NICE Tuberculosis 2016- Questions and controversies

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Background and rationale

- NICE 2016--- comprehensive and thorough review of all aspects of TB care
- Overall broad agreement but other national documents– unclear position
- Across YHNE region, members submitted 10 question areas, of TB diagnosis and treatment

Process

- Regional guidance produced and shared for comment with key stakeholders across region and in each locality
- After comment, consensus was reached and confirmed in the TB CAG
- Purpose: To provide local YHNE wide clinical guidance reflecting local incidence patterns and TB service availability

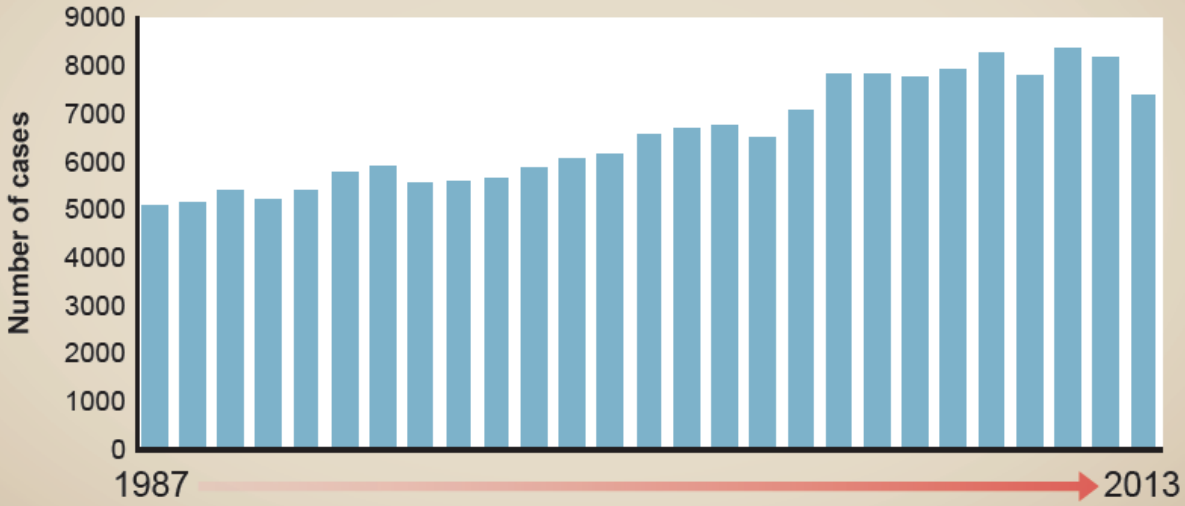
Public Health England

Protecting and improving the nation's health

Collaborative TB strategy for England 2015-2020

NHS England

The number of TB cases in England has increased to unacceptable levels



Our ambition

To bring together best practice in clinical care, social support and public health to strengthen TB control, with the aim of achieving a year-on-year decrease in incidence, a reduction in health inequalities, and ultimately the elimination of TB as a public health problem in England.

Systematically implement new entrant latent TB screening

In 2013, **3** out of **4** TB cases were born abroad, the majority due to reactivation of latent TB infection.

We need to identify and treat new migrants with latent infection

Ensure comprehensive contact tracing

In **2013**, **196** children born in **England** were diagnosed with TB, an indication of recent transmission

Enhanced contact tracing should improve **early diagnosis** and **reduce transmission**

Tackle TB in underserved populations

In 2013, **1** in **4** TB patients with social risk factors had not completed treatment by 12 months.

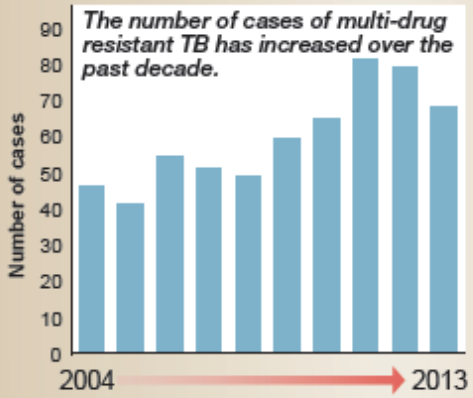
We need to improve the identification, management and support of TB patients with complex social needs

Ensure universal access to high quality diagnostics

In 2013, only **7** out of **10** pulmonary TB cases were culture confirmed.

