung biopsy specimens. Diffuse lymphocyte infiltrations were observed in the alveolar area (hematoxylin and eosin). (*A*) Original magnification, ×200; (*B*) original magnification, ×400).

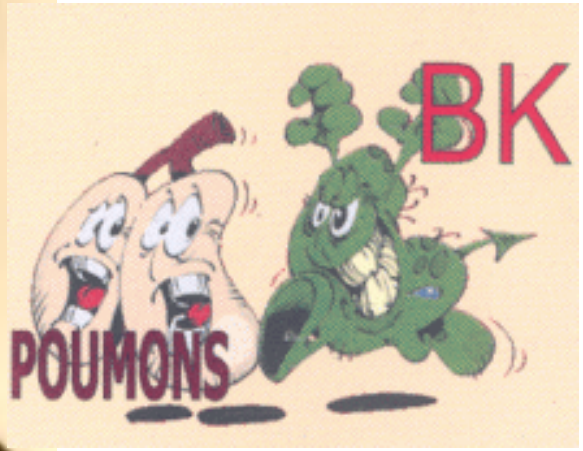
Fujita K. J Thorac Oncol 2016

CD4 T cell-derived IFN-γ plays a minimal role in control of pulmonary Mycobacterium tuberculosis infection and must be actively repressed by PD-1 to prevent lethal disease

PD1 facilite la résistance de l'hôte à *Mycobacteriun tuberculosis* en évitant la suproduction délétère d'INF-γ par les CD4+.



Sakai S. PLoS Pathog 2016;12(5): e1005667.



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