

NATIONAL INSTITUTE FOR HEALTH AND CLINICAL EXCELLENCE

Tuberculosis: clinical diagnosis and management of tuberculosis, and measures for its prevention and control (update)

Stakeholder Workshop

12 November 2012, London

The stakeholder scoping workshop is held in addition to the formal consultation on the scope which is taking place from the 29th November 2012 to the 10th January 2013.

The objectives of the scoping workshop were to:

- obtain feedback on the specified population and key clinical issues included in the first draft of the scope
- seek views on the composition of the Guideline Development Group (GDG)
- encourage applications for GDG membership.

The scoping group (Technical Team, NICE and GDG Chair) presented a summary of the guideline development process, the role and importance of patient representatives, the process for GDG recruitment and proposed constituency for this group, and the scope. The stakeholders were then divided into four groups which included a facilitator and a scribe and each group had a structured discussion based around pre-defined questions relating to the draft scope.

Comments received from each discussion group have been combined and summarised below. These are not necessarily the views of NICE, nor are they the collective view of everyone at the workshop.

General

- Emphasis is shifting from managing active TB to preventing through identification of latent TB – raises an important question about the balance of priorities between prevention and management for services as a whole
- Could do with more guidance on TB infection control and travel
- When is it appropriate for a clinician to diverge from guidance?

5.1 Population

Types of mycobacterium to be included

- A mixture of views were expressed
- Some agreed with the inclusion of M.Africanum and M.Bovis
- It was noted that there are small ways in which M. Bovis needs to be thought about differently, and that there may be some new literature on M.Bovis infection in humans

Groups at increased risk of infection

- Co-infection of TB and HIV is important, as are people who are otherwise immunocompromised (such as those on anti-TNF- α treatment)
- People who have had transplant surgery are also at increased risk of infection, both due to the potential for the transplanted organs to be infected and due to the immunosuppressant medications they will be taking
- Hepatitis C as a co-infection is on the increase. Additionally, hepatitis C treatment will transform over the next 3 years, leading to the possibility of new drug interactions (i.e. may change during the development of the guideline)
- Co-prescribing of anti-TB treatments with methadone is also on the increase
- People with renal failure – treatment may be slightly different, but in particular an important group to consider with regards to monitoring during treatment
- People with hepatitis – again, treatment may be slightly different, but in particular an important group to consider with regards to monitoring during treatment
- People with diabetes
- Pregnant women - not necessarily treated differently, but there is often a lot of anxiety amongst pregnant women surrounding TB medication. This could be a good group for which we could do some work on education / information and support
- TB brought into the UK:
 - Air travellers/staff (people travelling for more than 8 hours) – the British Thoracic Society have a paper on air travel and its risks
 - “have arrived or returned from high-prevalence countries within the last 5 years” (from CG117 scope) – time frame seems fairly arbitrary; individuals could have been here 20 years and not accessed healthcare services (some immigrant communities are particularly hard to reach in this sense)
 - Military personal who travel overseas/who are stationed in areas of high risk, or who are recruited from ethnic groups originally from countries of high TB prevalence
 - British citizens of selected ethnicities who travel overseas for extended periods (6-8 weeks upwards)
- Management of active TB in older people
- Healthcare workers, specifically older workers (65 years and older) who have been diagnosed with active TB as a direct result of exposure to people with TB through their work
- Non-NHS:
 - Private/commercial providers of NHS services
 - TB uncovered in private care amongst non-NHS patients
- People who are at a direct risk from mycobacterium bovis – also may be important to consider the large amounts of untreated milk currently being marketed
- Children should be covered separately at every stage of the pathway - inappropriate to generalise evidence and recommendations on adults to children (as has been done previously). Note: A particular area of clinical concern for children is drug resistant TB

Sites of disease:

- Abdominal and peritoneal TB should be included
- Could ophthalmological TB be included?

- The current recommendation 57 on diagnosis of “disseminated disease” is not being followed - there is no common understanding of what this is, and one is needed in the new guidance before staff know what would “trigger” this recommendation.

