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REVIEW

Recommendations for pediatric tuberculosis vaccination in Italy

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ABSTRACT

Bacillus Calmette-Guérin (BCG) vaccine is still the only vaccine approved for the prevention of tuberculosis (TB), and is widely used in highly endemic countries, where all newborns receive a single intradermal dose immediately after birth; however, the recommendations concerning its use in Europe vary widely from country to country. This document describes the recommendations of a group of Italian scientific societies concerning its pediatric use in Italy, the persistence of the protection it provides, its safety, its interference with tuberculin skin test (TST) responses, and the children who should be vaccinated. The experts conclude that BCG vaccination provides a good level of protection against tuberculous meningitis and disseminated forms, and a fair level of protection against pulmonary disease; the protective effective lasts at least 10 years, and revaccination offers no advantages over a single administration. The vaccine is safe in immunocompetent subjects, and affects the response to a TST for at least 6 y On the basis of these observations, we recommend its use in Italy in all TST-negative immunocompetent newborns and breastfeeding infants aged <6 months, and all TST-negative children aged between 6 months and 5 y who come from highly epidemic areas, or whose parents come from highly endemic areas, or who have been in contact with a family member with active TB without contracting the disease themselves.

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Introduction

Tuberculosis (TB) is a significant disease for pediatricians due to various diagnostic and therapeutic problems.[1] Its prevention is therefore highly important in epidemiological terms.

Bacillus Calmette-Guérin (BCG) vaccine, which was first administered orally to a child in 1921, is still the only vaccine approved for the prevention of TB. It is prepared from an attenuated live strain of *Mycobacterium bovis* that first obtained by Albert Calmette and Camille Guérin after 230 *in vitro*

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passages carried out over a period of 13 years;[2] it was then distributed and cultivated throughout the world, and used by various laboratories to produce the vaccine. This led to the emergence of genetic and antigenic differences among the marketed strains,[3] which gave rise to concerns about the safety and efficacy of the different vaccines.[4,5]

BCG vaccine is widely used in countries in which TB is highly endemic, and where all newborns receive a single intradermal dose immediately after birth or later in infancy.[6-8] It is estimated that it has so far been administered more than 4 billion times, and that 120 million children are vaccinated every year.[9] However, the recommendations concerning its use in Europe vary widely from country to country:[10] 12 (Austria, Belgium, the Czech Republic, Denmark, Germany, Iceland, Italy, Liechtenstein, Luxembourg, the Netherlands, Slovakia, and Spain) do not include it in their normal vaccination schedules; 11 recommend its use in all newborns at the time of birth (Bulgaria, Croatia, Estonia, Greece, Hungary, Ireland, Latvia, Lithuania, Poland, Portugal, and Romania), and the remaining 8 (Cyprus, Finland, France, Malta, Norway, Slovenia, Sweden, and the United Kingdom) recommend it only for certain categories of children considered at risk, mainly the children of parents coming from countries in which TB is endemic and those with a case of TB in their families. However, considering TB mortality and mobility of children and adults with TB between countries, BCG vaccination strategies in Europe should be modified and a unique schedule should be implemented.

This document describes the recommendations of a group of Italian scientific societies concerning the pediatric use of BCG vaccine in Italy, the persistence of the protection it provides, its safety, its interference with tuberculin skin test (TST) responses, and the children who should be vaccinated.

Methodology

The recommendations were drawn up using the Consensus Conference method and following the National Institutes of Health Guidelines and Italian National Guidelines Programme (Table 1).[11,12] Relevant publications in English were identified by systematically reviewing MEDLINE and the Cochrane Database of Systematic Reviews from their inception until 31 December 2014, using the key words "children[Title/Abstract] OR pediatric[Title/Abstract] OR paediatric[Title/Abstract] AND tuberculosis[Title/Abstract] AND vaccine[Title/Abstract] OR vaccination[Title/Abstract] or BCG[Title/Abstract] AND English[lang])." The Working Group agreed on a list of clinical problems related to the prevention of TB by means of vaccination. The evidence review procedures focused on patients aged 0–18 years, and included section-specific targeted searches and formal systematic reviews of selected topics. In addition, the clinical recommendations made in the updated, relevant international guidelines were reviewed and critically compared in the case of debated issues, and all of the data were included in tables of evidence for each topic.

