

Update on Tuberculosis

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Learning Objectives

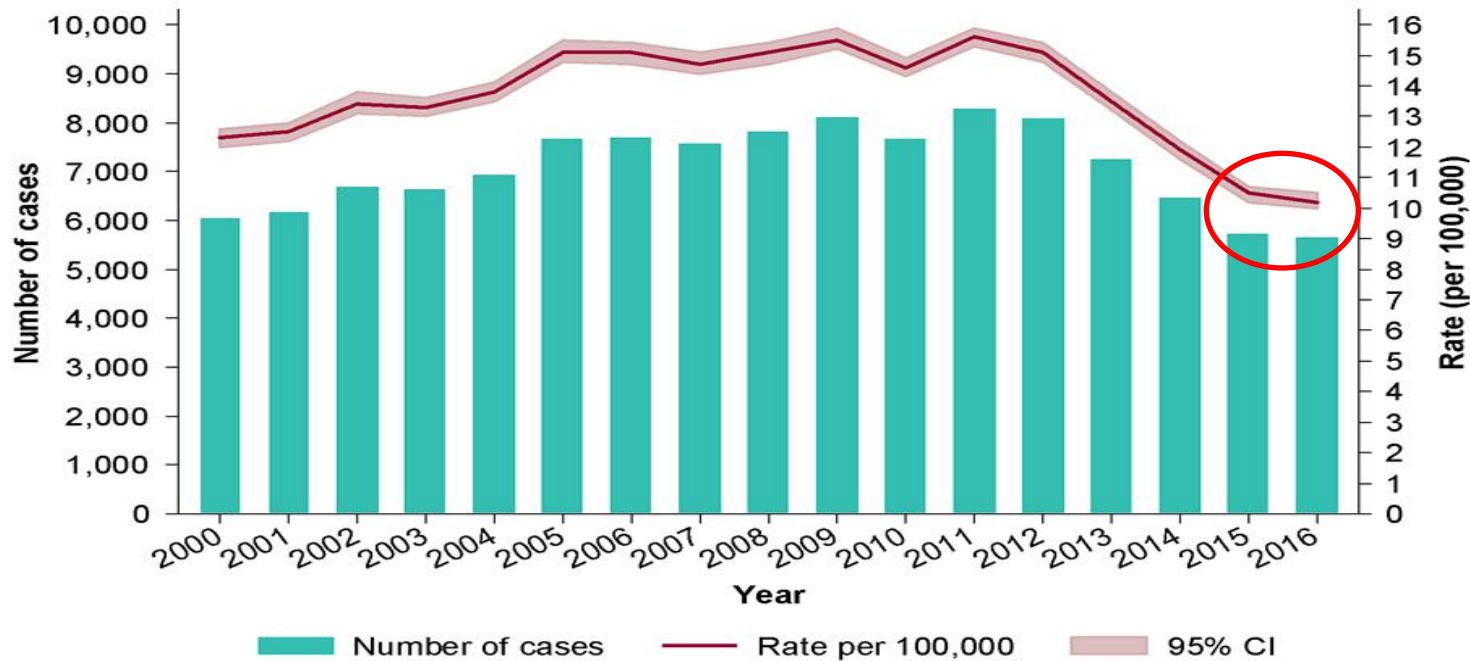
- TB epidemiology
- Illustrative cases



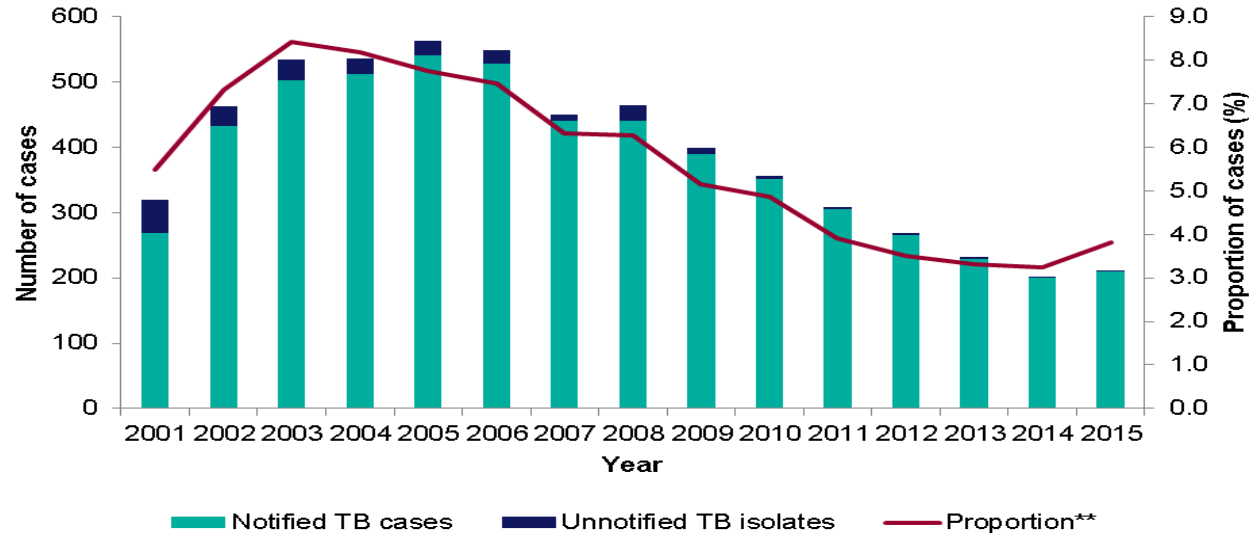
TB case notifications and rates, England, 2000-2016

