20 Tuberculosis

Key information

Mode of transmission	Inhalation of airborne droplets produced by people with pulmonary or laryngeal tuberculosis (TB). People with latent TB infection and non-pulmonary TB disease are not infectious.
Incubation period	Between 2 and 10 weeks from infection to primary lesion or significant tuberculin skin test (Mantoux) reaction.
Period of communicability	May be years with untreated pulmonary TB. Refer to the *Guidelines for Tuberculosis Control in New Zealand 2010*[1] (or current edition).
Burden of disease	Disseminated and meningeal TB are more common in very young children. The immunocompromised, particularly HIV-infected individuals, are more at risk of disease and complications. In New Zealand, TB is highest in those born in high prevalence countries.
Vaccine	Bacillus Calmette-Guérin (BCG) vaccine can only be administered by an authorised vaccinator with BCG endorsement. Live attenuated vaccine, which must be reconstituted. At the time of writing, BCG supply to New Zealand was interrupted by a global shortage.
Recommendations	Neonatal BCG vaccine should be offered to infants at increased risk of TB, defined as those who: • will be living in a house or family/whānau with a person with either current TB or a history of TB • have one or both parents or household members or carers who, within the last 5 years, lived for a period of 6 months or longer in countries with a TB rate ≥40 per 100,000 • during their first 5 years will be living for 3 months or longer in a country with a TB rate ≥40 per 100,000. (See Appendix 8 for a list of countries with a TB rate ≥40 per 100,000.)

Continued overleaf

Contraindications	Individuals receiving corticosteroids or other immunosuppressive treatment. Individuals suffering from malignant conditions such as lymphoma, leukaemia, Hodgkin's disease or other tumours of the reticulo-endothelial system. HIV-positive or potentially HIV-positive individuals. Infants of mothers who received DMARDs during pregnancy that are monoclonal antibodies (eg, adalimumab, infliximab). Generalised infected skin conditions. Other individuals in whom immunocompromise is known or suspected (see section 20.6.1).
Expected responses	90–95% of people develop a local reaction, which may scar within 3 months. A minor degree of adenitis is normal, not a complication. Suppurative adenitis may take months to resolve; usually no treatment is required.

20.1 Bacteriology

Human TB is caused by infection with *Mycobacterium tuberculosis* or *Mycobacterium bovis*.

20.2 Clinical features

M. tuberculosis or *M. bovis* infection most commonly causes disease in the lungs, but any part of the body can be affected.

The initial infection with *M. tuberculosis* usually goes unnoticed. Early infections can be cleared, progress rapidly to primary TB, or be contained in a latent phase (LTBI) – see Figure 20.1.

Primary TB occurs most commonly in young children aged under 5 years, individuals with immunocompromise or those infected by particularly transmissible isolates of TB.

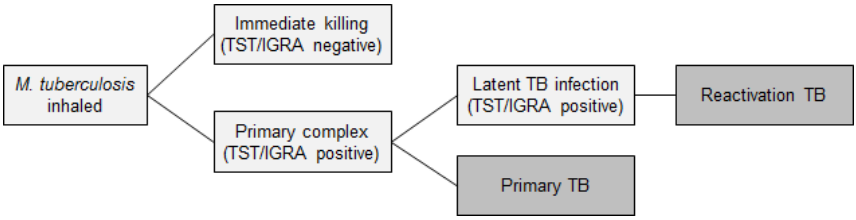
Latent TB infection has no symptoms and is diagnosed by a positive tuberculin skin test or interferon gamma release assay after the exclusion of active TB. Latent infection progressing to active TB is also called reactivation TB.

The lifetime risk for infected people progressing from this latent phase to active TB disease may be as high as 20 percent, but this risk is strongly affected by infecting dose, the age of the person, the presence of healed lesions on chest X-ray and immunocompromise.[2, 3]

The time from infection to clinical manifestations of primary TB varies, from one to six months after infection. Reactivation TB can occur at any time thereafter, even decades after infection. The most common site of infection is the lung (pulmonary TB), where TB infection classically causes an asymmetrical pulmonary infiltrate. The 'classic' TB pathology of caseation, cavity formation and fibrosis occurs late and in a minority of cases. Young children with active TB disease may be asymptomatic or present with symptoms of fever, lassitude and failure to thrive. Older children and adults with active TB disease may present with symptoms of anorexia, fatigue, weight loss, chills, night sweats, cough, haemoptysis and chest pain.