Trained personnel critically appraised the acquired literature using the Scottish Intercollegiate Guidelines Network methodological checklists[13] and, subsequently, the bibliographical material and a preliminary draft of the document were provided to the panel members. During various meetings, the published evidence was presented and discussed, and the Delphi method was used to reach a consensus when the evidence did not provide consistent and unambiguous recommendations.[13] The final text was revised on the basis of these discussions and submitted by e-mail to the participants at the Consensus Conference for final approval. The members of the multidisciplinary panel of clinicians and experts in evidence-based medicine were identified with the help of the participating scientific societies: it included experts in the fields of general pediatrics, pediatric infectious diseases, neonatology, infectious diseases, pneumology, microbiology, radiology and methodologists, and was coordinated by the Italian Society of Pediatric Infectious Diseases (SITIP). No panel member declared any conflict of interest concerning the guideline topics. The panel met on 3 occasions, but many of the consultations involved in developing the document took place interactively by e-mail or telephone. External reviewers from Italy as well as other European countries were involved in the evaluation of the final document.

Table 1. Quality of evidence and strength of recommendation.

	Quality of evidence
I	Evidence from more than one properly designed, randomized, controlled study and/or systematic review of randomized studies
II	Evidence from one properly designed, randomized, controled study
III	Evidence from cohort studies or their meta-analysis
IV	Evidence from retrospective case-controlled studies or their meta-analysis
V	Evidence from case series without control group
VI	Evidence from opinions of respected authorities, based on clinical experience
	Strenght of recommendation
A	The panel strongly supports a recommendation for use
B	The panel moderately supports a recommendation for use
C	The panel marginally supports a recommendation for use

What is the current role of BCG vaccination?

The bibliographical search for evidence concerning the efficacy of BCG vaccine identified 17 papers: 4 meta-analyses, 10 cohort studies, 2 randomized clinical trials, and one cost-efficacy study.[14-30]

A recent meta-analysis of the efficacy of BCG vaccine against the pulmonary, meningeal and disseminated forms of TB included 21 randomized or quasi-randomized clinical trials: 18 involving patients with pulmonary TB, and 6 involving patients with meningeal and/or military forms.[30] The vaccine's efficacy against pulmonary TB varied very widely from substantial protection in a British trial (relative risk [RR] 0.22, 95% confidence interval [CI] 0.16–0.31) to the absence of protection in an Indian trial (RR 1.05; 95% CI 0.88–1.25). Average protection was greater in school-aged children with a negative TST before being vaccinated (RR 0.26, 95% CI 0.18–0.37) and

subjects vaccinated at birth (RR 0.41, 95% CI 0,29–0.58). There were some differences related to latitude; average protection was lower in the studies conducted in places at latitudes of 0–20° and 20–40° than in those conducted at higher latitudes. There was strong evidence that protection was less in participants who were older than school age than in newborns. Vaccine efficacy was similar regardless of the strain used.

The six studies that reported data relating to tuberculous meningitis (TBM) and miliary TB found that BCG vaccine provided substantial protection (RR 0.15, 95% CI 0.08–0.31), with only small differences between them (p = 0.14). Protection against both was high in subjects vaccinated at birth (RR 0.1, 95% CI 0.01–0.77) and in children with a negative TST before being vaccinated (RR 0.08, 95% CI 0.03–0.2).

Another meta-analysis evaluated the efficacy of BCG vaccine administered at birth in protecting against TB and mortality due to TB in 5 prospective trials and 11 case-control studies [14], and found that the RR of TB in vaccinated *vs* unvaccinated subjects was 0.74 (95% CI 0.62–0.83); in the case-control studies, the odds ratio (OR) was 0.52 (95% CI 0.38–0.64), with a protective effect of 50%. The five studies reporting mortality data showed that BCG vaccine had a protective effect of 0.65 (95% CI 0.12–0.86); the five reporting data concerning meningitis showed a protective effect of 0.64 (95% CI 0.30–0.82); and the 3 reporting data on disseminated disease showed a protective effect of 0.78 (95% CI 0.58–0.88). There were no significant differences in efficacy depending on the strain used.