5,664 cases

10.2 cases per
100,000
population



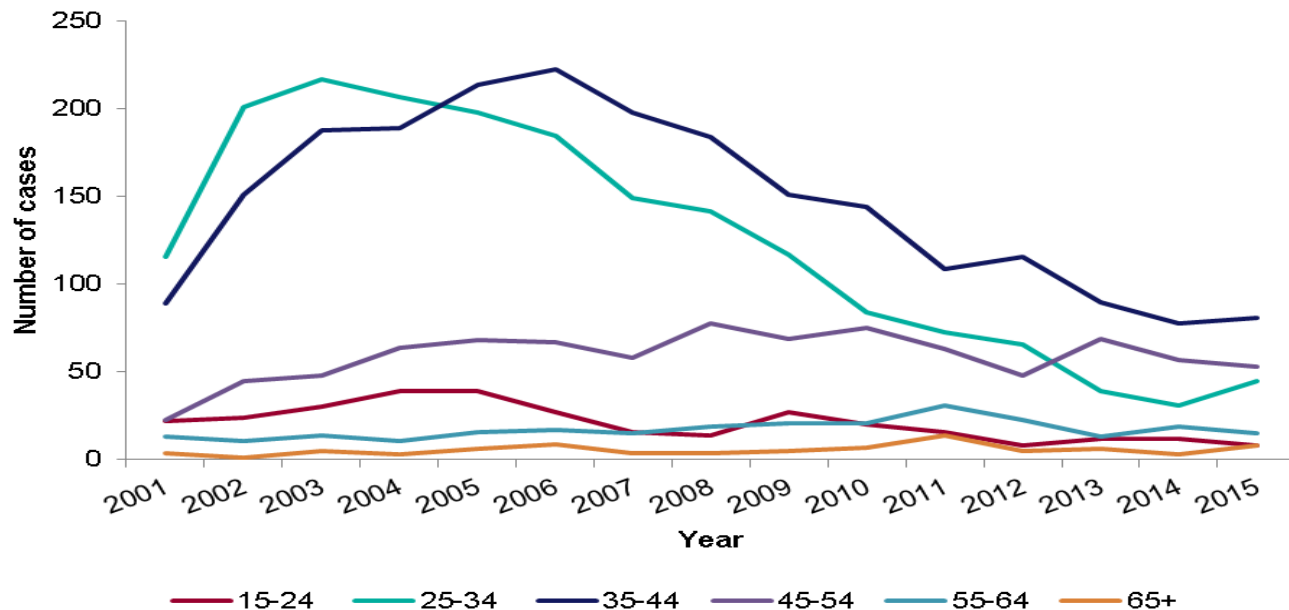
Number and proportion of TB cases with HIV co-infection*, England, 2001-2015



* Includes TB and HIV co-infected cases aged 15 years and older.