We need to ensure all pulmonary cases have a respiratory sample taken and processed

Reduce drug resistant TB



We need to improve the prevention and management of drug resistant TB

- Deliver collaborative strategy for England
- 10 questions

- NICE
- PHE
- Vaccine groups
- Green Book
- National TB programme

Clarity on the definition of ‘vulnerable migrants’

Vulnerable migrants

Vulnerable migrants may include undocumented migrants and those with no recourse to public funds. Some refugees, asylum seekers and new entrants to the country may also fall into this category.

1.6.2.3 Healthcare professionals, including primary care staff, responsible for testing new entrants should test all vulnerable migrants who have not previously been checked. This is regardless of when they arrived in England. People born in

difficult to access services for diagnosis and treatment in traditional healthcare settings. This includes adults, young people and children from any ethnic background, regardless of migration status, whose social circumstances, language, culture or lifestyle (or those of their parents or carers) make it difficult to:

- recognise the clinical onset of TB
- access diagnostic and treatment services
- self-administer treatment (or in the case of children and young people have treatment administered by a parent or carer)
- attend regular appointments for follow-up.

Mantoux 'cut off' change

- Previously +ve Mantoux= 6mm
- UK practice, Green book
- New NICE guidance, +ve Mantoux=5mm
- Harmonises UK with global standards

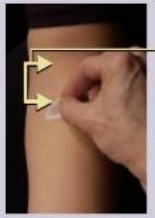
- YHNE- Agreement to adopt 5mm Mantoux as +ve

Mantoux
tuberculin skin test

1 Administration

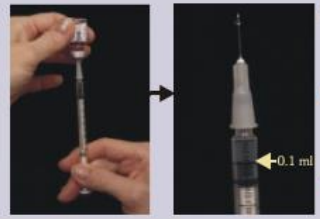
For each patient, conduct a risk assessment that takes into consideration recent exposure, clinical conditions that increase risk for TB disease if infected, and the program's capacity to deliver treatment for latent TB infection to determine if the skin test should be administered.

1 Locate and clean injection site



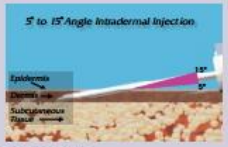
- 2 to 4 inches below elbow joint
- Place forearm palm side up on a firm, well-lit surface
- Select an area free of barriers (e.g., scars, sores) to placing and reading
- Clean the area with an alcohol swab

2 Prepare syringe



- Check expiration date on vial and ensure vial contains tuberculin (5 TU per 0.1 ml)
- Use a single-dose tuberculin syringe with a ¼- to ½-inch, 27-gauge needle with a short bevel
- Fill the syringe with 0.1 ml of tuberculin

3 Inject tuberculin

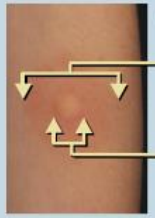


- Insert slowly, bevel up, at a 5- to 15-degree angle

2 Reading

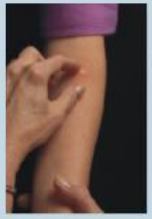
The skin test should be read between 48 and 72 hours after administration. A patient who does not return within 72 hours will probably need to be rescheduled for another skin test.

1 Inspect site



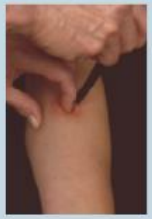
- Visually inspect site under good light
- Erythema (reddening of the skin) – do not measure
- Induration (hard, dense, raised formation)

2 Palpate induration



- Use fingertips to find margins of induration

3 Mark induration



- Use fingertip as a guide for marking widest edges of induration across forearm

4 Measure induration (not erythema)

3 Interpretation

Skin test interpretation depends on two factors:
- Measurement in millimeters (mm) of the induration
- Person's risk of being infected with TB and progression to disease if infected

The three cut points below should be used to determine whether the skin test reaction is *positive*. A person with a positive reaction should be referred for a medical evaluation for latent TB infection and appropriate follow-up and treatment if necessary. A measurement of 0 mm or a measurement below the defined cut point for each category is considered *negative*.