Colditz *et al.* made a meta-analysis of the efficacy of BCG vaccine in protecting against TB and mortality due to TB in 14 prospective trials and 12 case-control studies.[16] The clinical trials showed that the RR of TB in vaccinated *vs* unvaccinated subjects was 0.49 (95% CI 0.34–0.70), with a protective effect of 51%, and the case-control studies showed an OR of 0.50 (95% CI 0.39–0.64). The seven studies that included mortality data showed that BCG vaccine had a protective effect of 71% (RR 0.29, 95% CI 0.16–0.53), and 5 studies of TBM that its protective effect was 64% (OR 0.36, 95% CI 0.18–0.70). However, the studies included in this meta-analysis were heterogeneous in different aspects, including for the characteristics of the countries in which the studies were conducted, and did not permit to draw definitive conclusions.[16]

Pereira *et al.* carried out a randomized clinical trial in various of provinces of Brazil in order to evaluate the preventive effect of administering the BCG vaccine to school-aged children, and found that its overall efficacy in preventing tubercular disease was 25% (95% CI 3–43%).[18] In the province of Salvador, where its efficacy was 34% (95% CI 8–53%), it was found that it was necessary to vaccinate 381 children to prevent one case of TB, and that the cost-benefit ratio (based on the cost of a treatment cycle) was in favor of vaccination.[18]

Sixty years after a randomized, placebo-controlled trial of BCG vaccine involving native Americans, Aronson *et al.* found that overall efficacy was 53% (95% CI 14–74%) in the case of pulmonary TB, and 63% (95% CI 11–90%) in the case of extrapulmonary forms.[19]

Abubakar *et al.* conducted a prospective cohort study to evaluate an interferon-gamma release assay (IGRA) in all of the students in a high school who had come into contact with a case of infectious TB, and did not find that BCG vaccination was protective (OR 1.05, 95% CI 0.80–1.39).[20] One limitation of this study could be that, in the UK, the vaccine is only given to subjects at risk who are, by definition, at greater risk of infection.[20]

Kelekçi *et al.* analyzed 172 cases of TBM in a Turkish university hospital, and found that BCG vaccine significantly protected against death due to the disease (p = 0.05).[21]

Gaensbauer *et al.* carried out a cohort study of nursery school children exposed to teachers with infectious TB and found that the BCG vaccine had a protective effect against the disease, and that 11.3 subjects needed to be vaccinated to prevent one case of active disease.[22] However, this study did not consider the possible additional risks for TB in the vaccinated subjects, such as coming from a country in which TB is endemic.

Brantsaeter *et al.* evaluated in the difference in the incidence of TB by age group (0–14 and 15–29 years) in Denmark, Sweden, Norway and Finland, countries that have a similar incidence of the disease but different vaccination policies:[23] in Norway, BCG vaccination is offered to children aged 0–14 y with a negative TST; in Sweden, the universal vaccination of newborns was discontinued in 1975; in Denmark, then routine vaccination of TST-negative 7-year-olds begin to be gradually discontinued during the course of 1980 and stopped in 1985; and in Finland, all newborns were administered BCG vaccine until September 2006. The overall incidence in the population as a whole was lowest in Norway and, on the basis of these data, 21,699–25,125 vaccinations were necessary to prevent one case.[23]

Morán-Mendoza *et al.* studied all of the contacts of active TB carriers in Canada over a period of 12 y and, after adjusting for other risk factors, found that a previous BCG vaccination reduced the risk of developing active TB by 68% (hazard ratio [HR] 0.32: 95% CI 0.20–0.50).[24]

A cohort study conducted in Brazil by Barreto *et al.* showed that the overall efficacy of neonatally administered BCG vaccine was 37% (95% CI 13–55%).[25]

Eriksen *et al.* examined the protective effect of BCG vaccine against latent tuberculosis infection (LTBI) diagnosed by means of an IGRA in children attending a British nursery school who had been in contact with a teacher with infectious TB.[26] They showed that it had a protective effect by means of both univariate (OR 0.28: 95% CI 0.11–0.70) and multivariate analysis (OR 0.25: 95% CI 0.09–0.69), and calculated an efficacy rate of 66%. However, they did not find any association between tubercular infection and BCG vaccination in adults (OR 0.11, 95% CI 0.01–1.03).[26]