Any organ can be affected by extrapulmonary TB, causing meningitis, pleurisy, pericarditis, bone or joint infection, renal infection, gastrointestinal tract infection, peritonitis or lymphadenitis, or disseminating via the bloodstream and affecting multiple organs (disseminated TB). Disseminated and meningeal TB are more common in very young children. Immunocompromise, like HIV, is associated with higher rates of disseminated TB and less specific clinical features.[4]

Figure 20.1: Stages in the natural history of tuberculosis



Key: TST = tuberculin skin test; IGRA = interferon gamma release assay; TB = tuberculosis.

20.3 Epidemiology

20.3.1 Global epidemiology

Worldwide, the incidence rate of TB is slowly falling by about 1.5 percent per year, but TB remains a major global health problem. The majority of the TB burden exists in 30 high-burden countries. In 2015, TB was one of the top 10 causes of death worldwide and caused more deaths than HIV/AIDS. The WHO estimates there were 10.4 million new TB cases in 2015 and 1.4 million deaths.[5] People living with HIV accounted for 11 percent of all new TB cases (1.2 million) in 2015, and there were an additional 400,000 deaths resulting from TB disease among people living with HIV. There has been an increasing burden of multidrug-resistant TB (defined as resistance to at least isoniazid and rifampicin) with an estimated 480,000 new cases of multidrug-resistant TB in 2015.

In low-burden countries, such as New Zealand, the peak age for TB is in older adults, reflecting their exposure to TB in the past when incidence was higher. In high-burden countries TB is most common in children and young adults. The risk of TB in people who emigrate from high-burden countries is proportionate to the incidence in their country of origin.[6]

20.3.2 New Zealand epidemiology

For detailed TB information, see the *Tuberculosis in New Zealand: Annual Report*, available on the ESR website (https://surv.esr.cri.nz/surveillance/AnnualTBReports.php).

Notifications and rates

TB remains one of the most common notifiable infectious diseases in New Zealand. Cases of TB declined substantially between 1980 and 2007, but they have remained relatively stable since then.[7]

In 2015 there were 300 notifications, corresponding to a notification rate of 6.5 per 100,000, similar to the rate in 2014 (6.7 per 100,000).[7] Notification rates were highest in adults aged 20–29 years (12.3 per 100,000) and 30–39 years (10.2 per 100,000).

Asian ethnic groups had the highest notification rate in 2015 (35.9 per 100,000), followed by Pacific peoples (19.5 per 100,000) and Middle Eastern/Latin American/African (15.8 per 100,000).[7] The notification rate for Māori was considerably lower (3.9 per 100,000) and even lower for European/Other (0.6 per 100,000) groups. There is substantial regional variation in TB notification rates, with higher rates in Auckland and Wellington; cities where many new arrivals to New Zealand have settled.

Risk factors and transmission

Of the 286 new TB cases in 2015, 237 were born overseas (ESR, 9 February 2017). The highest disease rate was among those born in Southern and Central Asia (125.2 per 100,000), followed by those born in South-East Asia (45.6 per 100,000), the Pacific Islands (33.7 per 100,000) and North-East Asia (16.9 per 100,000).

The date of arrival was recorded for 208 of the 237 new TB cases who were born outside of New Zealand (ESR, 9 February 2017). The median interval between the date of arrival and the TB notification was 6 years.

Three children under 5 years of age were notified with TB in 2015, and none were BCG vaccinated.[7] One had miliary and renal tract TB.

Multidrug-resistant TB

Multidrug-resistant TB is rare but does occur in New Zealand. Between 2006 and 2015, on average, 1.2 percent (28 cases) of culture-positive cases were resistant (ESR, 9 February 2017); 26 of these multidrug-resistant TB cases were born overseas (23 in an Asian country) and are assumed to have acquired their resistant organisms overseas.

