Tuberculosis

- In 2005, WHO awaited number of

  New cases : $>10.^{7}$

  Death : $>3.10^{6}$

Global trend in resistance to antituberculous drugs

(NEJM 344:17:1294 ,2002)

- 58 geographic sites on six continents
- R to at least one drug in newly diagnosed tuberculosis:

  Median : 10,7 %

  from 1,7% in Uruguay to 36,9% in Estonia
- MDRTB among new cases:

  Median : 1 %

  BUT : Estonia :14,1%

  Latvia : 9 %

  Several places in previous USSR : 6-9%

  China : 10,8%-14,1%

  Iran : 5%

Tuberculosis in Belgium

- Incidence in 2004 :11,8/10^5
  Flanders/Wallonie : <$10/10^5$
  Brussels : $34/10^5$
  with 1/3 new cases in Brussels
- 2/3 patients are males
- More than 50 % are foreigners(3/4 in Brussels)
  In 1991: 18%
  NB : Incidence in foreigners :13 times the belgian one

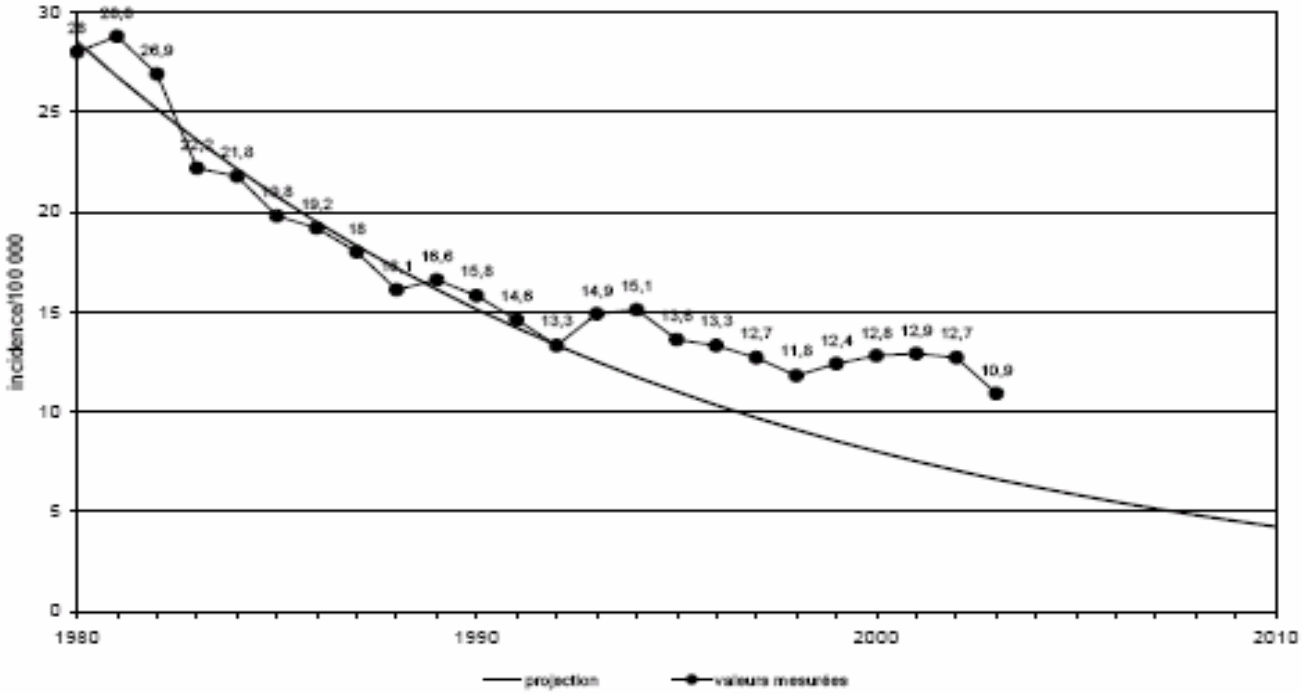


Figure 6. Evolution du taux brut d'incidence en Belgique, 1980-2003

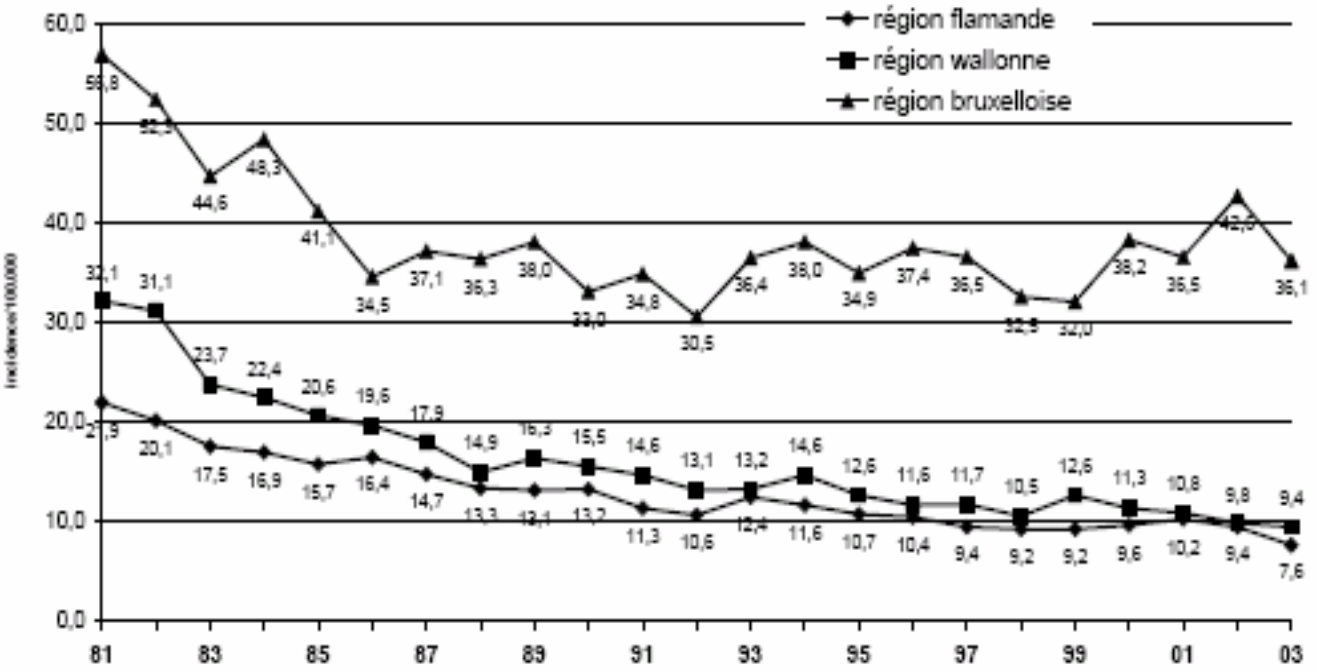


Figure 9. Evolution du taux brut d'incidence de la tuberculose dans les 3 régions, Belgique, 1981-2003