Basu Roy *et al.* estimated the correlation of BCG and IGRA positivity with vaccine administration.[27] The analysis included children who had been in domestic contact with cases of active TB, children tested for LTBI after having recently emigrated from highly endemic countries, and (in the case of Greece and Spain) children who were positive upon universal screening. Multivariate logistic regression showed that BCG vaccination significantly correlated with a positive TST (≥10 mm), with an OR of 3.22 (95% CI 2.41–4.32; p < 0.001) but a negative IGRA (QFT-GIT: OR 0.41; IC 95% 0.30–0.55 [p < 0–001]; T-SPOT. TB: OR 0.41; 95% CI 0–25–0–66 [p < 0.001]). Similar results were obtained in the subgroup of domestic contacts: i.e. there

were significant correlations between BCG vaccination and a positive TST (OR 2.08; 95% CI 1.36–3.20; p = 0.001) and a negative IGRA (QFT-GIT: OR 0.52, 95% CI 0.33–0.81 [p = 0.003]; T -SPOT.TB: OR 0.31, 95% CI 0.16–0.58 [p < 0.001]). It therefore seems to be clear that the vaccination also protects against LTBI.[27]

Eisenhut *et al.* used an IGRA to test the school contacts of a child with non-infectious pulmonary in the UK and found that BCG vaccine (a single dose administered at birth using the Danish strain 1331) protected against both LTBI and active disease (adjusted RR of LTBI 0.61, 95% CI 0.39–0.96 [a 38% reduction in RR]; adjusted RR of active TB 0.51, 95% CI 0.15–1.70).[28] After adjusting for ethnicity, closeness in class and shared activities, BCG vaccination continued to show a protective effect against infection (OR 0.16, 95% CI 0.05–0.54), with a corrected RR of 26% (95% CI 0.09–0.69) corresponding to a 74% reduction in RR (95% CI 31–91%).[28]

Soysal *et al.* evaluated the effect of BCG vaccine in reducing the risk of infection and tubercular disease in a cohort study of 979 Turkish children who had been in contact with cases of active TB [29]. Multivariate logistic regression showed that the vaccination was associated with 92% reduction in the RR of disease (95% CI 71–98%) and a 34% reduction in the RR of LTBI (95% CI 12–35%), even after correcting for possible confounding factors.[29]

How long does the protection provided by BCG vaccine last, and is a second vaccination useful?

The bibliographical search identified 5 studies concerning the duration of protection: 2 meta-analyses, 2 randomized clinical trials, and one cohort study.[14,17,19,25,31] The 2 meta-analyses documented protection lasting 10–15 y[14,17] The randomized study of Aronson *et al.* showed persistent efficacy for up to 60 years, with only a non-significant reduction over time.[19] Barreto *et al.* reported a duration of protection of 15–20 y in subjects vaccinated at birth (efficacy after 15–20 y 39%, 95% CI 9–58%),[25] and Weir *et al.* a duration of immunological memory of at least 14 y in subjects vaccinated at birth or during adolescence.[31]

The five BCG revaccination studies identified were 3 randomized clinical trials,[32-34] one cohort study,[35] and one case-control study,[36] none of which was carried out in Europe or North America. All of them showed that a second vaccination at the age of 19 months or during school age had no additional effect in comparison with a single administration,[32,33,35,36] although a follow-up study carried out 9 y after a clinical trial in Brazil has recently documented that, at higher latitudes, there may be some advantage in revaccinating children aged <11 y.[34]

IS BCG vaccine safe?

The bibliographical search identified 6 studies analyzing the adverse effects of BCG vaccine.[37-43]

One of these found that the risk of adverse effects is higher in HIV-positive subjects and those with primary immunodeficiency;[37] the most frequently reported adverse effect was loco-regional disease with lymphadenopathy (BCG-itis), whereas forms of disseminated TB (BCG-osis) are reported less frequently. An Irish study conducted between August 2002 and July 2004 (after the introduction of BCG vaccinations using the SSI strain) found that the prevalence of loco-regional complications was 1/931 vaccinated subjects, and that of suppurative lymphadenitis was 1/1,543.[38] A study of children vaccinated at the age of 7–14 y in Brazil reported a prevalence of loco-regional complications of 1/2,580 vaccine administrations in the children with a vaccination scar, and 1/5,990 in those without a scar.[39] The total incidence was 35/100,000, and none of the 71,347 vaccinated children had died or been affected by disseminated forms or permanent damage.