20.4 Vaccine

Note: Depending on world supply, BCG vaccine may not be available in New Zealand.

BCG vaccine types vary widely, with different strains. The incidence of side-effects with BCG vaccination differs between strains that are considered more reactogenic (ie, those that elicit stronger immune responses in animal models) and strains that are considered less

reactogenic.[8] The more reactogenic strains have also been associated with a higher rate of lymphadenitis and osteitis, especially among neonates. Reducing the vaccination dosage for the more reactogenic strains also reduces the incidence of lymphadenitis.

20.4.1 Licensed vaccine

BCG Vaccine SSI (Seqirus (NZ) Ltd) is a live attenuated vaccine, containing the less reactogenic Danish 1331 strain of *M. bovis*. The 0.1 mL dose for adults and children aged 12 months and older contains 2–8 × 10^5 colony-forming units of *M. bovis*, and the 0.05 mL dose for infants contains 1–4 × 10^5 colony-forming units. Other components and residuals include sodium glutamate, magnesium sulphate heptahydrate, dipotassium phosphate, citric acid, L-asparagine monohydrate, ferric ammonium citrate and glycerol.

20.4.2 Efficacy and effectiveness

The exact immune response elicited by BCG vaccination and the mechanism of action in the host are still not well understood. There is no reliable established laboratory correlate for immunity to *M. tuberculosis*,[9] though this remains an active area of study.[10]

BCG protection is partial and varies according to the age at which vaccination is administered and the disease phenotype in question. A meta-analysis of randomised controlled trials showed neonatal BCG had 59 percent efficacy against pulmonary TB (95% CI: 0.42–0.71) and 90 percent efficacy against meningeal TB (95% CI: 0.23–0.99).[11] Studies conducted since the advent of interferon gamma release assays suggest BCG may also be effective against *M. tuberculosis* infection. A meta-analysis has estimated BCG effectiveness against *M. tuberculosis* infection at 20 percent, though different methods in the included studies each had a wide range of estimates.[12] Thus, the principal role of BCG in New Zealand is to protect young children who are at greatest risk of disease, particularly miliary and meningeal disease.[8] BCG is less effective in adults and older children, particularly if they already have latent infection.

As BCG has been propagated *in vitro* for over 40 years, there are now several strains being manufactured.[13] Immunological responses vary considerably across vaccine strains, but the data to date cannot differentiate which strains, if any, are overall more effective.[14, 15]

In low-income countries, a birth dose of BCG significantly reduces overall infant mortality.[16]

BCG has had little effect in reducing the population rate and transmission of TB,[17] so there are no herd immunity effects. Duration of protection is unknown, possibly 10 to 15 years, but it may be much longer in some populations.[8]

There have been a number of different approaches to using BCG in the control of TB in middle- and high-income countries.[18] For example, the US has not had a BCG programme, whereas New Zealand (see Appendix 1) and the UK had programmes until 1990 and 2005, respectively. The WHO recommends that countries with low rates of active TB, such as New Zealand, target BCG vaccination at children who are at significantly increased risk of TB exposure through household contact.[19] New Zealand (see section 20.5) and the UK now only offer BCG vaccine to high-risk individuals. A study from the Netherlands suggests that around 9,000 children from countries with rates greater than 50 per 100,000 population would have to be given BCG to prevent a severe case.[20]

The current recommendation to use neonatal BCG vaccination in populations with high rates of active TB is part of a control and treatment programme for TB in New Zealand, which includes active contact tracing and treatment of latent TB infection.

There are large international efforts working to improve BCG vaccines and develop new, more effective vaccines.[21]

20.4.3 Transport, storage and handling

Transport according to the *National Standards for Vaccine Storage and Transportation for Immunisation Providers 2017*.[22] Store in the dark at +2˚C to +8˚C. Do not freeze.

There are variances in strain potency between brands of BCG vaccine so vaccinators should always follow the instructions in the vaccine data sheet (available on www.medsafe.govt.nz).