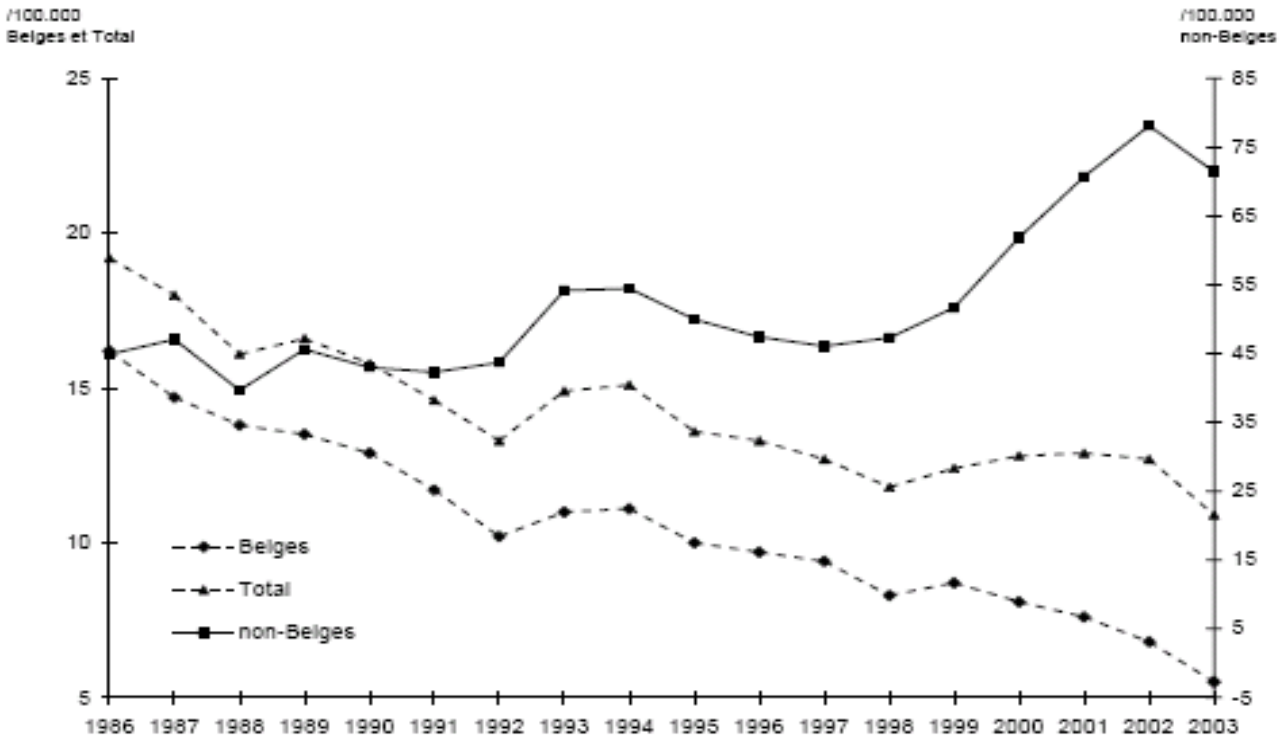


Figure 7. Evolution de l'incidence de la tuberculose chez les Belges et les non-Belges, 1986-2003[11]

Tuberculosis in Belgium

- In 2003,42 % are :
  Low income patients : 16 %
  Refugee : 16 %
  Illegal : 5 %
  Prisoners : 2 %
- Pulmonary infection in most cases : 75 %
  with half of the patients smear positive
  81,5 % culture positive
- 75 % are treated as long as indicated
- Death : 12,6 %, with : Foreigners : 4,2 %
  Belgians : **19,3 %**

Definition of MDRTB

- Strains of M.tuberculosis resistant to INH and Rifampicin
- Primary resistance:resistance among new cases or treated <1 month
- Acquired drug resistance:resistance among previously treated cases (>1 month)
- Probability of MDRTB developping by chance alone:

  product of the individual mutation rates,here:

  $10^6 X10^8=10^{14}$

Outcome of MDRTB

- Natural history: 50 % mortality over 5 years

- Cure rate with short course therapy:

  5-50 % JAMA 2000-MMWR 1999

→ Intensive medical and surgical therapy :

  up to 95 %

Suspicion of MDRTB

- Foreigners coming from countries with high prevalence of MDRTB
  - Eastern Europe
  - Africa
  - SE Asia
  - Latin America
- Direct contact with a MDRTB patient
- Potentially effective therapy with :
  - cultures remaining (+) after ≥4 months
  - cultures again (+) after transient negativation
  - increasing X-Ray lesions after months of therapy
- History of previous TB/ previous treament failure

MDRTB in Belgium-Risk factors

- For Brusssels and Wallonie-from 2001 to 2003
- univariate analysis : age - candidate refugee
- coming from outside Western Europe
- multivariate analysis : age(15- 44 and 45-64)
- candidate refugee
- previous TB

Evolution de la R en Belgique

- Multi R : 1,6 % chez les allochtones (4,4 % en 2002)
  0,5 % chez les belges (0,7 % en 2002)

- avec évolution de 1,2 % en ’95 à 2,6 % en 2002
  puis retour à 1,1 % en 2003

- En 2003, R à au moins un AB : 8,1 %
  - INH : 7,5 %
  - Rif : 1,1 %

MDRTB treated in Brussels (2001-2004)

- 33 patients, with 16 in 2004
- Male : 21(64%)
- Mean age : 33 (range 3-65)
- Origin :
  - Eastern Europe/Central Asia : 14
  - Africa :11
  - Belgium : 3
  - South America : 2
- Risk factors:
  - Candidate refugee : 23
  - Previous TB : 15
  - HIV/Other immunosuppression : 6