** Proportion is calculated using the number of notified TB cases with HIV co-infection plus the number of un-notified MTBC isolates which matched to an HIV case as the numerator, and the number of all notified TB cases (with or without HIV co-infection) plus the number of un-notified TB isolates which matched to an HIV case as the denominator.

Number of TB-HIV co-infected case notifications by age group*, England, 2001-2015

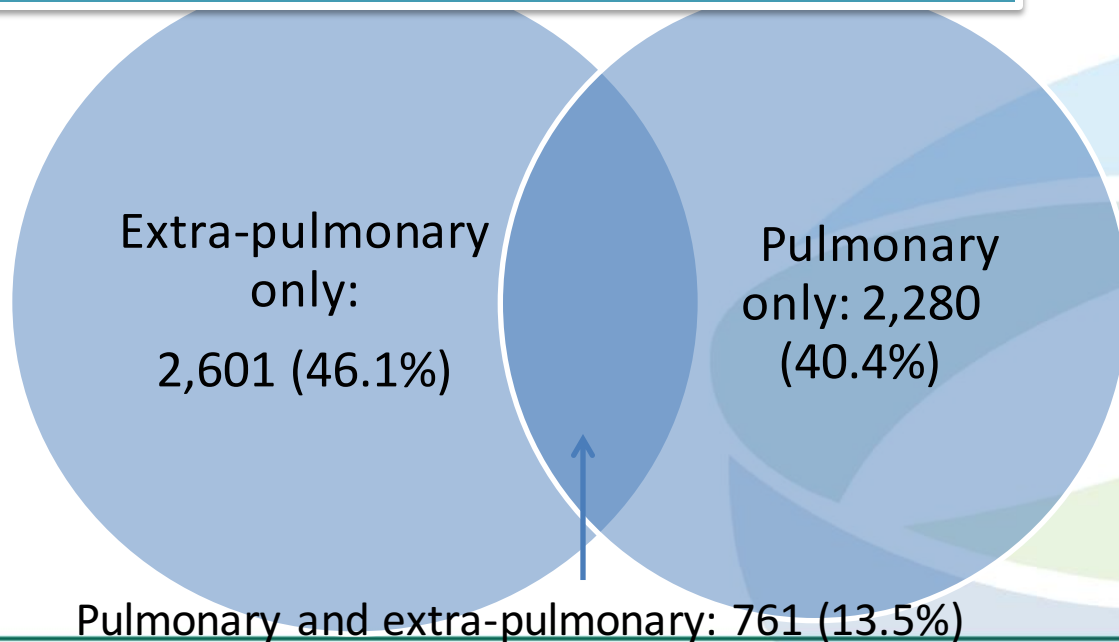


* Based on age at TB notification

TB case notifications by site of disease, England, 2016

5,642 TB cases notified where site of disease was known:

- 3,041 (53.9%) had pulmonary disease
- 3,362 (59.6%) had extra-pulmonary disease



Case1.

- A 25 year old lady presents with a dry cough, breathlessness, weight loss and night sweats.
- She has been unwell for 2 months
- HIV infected
- CD4 100
- Not on ARV's

Case 1.



Case 1.

- 900mls fluid drained
- Clear fluid – hint of blood
- High protein level
- Some inflammatory cells

Pericardial TB

- Would you give this patient steroids?



Pericardial TB

- If yes why?



Pericardial TB

1.3.7.20

At the start of an anti-TB treatment regimen, offer adults with active pericardial TB oral prednisolone at a starting dose of 60 mg/day, gradually withdrawing it 2–3 weeks after starting treatment. **[2016]**

1.3.7.21

At the start of an anti-TB treatment regimen, offer children and young people with active pericardial TB oral prednisolone in line with the [British National Formulary for Children](#). Gradually withdraw prednisolone 2–3 weeks after starting treatment. **[2016]**

Steroids in Pericardial TB

- Prednisolone and *Mycobacterium indicus pranii* in Tuberculous Pericarditis
 - Bongani Mayosi et al - IMPI Trial
 - New England Journal of Medicine 2014;371:1121-1130
 - 1400 patients with pericardial TB randomised to placebo or prednisone.
 - Prednisolone for 6 weeks (120mg, 90mg, 60mg, 30mg, 15mg, 5 mg)
 - Two thirds of the patients had HIV infection
 - Composite end point:- death, cardiac tamponade, constrictive pericarditis