5.2 Setting

- Should include further and higher education institutions, and language schools
- Prisons should be expanded to include other custodial settings such as immigration detention centres and young offender institutions
- Aircraft, if covered at all, should not be singled out over other forms of transport such as trains
- Ports, entry and pre-entry – although this may be covered by new screening program – as well as travellers coming to the UK as part of mass population events
- Clinical and public health settings need to be presented separately
- Request to include occupational health
- Note: many mental health care homes are private and would therefore fall out of the current list of settings

5.3 Topics of interest

5.3.1 Key issues that will be covered

Clinical diagnosis and management of active tuberculosis disease

Diagnosis of active respiratory and non-respiratory disease

- Will vary from case to case and clinician to clinician
- Would be affected by co-infection with hepatitis and HIV
- Symptom screen:
 - It is important to make sure the right suspicions are raised among clinicians early enough to use particular tests
 - WHO symptom screen is useful for respiratory TB, but not that useful for non-respiratory TB – a review of symptoms for non-respiratory TB could add value, particularly abdominal and peritoneal TB
 - It was also noted, however, that TB can cause nearly any symptoms and updating this may be of little value, although the potential usefulness of patterning symptoms was raised
 - Would there be anything on duration of cough? Or would this overlap too much with existing advice on seeing the GP if someone experiences cough?
 - Recommendations on symptoms need to consider the psycho-social context
- Types of test:
 - Should perhaps review previous guidance on cultures which inferred all samples should be sent and processed to check for TB - too resource intensive for little added value, particularly as diagnostic practices are moving further away from hospital sites
 - Should perhaps review the choice of samples used to test for active TB histology
 - Microscopy:
 - Would be good to have a question on PCR vs microscopy and covering microscopy methods - suggestion is that PCR should be used for diagnosis (before sputum-serum)
 - LED fluorescence microscopy may actually provide the most sensitive screen but looking at this area may help to provide definitive guidance on the best approach

- Number of sputum samples:
 - 3 sputum samples is accepted practice for the UK and European guidelines say 2 sputum samples. In UK practice it is likely that 2 sputum samples are only taken anyway for pragmatic reasons and as these would be the most indicative of infection. However, it was questioned – how much does third sample add in terms of diagnosis and does this have time delay/ cost implications?
 - Whether sputum samples should be considered within the guideline is based on what decisions are made around PCR based diagnosis
 - The group thought that what was done in CG117 on sputum samples was very detailed
 - Recommendations for children need to be explicit – the uptake of previous recommendations may have been poor because this was not done
 - Overall conclusion – this may not be a priority but it would be good to get a definitive idea on 2 or 3 samples and also looking at those who are unable to expectorate
- Radiological techniques:
 - CT is being used more often especially for extra pulmonary TB when you get very little from x-ray
 - May be useful to review computerised x-ray technologies, though this will depend on how much evidence is out there
- Rapid diagnostics:
 - Rapid diagnostics should be integrated within the appropriate diagnostic review areas, rather than as a separate review area (as in CG117) - they used to be extremely expensive and a niche area, but now they are being considered and used more and more alongside regular practice
 - In the case of rapid diagnostics for latent TB, it was felt that not all the available options should be reviewed. However, the use of rapid diagnostics for ruling out active disease in those with latent TB *should* all be looked at
 - Urine LAM test has so far only been studied in the HIV population, but should still be included in the diagnostics review
 - Serology is not a commonly used diagnostic, nor was it considered particularly useful
 - Molecular diagnosis guidance is coming soon from the HPA - NICE should acknowledge it or interface with it in our guidance
- IGRA:
 - Perhaps IGRA should be appraised as not covered by previous guidance. On the other hand, a major study is underway and it is unlikely that it will be completed by the time the guidance was finished
 - Guidance could be needed on what is the best way to go on and test whether a person has active or latent TB after they have tested positive with interferon gamma
- Good to get early confirmation - there needs to be timeframes/standards for a rapid access service model, especially against the backdrop of current lab reorganisations and restructuring, as well as the proliferation of rapid diagnostics. These standards should specify for which specimen, what tests, and how fast – i.e. a service model to describe optimal timings from clinical suspicion to diagnosis to treatment
- Diagnosis of “disseminated disease” – current recommendations are not being followed as there is no common understanding of what it is. A definition is needed in the new guidance before staff know what would “trigger” this recommendation
- Uncertain of any new evidence on the impact of different CD4 counts on diagnostic effectiveness