BCG vaccine requires reconstitution before administration. It is presented as freeze-dried vaccine in a multi-dose vial with diluent in a separate vial. The diluent must be added to the freeze-dried vaccine vial and mixed gently (do not shake vigorously). Protect the vial from light. Leave the reconstituted vaccine to stand for one minute until it forms an opalescent liquid. Reconstituted vaccine should be stored at 4˚C, protected from sunlight and used within four hours.

20.4.4 Dosage and administration

Only authorised vaccinators with BCG endorsement are able to administer BCG vaccine (see Appendix 4).

Administer a dose of:

- 0.05 mL to infants aged under 12 months
- 0.1 mL to children aged 12 months or older and adults.

The vaccine is administered by intradermal injection over the point of insertion of the left deltoid muscle (see sections 2.2.3 and 2.2.4).

No follow-up tuberculin skin testing is required.

Repeat BCG vaccination is not recommended.

BCG immunisation given in other countries

BCG is one of the vaccines that are part of the WHO Expanded Programme on Immunization. It is given at birth in most low-income countries.

The following Pacific Island countries[23] recommend BCG vaccination at birth: Cook Islands, Fiji, Kiribati, Nauru, Niue, Papua New Guinea, Samoa, Solomon Islands, Tonga, Tuvalu and Vanuatu.

Usually BCG vaccine is administered in the left deltoid area, but other sites of administration have also (although uncommonly) been used, such as the right deltoid. Revaccination with BCG is not recommended by the WHO.[19]

Co-administration with other vaccines

BCG can be given simultaneously with any other vaccine. However, it must be administered into a separate site in a separate syringe. Because of the risk of local lymphadenitis, no further vaccinations should be given into the arm used for BCG for at least three months. If not given concurrently, BCG should be given at least four weeks after MMR or VV. Note that no time interval is required between administration of BCG and rotavirus vaccines.

HBIG (given at birth to babies of mothers with chronic HBV infection) or human normal immunoglobulin is thought not to reduce the effectiveness of BCG immunisation, which principally acts through cell-mediated immunity.

20.5 Recommended immunisation schedule

20.5.1 Tuberculin skin testing (Mantoux) before BCG vaccination

Tuberculin skin testing is not needed if BCG is given before age 6 months unless a history of contact with a known or possible case of TB is obtained. Although the tuberculin skin test is usually positive in the year following BCG vaccination, at least 50 percent of children will be negative beyond that time, so tuberculin skin testing still has utility for diagnosing TB infection.

20.5.2 BCG eligibility criteria

TB is more common in migrants or families of migrants from high-incidence countries. However, all pregnant women should have a discussion with their lead maternity carer about the risk of TB for their baby.

Neonatal BCG is recommended and funded for infants at increased risk of TB, as defined in Table 20.1.

Table 20.1: Neonatal BCG eligibility criteria

Neonatal BCG is recommended and funded for infants at increased risk of TB, defined as those who:
• will be living in a house or family/whānau with a person with either current TB or a history of TB
• have one or both parents or household members or carers who within the last five years lived for a period of six months or longer in countries with a TB rate ≥40 per 100,000*
• during their first five years will be living for three months or longer in a country with a TB rate ≥40 per 100,000.*

* A list of high-incidence countries and their TB rates is available in Appendix 8.

As a general indication, the following global areas have TB rates ≥40 per 100,000:

- most of Africa
- much of South America
- Russia and the former Soviet states
- the Indian subcontinent
- China (including Hong Kong) and Taiwan
- South East Asia
- some parts of the Pacific (Kiribati and Papua New Guinea have consistently high rates; see Appendix 8 for a list of the high-incidence countries).

Neonates at risk should be identified antenatally by lead maternity care providers and antenatal referral made to the neonatal BCG service. Health care providers can also identify and refer neonates at risk. Immunisation is desirable before infants leave hospital. If this does not happen, immunisation should be arranged through the local medical officer of health.

Children who have missed vaccination at birth may be vaccinated at any time up to age 5 years. If the child is 6 months or older they should have a pre-vaccination tuberculin skin test to detect whether they have already been infected, with vaccination only being given if the child is uninfected.