Steroids in Pericardial TB

- Results
 - There was no difference in the primary outcome between patients who received prednisone and placebo (23.8% vs 24.5%, HR 0.95 95%CI 0.77- 1.18)
 - There was a higher incidence of cancer in the prednisone group (1.8% vs 0.6% p=0.03)
 - Prednisolone reduced the incidence of constrictive pericarditis (4.4% - 7.8% HR 0.56 95%CI 0.36 - 0.87)
 - (Secondary outcome)

ATS TB Guidelines 2016

- Adjunctive corticosteroids should not be used routinely in the treatment of pericardial tuberculosis
- Selective use of corticosteroids in patients at high risk of inflammatory complications may be appropriate (e.g. large effusion, raised inflammatory cells or markers in fluid, signs of early constriction.)

TB Treatment - BHIVA

- We recommend daily administration of standard TB therapy (2RHZE/4RH) in those with drug sensitive TB (1A)
- We recommend using fixed-dose combination tablets (RHZE, RHZ and RH) wherever possible (GPP)
- We recommend that rifampicin is substituted with rifabutin if drug-drug interactions preclude the use of rifampicin (1C)
- **We recommend that patients with TB meningitis receive corticosteroids (1A)**
- **We recommend against the use of corticosteroids in TB pericarditis (1A)**

Case 2.

- 34 year old lady
- Born in Somalia
- HIV infected
 - CD4 96 (9%)
 - Viral load 705,000

Case 2.

- Difficult social circumstances
- Chaotic lifestyle
- Presented with fever and abdominal pain
- Some ascites

Case 2.

- Ascitic fluid - grew
 - *mycobacterium tuberculosis*
 - Rifampicin probe – negative
- Culture
 - R S
 - H R
 - Z S
 - E S



Case 2.

- What treatment would you give?
 - A. RHZE
 - B. REZ
 - C. REZM

Case 2.

- What treatment would you give?

A. RHZE

B. REZ

C. REZM

Case 2.

- Developed rash on treatment
- Felt flushed after taking TB pills
- What would you do?

Case 2.

- Type I – Immediate in onset and mediated by IgE and mast cells/basophils.
- Type II – Delayed in onset and caused by antibody (usually IgG) mediated cell destruction.
- Type III – Delayed in onset and caused by IgG:drug immune complex deposition and complement activation.
- Type IV – Delayed in onset and T cell-mediated

Rifampicin Oral Desensitisation

Time from Start (h:min)	Rifampicin dose (mg)
0	0.1
45	0.5
1:30	1.0
2:15	2.0
3:00	4.0
3:45	8.0
4:30	16.0
5:15	32.0
6:00	50.0
6:45	100
7:30	150
11:00	300
Next morning	600

Given
with
ranitidine

Case 2.

- Patient tolerated reintroduction
- No rash
- Some flushing
- Discharged home on RZE / cetirizine

Case 2.

- Completed TB treatment
- Kept on
 - Raltegravir / kivexa
- Remains well 12 months on

Case 3

- 40 year old man born in Ghana
- Came to UK 2016
- TB IGRA +ve
- (HIV –ve, Hep C – ve)
- Hepatitis B Sag +ve
- ALT 15iu

Case 3.

- Started on rifampicin / isoniazid
- 2 weeks later
 - Feels very nauseous
 - ALT 1000
- RH stopped
 - US liver NAD
 - ALT 20 after 10 days

Case 3.

- What could be going on?

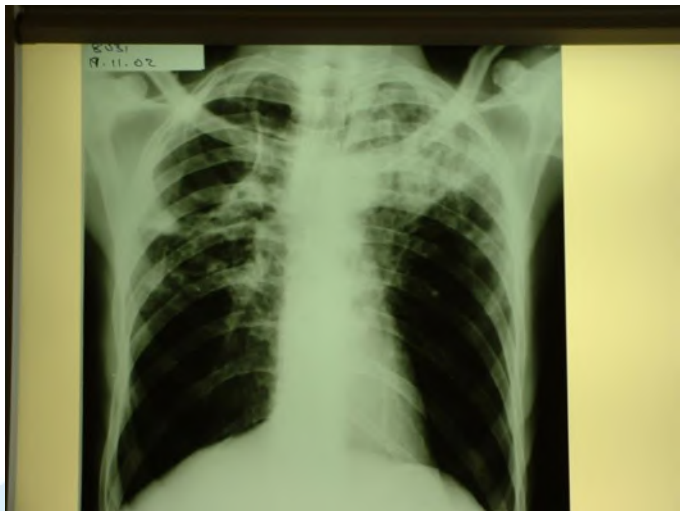


Case 3.