Induration of ≥5 mm is considered positive in

- Human immunodeficiency virus (HIV)-infected persons
- Recent contacts of TB case patients
- Persons with fibrotic changes on chest radiograph consistent with prior TB
- Patients with organ transplants and other immunosuppressed patients (e.g., receiving the equivalent of ≥15 mg/d of prednisone for 1 month or more)

Induration of ≥10 mm is considered positive in

- Recent immigrants (i.e., within the last 5 years) from countries with a high prevalence of TB
- Injection drug users
- Residents and employees* of the following high-risk congregate settings:
  - prisons and jails
  - nursing homes and other long-term facilities for the elderly
  - hospitals and other health care facilities
  - residential facilities for patients with acquired immunodeficiency syndrome (AIDS)
  - homeless shelters
- Mycobacteriology laboratory personnel
- Persons with the following clinical conditions that place them at high risk:
  - silicosis
  - diabetes mellitus
  - chronic renal failure
  - some hematologic disorders (e.g., leukemias and lymphomas)
  - other specific malignancies (e.g., carcinoma of the head, neck, or lung)
  - weight loss of ≥10% of ideal body weight
  - gastrectomy
  - jejunoileal bypass
- Children <5 years of age
- Infants, children, and adolescents exposed to adults at high risk for developing active TB

Induration of ≥15 mm is considered positive in

Ignore BCG vaccination status with Mantoux testing

- NICE recommends ignore BCG status
- Many clinicians feel uncomfortable with this
- Risk of false +ve, inappropriate treatment

OPEN ACCESS

ORIGINAL ARTICLE

The impact of BCG vaccination on tuberculin skin test responses in children is age dependent: evidence to be considered when screening children for tuberculosis infection

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ABSTRACT

Background Following exposure to TB, contacts are screened to target preventive treatment at those at high risk of developing TB. The UK has recently revised its recommendations for screening and now advises a 5 mm tuberculin skin test (TST) cut-off irrespective of age or BCG status. We sought to evaluate the impact of BCG on TST responses in UK children exposed to TB and the performance of different TST cut-offs to predict interferon

Key messages

What is the key question?

- The impact of BCG vaccination on tuberculin skin test response is poorly understood in children; we set out to determine the impact of previous BCG vaccination on tuberculin skin

Table 3 Odds of having a positive TST response of 5 mm, 10 mm and 15 mm between IGRA negative children who had been vaccinated with BCG at birth versus children who had not been vaccinated with BCG

	5 mm		10 mm		15 mm	
Age (years)	**OR (95% CI)**	**p Value**	**OR (95% CI)**	**p Value**	**OR (95% CI)***	**p Value**
All children	5.80 (2.58 to 13.0)	<0.001	4.03 (1.73 to 9.39)	<0.001	3.04 (1.14 to 8.10)	0.02
0 to <2	16.2 (1.69 to 155)	0.001	8.31 (0.94 to 73.5)	0.02	–	0.05
2 to <5	9.85 (1.11 to 87.7)	0.01	7.43 (0.85 to 65.1)	0.03	6.00 (0.69 to 52.4)	0.06
5 to <10	3.05 (0.93 to 10.0)	0.05	2.71 (0.72 to 10.3)	0.13	1.92 (0.39 to 9.52)	0.41
10 to <15	4.16 (0.77 to 22.3)	0.07	2.10 (0.39 to 11.2)	0.38	0.90 (0.15 to 5.32)	0.91

*Unable to calculate ORs where a zero exists in one of the four cells needed to generate the OR. No BCG-unvaccinated children under 2 years with negative IGRA results had a TST induration of greater than 15 mm. IGRA, interferon γ release assay; TST, tuberculin skin test.

Results Of 422 children recruited (median age 69 months; IQR: 32–113 months), 300 (71%) had been vaccinated with BCG. BCG vaccination affected the TST response in IGRA-negative children less than 5 years old but not in older children. A 5 mm TST cut-off demonstrated good sensitivity and specificity in BCG-unvaccinated children, and an excellent negative predictive value but was associated with low specificity (62.7%; 95% CI 56.1% to 69.0%) in BCG-vaccinated children. For BCG-vaccinated children, a 10 mm cut-off provided a high negative predictive value (97.7%; 95% CI 94.2% to 99.4%) with the positive predictive value increasing with increasing age of the child.

Discussion BCG vaccination had little impact on TST size in children over 5 years of age. The revised TST cut-off recommended in the recent revision to the UK TB guidelines demonstrates good sensitivity but is associated with impaired specificity in BCG-vaccinated children.

CONCLUSION

Our data suggest that the impact of infant BCG vaccination on TST responses in children exposed to TB wanes with age. In BCG-vaccinated children a TST cut-off of 5 mm is associated with poor specificity.