Treatment of active TB disease

- The first line standard recommended regimen is well accepted, and supported by evidence and therefore could be left out of the scope
- Recommendations about children is a gap in the current guidance - there is new evidence on the use of the standard regimen in this population
- Duration of treatment:
 - May be a lot of NHS practice in which treatment is shorter than 6 months, but some clinicians are also arbitrarily extending the treatment period – clarity is needed
 - Especially important in complex cases
 - Even the ‘six month’ treatment period of the standard recommended regimen is being interpreted differently around the country (for example, calendar months vs counting a month as four weeks)
 - There may be new evidence in the next couple of years so if duration was looked at, it may be out of date by the time it is published
 - There could be nationally-set ‘grounds for continuing treatment’ based on:
 - patient sub-group
 - drug resistance
 - adherence
 - strain
 - Some patients are still infectious after 2 months of treatment, even though current isolation time is just 2 weeks – current recommendations are too ‘reassuring’ in terms of their impact on infection control
- Intermittent vs daily dosing - this could be one over-arching review, rather than doing a separate analysis for each site of disease and subpopulation (although sub-group analysis may still be useful)
- Impact of co-morbidities raises treatment issues – for example:
 - HIV
 - hepatitis
 - renal disease
 - co-prescribing of methadone
 - co-prescribing of erythromycin
- Should consider side effects, intolerance, allergy to drugs etc
- Steroids:
 - Specific indications only, and this has not changed (i.e. well established)
 - Should particularly be reviewed for pericarditis
- Surgery:
 - It was agreed that surgery should be reviewed, for all sites of disease, though thoracic surgery should be considered in particular
 - Some felt that pulmonary surgery should not be considered for MDR-TB, others felt this to be an important area for review
 - It was thought that spinal surgery would need updating, although spinal surgery is not currently performed unless it really needs to be – plus, it is uncertain about how much new evidence there will be for review

- Many thought low level laser surgery was not used in the UK – not enough evidence available at this stage
- High dose rifampicin for meningeal TB – a big trial is to report soon, so we might want to incorporate this into the guidance
- Management of paradoxical reactions could be covered
- Some felt that we should try to recommend a standard second line treatment; however others felt that we shouldn't, as there is no established one. It was suggested that instead, we could perhaps specify a service model, such as:
 - Should these people be handled nationally (as opposed to locally)?
 - In areas where there are small numbers, should people be sent to centres of excellence? Or instead of referral, could there be some standardised process whereby they are managed 'in consultation' with a centre of excellence?
 - Lots of treatment for TB is unlicensed (not just off-label) – plus, new drugs are coming/have come out, some of which may be licensed during the development period
- Need to consider the implications of the Public Health Act

Identification of isolated, combined and multiple drug resistances

- Risk factors for further investigation of drug susceptibility should be reviewed again – those in the previous guideline are, in places, unhelpful or even wrong
- Drug susceptibility testing needs review, and should include a review of rapid diagnostics

Treatment of non-MDR drug resistant-TB

- Second-line use of moxifloxacin - a very important area for review due to its wide usage
- The group thought that 'how' second-line drugs should be delivered would be a better question to answer rather than detail on the effectiveness of individual drugs
- TB nurses would appreciate guidance on how to monitor the side effects of second-line drugs

Management and referral of drug resistant-TB

- There were mixed feelings on the inclusion of treatment of MDR-TB. Some felt that outlining some general, good practice principles in the management of MDR-TB (such as never add a single new drug to a failing regimen) could add value, though being overly prescriptive in terms of defining treatment regimens should be avoided. Others felt that it *should* be covered, although agreed that MDR-TB is perhaps more about organisation of strategies, rather than individual practitioners managing these cases – i.e. specialist services should manage these
- Referral guidelines, or access to expert advice, needed for MDR cases and other complex cases - currently there is an MDR advisory group that provides recommendations
- Contact-tracing following diagnosis of MDR-TB is important – perhaps more of a service model question
- It was noted that children with MDR-TB should be looked at in terms of treatment and sequencing, but also need to know whether to keep them off school if they have a cough etc – note: will be case series available, but not RCTs