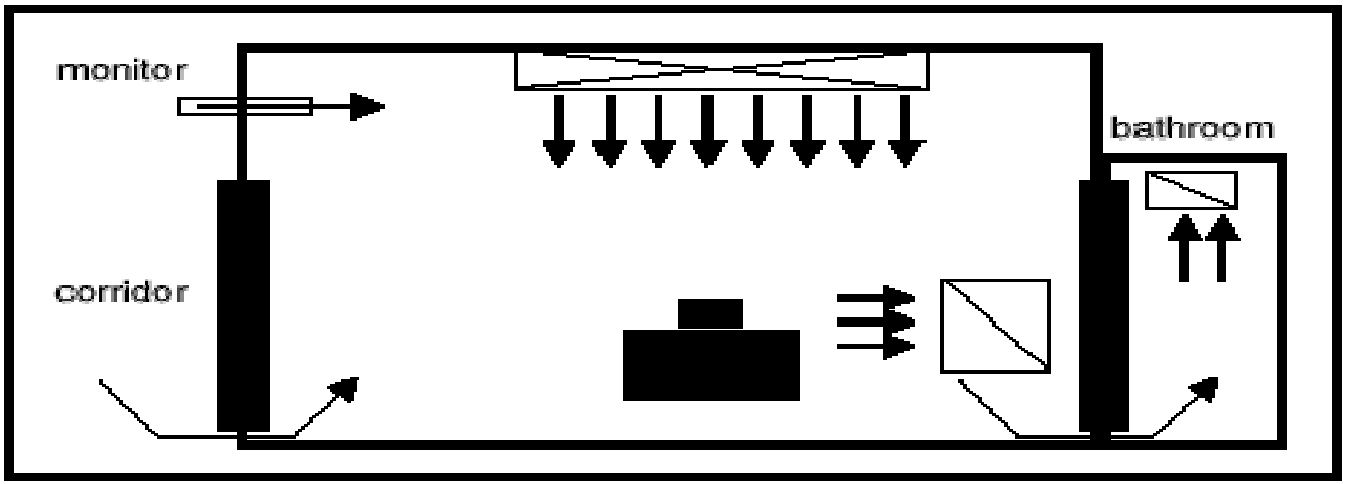
Typage des souches de BK multi R

- Sur 141 isolats provenants de 123 patients,de 1994 à 2004 :
- 11 étaient des faux (+):contamination de laboratoire
- Tous étaient R INH et RIF,71% à rifabutine,58 % à éthambutol,
  47 % à pyrazinamide
- Cinq grandes familles génotypiques
- Stabilité du profil au cours du temps chez même patient

Management of MDRTB patients

- Negative pressure rooms with sas,
  in two ID units of 15 beds each.
- Patients restricted to
  - the unit IF impossible to remain in their room
  - the hospital yard after several weeks (….) with
    a member of the staff (walking, smoking,…)
- FFP2 masks used by the staff
- Mask for the patient outside the room, and inside when
  coughing a lot/staff in the room

FIGURE 3. Example of negative-pressure room control for airborne infection isolation (AII)*†



Source: Adpted from Heating/Piping/Air Conditioning (HPAC) Engineering, October 2000, Penton Media, Inc.

Note: Stacked black boxes represent patient's bed. Long open box with cross-hatch represents supply air. Open boxes with single, diagonal slashes represent air exhaust registers. Arrows indicate direction of airflow.

* Possible uses include treatment or procedure rooms, bronchoscopy rooms, and autopsy.

† Negative-pressure room engineering features include

- negative pressure (greater exhaust than supply air volume);
- pressure differential of 2.5 Pa (0.01-in. water gauge);
- airflow differential >125-cfm supply versus exhaust;
- sealed room, approximately 0.5-sq. ft. leakage;
- clean to dirty airflow;
- monitoring;
- ≥12 air exchanges/hr (ACH) new or renovation, 6 ACH existing; and
- exhaust to outside or HEPA-filtered if recirculated.

MDRTB-Important points

- Starting of treatment as early as possible is crucial
- Aggressive treatment regimen, with≥ 3 in vitro active drugs
- High-end dosing (but high risk of side effects…)
- DOT (or other strategies to improve adherence)

Errors in therapy of MDRTB

- Most frequent in the litterature :
  - inadequate primary regimen
  - addition of a single drug in case of failure/R in vitro
  - failure to recognize/ensure compliance

Initiation of therapy

- Try to have ≥4 drugs potentially actives
- With : Ethambutol if S(at 20-25 mg/kg/d-ophtalmo f.up)
  Pyrazinamide if S or R(35 mg/kg/d)
- INH : also at the beginning for the strains still sensitive
  or Ethionamide if S
- Amikacin :Yes!
- Fluoroquinolones :Yes
- Others : if necessary, as : clofazimine, betalactame,….