BCG vaccination

- Supplementary recent information
- Clinicians should be aware
- BCG vaccination lowers specificity of Mantoux testing especially in younger children

Supply and demand of BCG vaccine

- National problems in the supply of BCG vaccine
- Guidance issued through Vaccine updates from Public Health England

- SSI – Statens serum Institute
  - Used remaining stock

BCG

- Intervax brand
- Unlicensed though MHRA have not objected
- WHO licensed for global use

Groups eligible for vaccination

HIGHEST PRIORITY

A. All infants (aged 0 to 12 months) with a parent or grandparent who was born in a country where the annual incidence of TB is 40/100,000 or greater.[1]

B. All infants (aged 0 to 12 months) living in areas of the UK where the annual incidence of TB is 40/100,000 or greater.[2]

C. Previously unvaccinated children aged one to five years with a parent or grandparent who was born in a country where the annual incidence of TB is 40/100,000 or greater. These children should be identified at suitable opportunities, and can normally be vaccinated without tuberculin testing.

Guidance

Intervax BCG vaccine: training material for healthcare professionals

From: Public Health England
First published: 28 June 2016
Last updated: 22 September 2016, see all updates
Part of: Immunisation

Training material for healthcare professionals on the use of the unlicensed Intervax BCG vaccine.

Documents

[Intervax BCG vaccine: factsheet for healthcare professionals]

Ref: PHE publications gateway number 2016114
PDF, 446KB, 13 pages

This file may not be suitable for users of assistive technology. Request an accessible format.

[Intervax BCG vaccine: training slideset for healthcare professionals]

MS Powerpoint Presentation, 8.42MB

This file may not be suitable for users of assistive technology. Request an accessible format.

Public Health England
Protecting and improving the nation's health

VACCINE UPDATE

Issue 247, June 2016

BCG vaccine for the national immunisation programme

Use of any remaining SSI stock

Deliveries of a UK licensed BCG vaccine from the Statens Serum Institut (SSI) Denmark continue to be delayed due to manufacturing issues and this vaccine is currently unavailable to order through ImmForm.

Locally held remaining stocks of SSI BCG vaccine are likely to be the most recent distributed by PHE (batch 114022A) and have a labelled expiry of 29 February 2016. PHE recommends that batch 114022A continue to be used for up to six months past its labelled expiry date, based on the known stability of the SSI BCG vaccine and on review of additional information provided by the manufacturer. Further information is availablehere at web link 1. SSI BCG vaccine of batch 114022A should therefore continue to be administered up to 31 August 2016.

An alternative unlicensed BCG vaccine will be available shortly

PHE has secured an alternative BCG vaccine. This brand of BCG vaccine is supplied by InterVax Ltd, and manufactured by BB-NCIPD Ltd. In the UK it is being supplied as an unlicensed product, which means it does not have a valid marketing authorisation (licence) in the UK. This vaccine is being provided in accordance with medicines legislation that allows an unlicensed medicine to be supplied when a licensed alternative is not available and the Medicines and Healthcare Products Regulatory Agency (MHRA) has not objected to its importation.

InterVax BCG vaccine is supplied to over 100 countries world-wide including the Netherlands, France, Belgium, Norway and Sweden. Although InterVax Ltd and BB-NCIPD Ltd have not applied to licence the product in the UK, it is a WHO prequalified vaccine meaning it can be used around the world for immunisation against TB. It is also licensed in other EU countries. InterVax BCG vaccine can be used for the national BCG immunisation programme until SSI is able to resume deliveries, expected in 2017.

Where doses of SSI BCG vaccine lot 114022A remain, these should continue to be used until the recommended date of 31 August 2016, and in preference to the alternative unlicensed InterVax BCG vaccine.

Availability of PPD

- Current UK position– manufacturing delays
- PPD2TU – limited supply- 1 pack per fortnight for NHS customers
- PPD10TU- currently unavailable- expected delivery this year

Public Health England

NHS

Pregnancy and Tuberculosis

Information for clinicians

Pregnancy clarification regarding immunisation- No BCG

Live attenuated vaccines: avoid use in those who are clinically immunosuppressed

Immunisers are reminded that live attenuated vaccines should not routinely be given to people who are clinically immunosuppressed (either due to drug treatment or underlying illness). Following reports of administration of live vaccines to immunosuppressed individuals, the Medicines and Healthcare Products Regulatory Agency (MHRA) have published a drug safety alert. This alert highlights in particular the dangers of BCG vaccine in neonates born to mothers receiving anti-TNF agents in pregnancy and shingles vaccine in immunosuppressed elderly patients.