Between January 1993 and April 2002, 15 serious adverse events due to BGC vaccine were reported in Canada, including 6 cases of disseminated forms all of which occurred in patients with primary immunodeficiency or HIV infection.[40] As no data concerning the number of vaccine doses administered were available, the study could only estimate that the incidence of disseminated TB was 205 per one million doses (95% CI 62–678).

In a prospective study carried out in France from 12 February to 30 June 2007, 17.8% of the 2,435 vaccinated children presented loco-regional complications, which consisted of erythema in 301 cases (12.4%), infiltration in 296 (12.2%), ulceration in 21 (0.9%), abscess in 60 (2.5%), and lymphadenopathy in 3 (0.1%). Two patients (8.2/10,000) experienced serious adverse effects.[41] Multivariate showed that a lower risk of adverse events was significantly associated (p < 0.05) with an age of <12 months at the time of vaccination (OR 0.35 [95% 0.2–0.6] for an age of <28 days; 0.29 [95% CI 0.2–0.42] for an age between 29 d and 2 months; 0.53 [95% CI 0.37–0.74] for an age of 3–11 months), the presence of a visible papule after the vaccination, a vaccine underdose, and the type of vaccinating doctor (general practitioners *vs* pediatricians).[41]

A prospective study of vaccinated subjects of all ages between one day and 5 4y conducted in Australia recorded a 5% prevalence of adverse reactions,[42] of which the most frequent were abscesses, lymphadenitis and severe loco-regional reactions. Abscesses and severe loco-regional complications were significantly less frequent among breastfeeding children (RR 2.96, 95% CI 1.11–7.90) than in older subjects (RR 4.93, 95% CI 1.11–21.90). Furthermore, their prevalence was lower in adult patients who had undergone a TST (RR 0.27, 95% CI 0.09–0.77), and if the vaccine had been administered by expert personnel (RR 0.24, 95% CI 0.09–0.68); their incidence was higher in adult women than men (RR 7.18, 95% CI 1.59–32.45). The development of adverse reactions did not correlate with the recent administration of other vaccinations, previous BCG vaccination, or the vaccine batch.[42]

Hesseling *et al.* carried out a prospective study of the rate of disseminated disease due to BCG in HIV-infected patients in South Africa, and found that it was much higher (minimum estimate110–139 cases/100,000 subjects/year) than in uninfected children (0.72–0.74 cases/100,000 subjects/year).[43]

Does BCG vaccination affect TST responses?

A study of 5,117 healthy subjects carried out in Switzerland between 1991 and 1998 showed that a TST result of <18 mm

in adults aged <40 y is more likely to be the result of prior vaccination than infection and should not systematically lead to preventive treatment.[44] However, many pediatric studies have not found any significant difference in the rates of TST positivity between vaccinated and unvaccinated children.[45]

The bibliographical search identified 6 cohort studies that have evaluated the effect of BCG vaccine on TST responses,[27,29,47-49] and recent studies comparing the TST and IGRA responses of vaccinated subjects have shown that BCG vaccination does affect TST positivity.[27,29,46]

A multicentre study by Basu Roy *et al.* found that previous BCG vaccination correlated with TST positivity (>10 mm: OR 3.22, 95% CI 2.41–4.32; $p < 0.001$) and IGRA negativity (QFT-GIT: OR 0.41; IC 95%. 0.30–0.55 [$p < 0.001$]; T-SPOT.TB: OR 0.41; 95% CI 0.25–0.66 [$p < 0.001$]).[27] Vaccinated children showed significantly larger areas of hardening (median 14 mm; interquartile range 10–17 mm) than unvaccinated children (median 10 mm; interquartile range 0–14 mm; $p < 0.001$).[27]

Soysal *et al.* evaluated the pediatric contacts of patients with infectious TB, and found a significant difference in the concordance of TST and ELISpot results in those vaccinated with BCG;[29] multivariate analysis showed that the protection provided by the vaccine against tuberculous infection was significantly greater when evaluated by means of ELISpot (OR 0.60, 95% CI 0.43–0.83 *vs* 1.18, 95% IC 0.85–1.63; $p < 0.0001$). When the TST cut-off value was increased to 15 mm, the absence of BCG vaccination was a risk factor for infection.[29]

In a study of children at high risk of TB in Athens, the concordance between TST and IGRA responses was optimal in the unvaccinated children, but was only 60% in those who had been vaccinated.[46]