Approaches to promote adherence as it relates specifically to the treatment of active TB

- Risk assessment for non-adherence important
- DOT:

- RCN currently sets the standards for DOT
- Some disagreement with the last guidance on the issue of DOT (recommendations may be out of date) – its not being used much for this reason
- The important question to ask is not so much ‘should we do it?’, rather ‘how should we do it?’ – for example, who should do it (healthcare worker, community worker, family member etc), where should it be done (clinic, pharmacy, in the community etc), how should it be done (face-to-face, using technologies such as Skype, text messages, smartphone apps etc). However, some felt that PH37 sufficiently covers ‘how’ to deliver DOT and that it doesn’t need to be redone
- There is a need for the latest research evidence (if any exists) on what are good predictive methods for determining who would benefit from DOT

Approaches to respond to treatment interruptions

- Considered to be an important area for review
- No guidance at the moment
- Should treatment be restarted in part or in full, and when should this be done (e.g. if person stops early in treatment, or stops too soon before completing treatment)?
- Note: not sure how much evidence will be available, although there is perhaps some BTS guidance on this issue that could be updated
- There should also be a statement within the guideline on how to manage failure of treatment

Preventing and controlling the spread of infection

General

- Increasingly difficult to know whether TB is imported or acquired locally

Infection control measures to ensure that those with infectious, active disease (including drug resistant TB) do not infect others

- Considered to be an important area for review
- Need criteria for wearing masks, both for patients and staff (and visitors) - variation in practice around these criteria and clear guidance needed
- Isolation duration:
 - Warrants review, particularly for children and people who are immunocompromised
 - Is there technology to assess risk of infectiousness, so some people could have reduced isolation?
 - Some patients are still infectious after 2 months of treatment, even though current isolation time is just 2 weeks – current recommendations are too ‘reassuring’ in terms of their impact on infection control
- There needs to be criteria to alert surgeons to cases where they need to flag if a lesion/growth they have removed could possibly be TB to the histopathology lab staff - perhaps a decision-aid such as a checklist? A service delivery question?

Treatment of latent infection without disease (prophylaxis)

- Treatment of latent TB where drug resistance is suspected is potentially an important area for review, although it is unlikely that there will be much evidence
- Risk of progression from latent to active TB needs looking at.

- CG117 recommendations on treatment of latent TB infection in people with evidence of TB scars on chest X-ray need revising – the risk of hepatotoxicity etc in those who have already been treated for TB can outweigh giving prophylactic treatment. It is not clear what the term means in the current guidance and it needs costs of treatment evaluating
- The use of rifapentine should be reviewed

Approaches to promote adherence as it relates specifically to the treatment of latent TB

- Considered to be an important area for review.

Approaches to promote uptake of treatment amongst those with latent TB infection who are at an increased risk of progressing to active TB

- Considered to be an important area for review.

BCG vaccination uptake

- Important to ensure that there is no conflict with the Green Book.
- Issues to consider include when to vaccinate neonates, when are variations in immunisation practice appropriate e.g. across high/low prevalence areas, methods to increase uptake of BCG vaccination (although considered low priority), BCG vaccine after IGRA, and the duration of protection from TB of the BCG vaccine.
- Consider developing criteria for universal or targeted BCG vaccination strategies in a given geographical area.

Approaches designed to educate or raise public and/or clinician awareness of issues surrounding the diagnosis, management, prevention and control of TB

- Considered to be an important area for review.
- Specific groups to consider include patients, frontline workers (e.g. GPs and A&E staff), non-TB specialist healthcare workers who work with people at high-risk of TB, people with MDT-TB, staff in residential/custodial facilities, hard to reach groups including people who are living illegally in the UK.
- PH37 contains good advice and recommendations that would be useful to incorporate (it was noted that a significant amount of information could be transferred from PH37 for this update).
- Consider the importance of reaching people early and the need for NICE guidance to focus on whose role it is to educate people and sustain awareness, and the associated challenges.
- For this review area, important to draw on lessons learnt from other communicable diseases.
- Refer to the national TB knowledge database (National Knowledge Service) for useful information.