Frequently used drugs in MDRTB

- Rifabutine : high (90 %?) level of cross R with rifampicin
  side efects similar to rifampicin
- Amikacine : most streptomycin R strains still S to amika
  - administred IV,OD,15 mg/kg/d,for 3 months
    (others : 4 to 12 months)
  - F Up of through levels
- Fluoroquinolone : keystone of the treatment; bactericidal
  - R rare,but rapid emergence if used alone
  - total cross R between FQ
  - in vitro : moxi > others; in vivo?
  - continued throughout the treatment course

Frequently used drugs in MDRTB

- Ethionamide/prothionamide :
  bactericidal,but more weakly
  most strains still S
  frequent GI side effects:increase dose gradually
  to 2-3 x250 mg/d
- Cycloserine : weakly bacteriostatic
  frequent CNS/psychiatric side effects,
  decreased with pyridoxine 100- 250 mg/d
  avoid in psychiatric patients
  (we use neuroleptics prophylact.)
  increase dose gradually:250 mg OD to BID/TID if possible
- Clofazimine : limited data in TB/MDRTB
  100- 300 mg/d
  skin problems : orange brown pigmentation,…

Treatment

- DOT not always used
- Compliance evaluated with random sampling of the urines,

  if Rif used.

Duration of therapy

- If possible (often limited by side effects!)
- ≥ 18 months if first line drugs included
- ≥ 24 months if second line drugs used

Evolution of MDRTB treated in Brussels (2001-2004)

- Cure : 7 (clinical cure and negative culture at the end of treatment)
- Possible cure : 12 (clinical cure with neg.culture during treat. but not available at the end)
- Failure : 1 (relapse with same sensitivity)
- Death : 4 (2 related, 2 unknown)
- Lost of follow up : 6

Treatment of MDRTB in Turkey

(NEJM 345:3:170,2001)

- 158 consecutive patients in Istambul,from 1992 to 1999
- Treated with ≥3 active drugs for ≥18 months after the conversion to a negative culture
  - Cure : 49 %
  - Probable cure : 27 %
  - Failure : 8 %
  - Death : 4 %
  - Lost of follow up : 11 %
- Negative culture in 95 % after a mean of 1,9 month
- Surgical resection in 36 patients
- Successful outcome associated with a younger age and the absence of previous treatment with ofloxacin

New treatment modalities

- Amoxicillin/clavulanate : active in vivo, but less than INH,
  - at least 3 g/d,only active on the extracellular bacteria
    → most of the activity during the first days/weeks
- Inhaled aminoglycosides : shown active without signif. toxicity in short series
- Linezolid : good in vitro activity and promising results in small series BUT : significant hemato and peripheral neurotoxicity after 2-4 weeks.
- Aerosol Gamma interferon : good clinical and bacteriologic results in a small open trial,
  BUT relapse when treat. discontinued
- Totally new drugs : diarylquinolines,….

Surgery

- To be considered for patients with destruction of a lobe or entire lung,

  and/or large/persistent cavities.

  Failure to eradicate M.tuberculosis after 3-4 months of treatment
- If performed, try to treat first 3-4 months and to have mycobacterial eradication (negative smears)
- After surgery, therapy continued for ≥18-24 months
- Major complication : bronchopleural fistula
- Surgery never performed in St Pierre (2 potential cases)

  Problems with the staff; unable to convince them that their risk was VERY small.

Bacteriologic Follow Up

- First control 10-14 days after initiation of therapy
- Thereafter : 2-3 times/week(FARES:≥1/w), until
  - 3 consecutive sputum with negative cultures (CDC requirements)

(FARES : 6 negative sputum smears with ≥ 72 h interval)

Treatment of MDRTB in Iran (Int J. Infect. Dis 9:317-2005)

- Tehran,from 2000 to 2002
- 39 consecutive patients, with 17 eligible
  - (15 lost of F Up after <6 months of therapy,)
  - (7 without culture)
  - →17 eligible
- Mean age : 34
- Male : 71 %
- Evolution: Cure 41 %
  - Probable cure : 23 %
  - Failure 23 %
  - Death 5,9 %
  - Relapse 5,9 %