A study of native American children in Canada found that vaccinated children were more like to have a positive TST than those who had not been vaccinated (5.7% *vs* 0.2%; $p < 0.001$). Only five of the 65 BCG vaccinated children with a TST result of >10 mm had a positive IGRA (7.7%, 95% CI 2.5–17.0%), but the correlation increased in the patients with a TST result of >15 mm ($p = 0.047$).[47]

Piñeiro *et al.* found that the vaccinated children in a cohort of children who had been adopted in, or had emigrated from highly endemic areas were at greater risk of a positive TST than those who had not been vaccinated (OR 2.35, 95% CI 1.32–4.21), but this only applied during the 3 y after vaccination.[48]

Bozaykut *et al.* found a significant difference in TST responses between vaccinated and unvaccinated children aged 1–6 years, without any variation between one age and another.[49]

Conclusions

On the basis of the published evidence and their clinical experience, the group of experts reached the following conclusions:

1) BCG vaccination offers a good level of protection against tuberculous meningitis and disseminated TB **[I-A]**, and a fair level of protection against pulmonary disease **[I-A];**
2) the protective effect of BCG vaccine lasts for at least 10 years, and BCG revaccination offers no advantage over a single vaccination **[I-A]**;
3) BCG vaccine is safe in immunocompetent subjects: its most frequent significant adverse effects are the abscesses and suppurative lymphoadenopathy **[III-B]**;
4) BCG vaccination is not recommended in patients with HIV infection or other forms of T lymphocyte or phagocytic oxide reductase metabolism immunodeficiency because they are at increased risk of serious adverse effects and disseminated disease **[III-B]**;
5) the adverse effects of BCG vaccine are less frequent in breastfeeding infants and children who are TST negative before being vaccinated **[III-B]**;
6) the adverse effects are more frequent in subjects receiving a second vaccination **[III-B]**;
7) BCG vaccination affects TST responses for at least 6 y **[III-B]**;
8) in subjects who have undergone BCG vaccination, a TST response can be considered certainly positive if it is >15 mm and further examinations are requested to confirm LTBI or active TB **[III-A]**.
9) in BCG vaccinated subjects with a TST response of <15 mm, an IGRA can distinguish vaccinated from infected subjects aged >5 y **[III-B]**. In the absence of symptoms, a TST response of <15 mm should not be considered positive unless confirmed by an IGRA **[III-B]**.

On the basis of these conclusions, the working group makes the following recommendations:

- BCG vaccination is recommended in Italy for all TST-negative newborns/breastfeeding infants aged <6 months coming from areas in which TB is highly endemic, or whose parents come from areas in which TB is highly endemic **[I-B]**;
- BCG vaccination is recommended in Italy for all TST-negative newborns/breastfeeding children aged <6 months who have come into contact with a family member affected by active TB and in whom the presence of the disease has been excluded **[I-B]**;
- BCG vaccination is recommended in Italy for all TST-negative children aged from 6 months to at least 5 y coming from areas in which TB is highly endemic, or whose parents come from areas in which TB is highly endemic **[I-B]**;
- BCG vaccination is recommended in Italy for all TST-negative children aged from 6 months to at least 5 y who have come into contact with a family member affected by active TB **[I-B]**;
- previously vaccinated children should not receive a second vaccination **[I-A]**;
- before vaccinating a newborn, it is necessary to ascertain that the mother was screened for HIV during her pregnancy. If she was not screened, BCG vaccination should be postponed until HIV infection has been excluded **[III-A]**;
- before administering BCG vaccine, an anamnesis should be recorded in order to establish whether or not there is a family history of primary immunodeficiency and/or symptoms attributable to defects in the immune system. In the case of any suspicion, BCG vaccination should be postponed until investigations have been made **[III-A]**;

- all subjects other than breastfeeding children aged <6 months should undergo a TST before receiving a BCG vaccination [**III-A**]. BCG vaccinations should only be administered to immunocompetent whose TST result indicates an infiltrate diameter of <5 mm [**III-A**]. Live viral vaccines inhibit responses to tuberculin; consequently, the evaluation should be made at least 4 weeks after the administration of an anti-measles, parotitis, rubella or varicella vaccination [**III-A**].

Disclosure of potential conflicts of interest

No potential conflicts of interest were disclosed.

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