Information and support for people affected by TB

- Considered an important area for review.
- Specific groups to consider include employer's dealing with a TB 'cluster', people who have been recently diagnosed, people who are infectious and need to be isolated, people with MDR-TB, people completing their treatment for TB and people who are not engaging with treatment.
- Consider the value of providing information e.g. leaflets and sign-posting to support networks.

5.3.2 Issues that will not be covered

Recommendations to be incorporated from CG117 without updating the underlying evidence reviews

Monitoring of patient response to treatment, and follow-up after treatment completion

- Some noted that the monitoring of blood tests during treatment is subject to national variation (due to its link to the perceived need to extend the duration of treatment) and could do with guidance, although others noted that the principles themselves are well established and non-controversial
- TB nurses would appreciate guidance on how to monitor the side effects of second line drugs
- The question on follow-up after treatment completion could be covered, though was not considered a priority

Diagnosis of latent infection using Mantoux testing and interferon-gamma release assays in the context of case-finding activities

- Diagnosis of latent TB:
 - Is Mantoux testing necessary at all? If so, when?
 - Previous guideline did not review the Mantoux thresholds for going onto an IGRA in those who have received a BCG or in those who have not, yet still gave values – these values are odds with those used by the rest of the world
 - The guidance could look at the efficacy of the different IGRA tests, though it was noted that QuantiFERON-TB Gold was the standard test
 - What are the criteria for repeat IGRA testing?
 - What is the effectiveness of IGRA testing in cases of co-infection such as HIV or gut worms?
 - The 35-year age limit for IGRA is “historic” and could be revisited - how strictly should it be applied? Difficult to explain to patients and may be based on very limited evidence
 - Previous guideline is not clear enough on the use of x-rays in screening – is an IGRA and symptom check alone sufficient? Or should an x-ray be performed if symptoms suggest the possibility of active TB?
 - Cost-effectiveness:
 - It was noted that the last guidance’s economic analysis on the diagnosis of latent TB (CG117) did not look at the knock-on effects of infection, including employment aspects
 - It was noted that there is now new economic data on QuantiFERON testing
- Case-finding:
 - Agreement that strain typing should be reviewed
 - Testing for latent TB in primary care – needs set criteria
 - TB services are working on an old staffing-formula that is focused on treatment. This is not appropriate to today’s services where the focus is on spending time on prevention (including case finding). Could these formulas be revisited?
- Contact tracing
 - Considered important area for review.
 - Areas considered to be important include timing of and time-frame for contact-tracing, community response, non-pulmonary TB, clusters (including definitions of this concept), information/data to collect, location, impact of MDT-TB and strain typing.
 - Consider the resource use and costs associated with contact tracing, alongside the cost-effectiveness of contact tracing.
- New entrant screening:

- Need to know which new entrants should be screened as 2011 update differs from the 2006 guideline for the Indian subcontinent
- Need to be clear what to do with those staying in the country permanently and those staying for less than 6 months
- Australia and Canada screen for active and latent TB – should the UK?
- Need to look at current patterns of migration
- Should note the UK Border Agency’s new pre-entry tuberculosis TB screening programme – aimed at migrants from countries with a high incidence of TB wanting to enter the UK for more than 6 months (includes clinical algorithm)
- Occupational health:
 - Important area – needs more guidance
 - Need to know what to do with older healthcare workers with positive IGRA
 - Need to consider those who work in prisons, homeless shelters etc

Excluded issues

Effectiveness of BCG vaccination

- Remit of the JCVI

Service models (including service configuration and delivery)

- Considered an important area for review, particularly given the different needs with regards to service delivery within high and low prevalence areas. Considered that effective service delivery is central to the successful control and management of TB. However, caution needed by NICE not to create issue of local flexibility by producing national guidance on the subject area.
- Input from local authorities and wider representation (for example, TB Alert,) is needed.
- The following issues relating to service models could benefit from review; where and how to target services, how to complete contact tracing, management of source cases to minimise spread of disease, value of centralised laboratories vs point of care test for diagnosis, optimal and appropriate waiting times from symptom onset to diagnosis and initiation of treatment, referral of people to specialist services, second-line treatment delivery for active TB, management of MDR-TB locally vs nationally, and BCG vaccination uptake.
- Consider skills of staff providing services to people with TB, compare different service delivery model structures and review service delivery in the context of high vs low incidence areas.