If there is doubt about the immune status of an individual, immunisation should be deferred until secondary care specialist advice has been sought, including advice from an immunologist if required. In addition, as a precautionary measure, babies whose mothers have received immunomodulating biologics (such as monoclonal antibodies or receptor antagonists which interfere with the immune system e.g. anti-

Pregnancy and breast-feeding

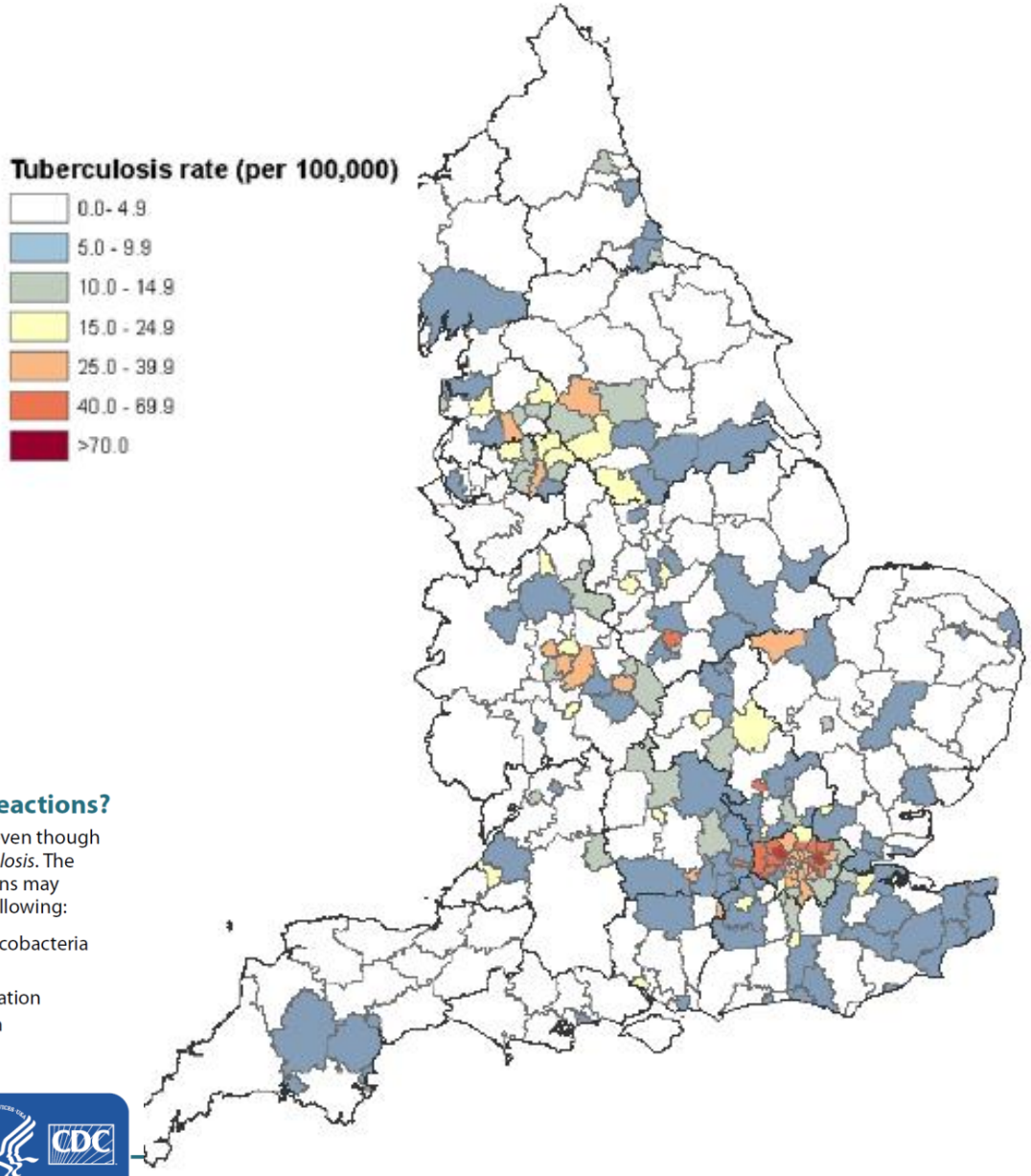
Although no harmful effects on the fetus have been observed from BCG during pregnancy, it is wise to avoid vaccination, particularly in the first trimester, and wherever possible to delay until after delivery. A further tuberculin test may be required if more than three months has elapsed since the test on which a recommendation for BCG was based. Breast-feeding is not a contraindication to BCG.