- Hepatitis B viral load
 - >1,000,000 iu
- Started on tenofovir
- RH restarted – tolerated for 3/12
 - No ALT rise

Case 4.

- 28 year old lady from Burkina Faso
- Presents with cough,
- fever, sweats
 - HIV infected – CD4 -600 cells/L, viral load 2000
- Cephid probe
 - Mycobacterium tuberculosis – rifampicin mutations
 - Culture positive after 5 days – WGS – mutations only to rifampicin



Case 4.

- What regimen would you give this patient?

A. RHZEM	18 months
B. HZE	18 months
C. MDRTB regimen	20 months
D. 6 KmMPtoCfzZHE / 5MCfzZE(H)	9 months
E. Something else	

Case 4.

- What regimen would you give this patient?
- | | |
|--------------------------------|-----------|
| A. RHZEM | 18 months |
| B. HZE | 18 months |
| C. MDRTB regimen | 20 months |
| D. 6 KmMPtoCfzZHE / 5MCfzZE(H) | 9 months |
| E. Something else | |

THE SHORTER MDR-TB REGIMEN



CRITERIA: Do any of the following apply ?

1. Confirmed resistance or suspected ineffectiveness to a medicine in the shorter MDR-TB regimen (except isoniazid resistance)
2. Exposure to >1 second-line medicines in the shorter MDR-TB regimen for >1 month
3. Intolerance to >1 medicines in the shorter MDR-TB regimen or risk of toxicity (e.g. drug-drug interactions)
4. Pregnancy
5. Extrapulmonary disease
6. At least one medicine in the shorter MDR-TB regimen not available in the programme

If the answer to all these questions is no then the shortened regimen can be used.

Suitable
for HIV
infected
patients

Treatment shortening with existing drugs; the 'Bangladesh regimen'

Serial adapted multi-drug MDR-TB regimens from 1997-2004

Final regimen reported 89% relapse-free cure¹

4 months (intensive phase)*:

Kanamycin (500-1000mg)
Prothionamide (500-1000mg)
High dose isoniazid (400-600mg)
Gatifloxacin (400-800mg)
Clofazimine (50-100mg)
Pyrazinamide (800-2000mg)
Ethambutol (800-1200mg)



5 months (continuation phase):

Gatifloxacin (400-800mg)
Clofazimine (50-100mg)
Pyrazinamide (800-2000mg)
Ethambutol (800-1200mg)

*Intensive phase extended until sputum smear conversion if not smear negative at 4 months

Authors highlight

- Use of clofazimine & high dose 4th generation fluoroquinolone
- Follow-up under routine conditions
- Low cost - €200 (US\$218) per patient

Bangladesh-style regimens in other settings

Further countries propose 'short' MDR-TB regimens

- Benin
- Cameroon
- Central African Republic
- Côte d'Ivoire
- DR Congo
- Niger
- Swaziland



Cameroon – 89.3% relapse free survival (75% F/U at 24 months)¹

- Used lower dose of gatifloxacin (400mg, all patients)
- Used standard dose isoniazid (300mg, all patients)
- 12 month total therapy for all patients
- Prothionamide carried into continuation phase treatment



Resources

- Public Health England TB resources
 - www.gov.uk/government/collections/tuberculosis-and-other-mycobacterial-diseases-diagnosis-screening-management-and-data
- TB drug information
 - <http://www.tbdrugmonographs.co.uk/>
- British Thoracic Society drug resistant TB advice
 - <https://www.brit-thoracic.org.uk/standards-of-care/lung-disease-registries/bts-mdr-tb-clinical-advice-service/>
- NICE guidelines CG 33
 - <https://www.nice.org.uk/guidance/ng33>



Thank you

- Questions?