5.5 Economic aspects

- It was felt that the following would benefit from a cost-effectiveness analysis:
 - Diagnostics:
 - Rapid diagnostics – centralised labs vs point of care testing
 - Cost of Gene Xpert - some difference in opinion within group - initial equipment purchase expensive, but can be used for tests other than TB
 - Rate of culture confirmation and methods to achieve that culture
 - Case-finding:
 - IGRA and contact-tracing
 - New entrant screening, including the threshold of TB incidence in country of origin
 - Any economic modelling of screening needs to consider the downstream costs and benefits of prophylaxis against the progression of latent TB to active TB

- When/how often should healthcare and laboratory workers, prison staff and other high-risk workers be screened as part of occupational health measures? e.g. in the US they routinely screen each year, we don't
- Need guidance on where/how to target screening programmes, including cost effectiveness thresholds – e.g. consider the cost-effectiveness of contact-tracing in terms of the scale of clusters
- Transmission models: imported vs acquired TB
- Treatment of latent TB infection particularly among target groups
- DOPT - significant implications on case management
- Vaccination of healthcare workers and students – all or just those at increased risk of infection? Currently recommend that all should receive a BCG, even in low incidence areas
- It is important to consider the costs and benefits of accommodation (e.g. isolation/residence of those with active TB in hospital vs social housing), including the costs of getting people back into the community (note: this was covered in PH37 – could be more explicit in the forthcoming local government briefing, so maybe not important for this guidance)
- Cost effectiveness of not using NICE recommendations – particularly important going forward for getting GP consortia to commission services as there are so many priorities

Guidance production process and guidance presentation issues

- Consider ease of access to the final guidance by a range of different users. Quick reference guides were considered to be helpful for clinicians to access relevant sections.
- Organisations should be able to take NICE guidance and produce local derived guidelines in a way that is useful – either paper or electronic - may be easier for some groups (physicians rather than GPs for example) than others
- It was felt that the final guidance should be presented as a single product (i.e. in collaboration with the current PH37)
 - American guidance is being developed around key questions (common issues, thematic) - would be helpful to follow this format
- It would be useful to have a single pathway that distinguishes (perhaps by colour coding?) between:
 - Newly updated areas and recommendations that have been incorporated from previous guidance
 - Clinical and public health recommendations
- Would be useful to widen the pathway - a diagram describing the patient pathway through to outpatient / treatment completion – including possibly links with social care too – would help to clarify the roles and responsibilities in the move from inpatient to outpatient (there is a lot of confusion both with clinicians and patient / carers at this point)
- Pathways are good but you can't access pathways on mobile phones and there are other demands on computers (e.g. nurses trying to get blood results) - need a quick reference guide to be published alongside final guidance
- Implementation will be important - some implementation issues around uptake of previous guidance on TB
- NICE pathways do not necessarily apply well to public health management when guidance in this areas when it can cover a number of areas within a pathway

GDG composition

- The roles of TB specialist, infectious diseases physician and respiratory physician could be brought together (same for paediatrics)
- The paediatric respiratory nurse role would be covered by a general respiratory nurse or TB specialist nurse
- The roles of Director of Public Health, TB coordinator or a local director of TB prevention and control program' and Consultant in Communicable Disease Control could be brought together
- 'Representative from community-based TB outreach project' should be loosened to the more general 'individual with experience in community-based TB outreach work' – although this could be brought together with both 'local TB case worker or a community-based TB nurse' and 'social or community worker'
- There should be representation of both high- and low-TB incidence areas - don't want to be London-centric, though it would be interesting someone to have someone who hasn't got TB on their horizon yet – expert testimony perhaps? Or could we do some desk research / interviews?
- Need to add a pharmacist
- The following could be co-opted rather than full members:
 - Radiologist
 - Paediatric radiologist
 - Someone from A&E
 - Microbiologist
 - Someone from occupational health - they do both workplace and med students though they could be co-opted in to the control discussions
 - Rheumatologist - anti-TNF- α treatment increases risk of TB
 - Renal specialist
 - HIV specialist
 - Transplantation – haematologist would be useful as TB can be an issues (note: suspect this is quite a small and specialist issue)
- Perhaps we could look for overlapping expertise as much as possible