- 1. Pregnancy– No BCG
- 2. Neonates – No BCG with mothers receiving αTNF

Treating Latent TB on the basis of the skin test alone

- NICE has stated treat Latent TB on basis of skin test alone
- Concern over risks of inappropriate treatment
- False +ve rates
- National TB team have made clear, Mantoux is not to be used in programmatic screening of Latent TB

Figure 2: TB rate per 100,000 by local authority and PHE centre, England 2011–2013



What Are False-Positive Reactions?

Some persons may react to the TST even though they are not infected with *M. tuberculosis*. The causes of these false-positive reactions may include, but are not limited to, the following:

- Infection with nontuberculosis mycobacteria
- Previous BCG vaccination
- Incorrect method of TST administration
- Incorrect interpretation of reaction
- Incorrect bottle of antigen used

Latent TB treatment

- New entrant screening

IGRA based assay, no Mantoux required-

- TB contacts, use two-step assay
  - Mantoux, if +ve, IGRA
- Increases confidence of true positive result
- Commissioners- Reduce referrals, requires provision of IGRA blood testing

1.2.1 Diagnosing latent TB in adults

1.2.1.1 Offer Mantoux[1] testing to diagnose latent TB in adults aged 18 to 65 who are close contacts of a person with pulmonary or laryngeal TB.

- If the Mantoux test is inconclusive, refer the person to a TB specialist.
- If the Mantoux test is positive (an induration of 5 mm or larger, regardless of BCG history), consider an interferon-gamma release assay.

New age range for Latent TB treatment

- Old age range 16-35 years
- NICE 2016- 16-65 years

- Offer standard LTBI treatment to patients 16-35 years of age

- Patients aged 35-65 years, should be seen and offered treatment with risk assessment and the benefits and risks of treatment should be carefully explained.

Clinical case example

- 46 year old man, New entrant from Zambia, now a Geordie
- Very well
- Mantoux 5mm, BCG vaccinated, HIV –ve

- Most would not treat without further testing
- IGRA based assay, two-step testing enables a better informed choice

NICE guidance Age 16-65 years

- NICE: adopt new age range
- Need to acknowledge cost and workload implications on TB referral and workload

Infection control and whether healthcare workers should wear face masks (FFP3)

- NICE recommends: use facemasks with suspected confirmed MDRTB only
- Use a side room for infectious pulmonary or laryngeal TB (suspected smear +ve)

YHNE recommendations

- Sensitive issue, local infection control policy should apply
- Units use FFP3 masks with infectious TB
  - Reassure patients and public
  - Protect staff
  - Ensures consistency of approach and avoid outbreaks

Access to PCR

- Early diagnosis of TB is critical to good outcomes
- PCR offers rapid confirmation of TB and specificity
- Awareness and access to PCR may limit diagnostic confirmation of TB

What is PCR ?

- Testing of TB sample at reference lab
- Gene probe, GeneXpert, WHO
- Confirms mycobacterium tuberculosis

How good is PCR?

- Does so rapidly
- Increases pickup rate of TB (sensitivity) by 23% above smear
- Confirms Mycobacterium tuberculosis in an AAFB +ve sample
- Rules out MDRTB, rpo gene analysed

Access to PCR

- Make PCR available to all across YHNE network
- Sputum samples are not routinely tested for PCR
- On request, PCR performed on suspected sample which goes to Birmingham
- Result returns typically within 48 hours

PCR Clinical uses

- Q1. Is this TB?
- Q2. Is this AAFB +ve sample, *mycobacterium tuberculosis* or an atypical?
- Q3. Can I rule out MDRTB rapidly?

Summary

- NICE guidance is generally a major update
- YHNE policy advice offers clinical guidance to resolve dilemmas
- Adopted NICE changes and reflected implications for practice to those involved with TB and commissioners

REFERENCES

- NICE

https://www.nice.org.uk/guidance/ng33

- Collaborative strategy for England 2015-2020

https://www.gov.uk/government/uploads/system/uploads/attachment_data/file/403231/Collaborative_TB_Strategy_for_England_2015_2020_.pdf

- Patients

http://www.nhs.uk/conditions/Tuberculosis/Pages/Introduction.aspx

- Vaccine update

https://www.gov.uk/government/publications/vaccine-update-issue-247-june-2016-special-edition

- Intervax for healthcare professionals

https://www.gov.uk/government/publications/intervax-bcg-vaccine-training-slideset-for-healthcare-professionals

- The Green Book: Tuberculosis

https://www.gov.uk/government/publications/tuberculosis-the-green-book-chapter-32

- Pregnancy

https://www.gov.uk/government/uploads/system/uploads/attachment_data/file/487319/Pregnancy_TB-Clinicians.pdf

Thank you