Infants born before 34 weeks' gestation should have their BCG vaccination delayed until 34 weeks' post-conceptual age.[24] Babies born after this or with low birthweight appear to produce an adequate response, based on tuberculin skin test responses.[25, 26, 27]

If the baby has not been vaccinated before leaving hospital, and if there is a history of *current* TB in a relative who has had contact with the baby, *do not vaccinate immediately*. Withhold vaccination, conduct tuberculin skin testing, seek paediatric advice and vaccinate only after the possibility of infection in the baby has been excluded. Vaccination may not protect the baby who is incubating disease, and may prevent the tuberculin test from assisting with the diagnosis of disease.

A parent's/guardian's request in itself should not be accepted as an indication for immunisation. Parents/guardians seeking vaccination of children who do not meet the above criteria should be referred to the local medical officer of health to discuss the risks and benefits of immunisation before a final decision is made.

The NIR collects information on neonatal BCG immunisation, unless the individual or their parent/guardian has opted off the NIR (see section 2.3.5). The BCG vaccinator usually documents the immunisation data on a paper form, which is then sent to the DHB NIR Administrator to enter onto the NIR.

BCG vaccine information for parents

Information about the BCG vaccine is available in English and other languages from the HealthEd website (www.healthed.govt.nz). This includes information for parents on why the vaccine is recommended, what to expect and how to care for the vaccination site.

20.5.3 Other high-risk individuals or groups

Repeat BCG vaccination is not recommended.

Funded BCG may be offered to the following at-risk people if they are tuberculin skin test- or interferon gamma release assay-negative:

- contacts of active TB cases aged under 5 years (note that a contact exposed to TB in the preceding three months will need two negative tuberculin skin tests, 8 to 12 weeks apart, before vaccination)
- immigrants aged under 5 years from countries with a rate ≥40 per 100,000
- health care workers and laboratory staff, depending on their risk of exposure (refer to the *Guidelines for Tuberculosis Control in New Zealand 2010*,[1] or the current edition)
- people exposed to animals that are likely to be infected.

Vaccination in New Zealand for overseas travel is not available.

20.5.4 Pregnancy and breastfeeding

BCG vaccine is not routinely recommended for pregnant or breastfeeding women.

BCG is a live vaccine, therefore its use in pregnancy is not recommended (see section 20.6.2). If indicated, BCG vaccine may be given to breastfeeding women.[28]

20.6 Contraindications and precautions

See also section 2.1.3 for pre-vaccination screening guidelines and section 2.1.4 for general contraindications for all vaccines.

20.6.1 Contraindications

BCG vaccine should not be given to individuals:

- known to be hypersensitive to any component of the vaccine
- receiving corticosteroids or other immunosuppressive treatment, including radiotherapy (see section 4.3.3)
- suffering from malignant conditions such as lymphoma, leukaemia, Hodgkin's disease or other tumours of the reticulo-endothelial system
- in whom immunocompromise is known or suspected, such as individuals with hypogammaglobulinaemia – primary immune deficiencies in children are often not detected until after the first few weeks of life (ie, after BCG vaccine is given), so a family history of immune deficiency should be sought and, if present, discussed with a paediatrician before vaccination
- known to be infected with HIV, including neonates where the mother's HIV status is unknown – maternal HIV infection should be excluded prior to neonatal vaccination; testing should have been offered as part of the National Antenatal HIV Screening Programme, and infants born to HIV-infected mothers should be under the care of a paediatrician
- aged under 8 months whose mothers received DMARDs during pregnancy that are monoclonal antibodies (eg, adalimumab, infliximab; see Table 4.3) – BCG vaccination should be delayed until the infant is at least 8 months old;[29] these drugs may cross the placenta and cause immunosuppression in the infant
- with generalised infected skin conditions.

20.6.2 Precautions

- BCG vaccine should be avoided in those who are pregnant (this is a counsel of caution, as no harmful effects to the fetus have been observed following accidental immunisation of the mother during pregnancy).
- In the case of eczema, an immunisation site should be chosen that is free of skin lesions.

- Infants born before 34 weeks' gestation should have their BCG vaccination delayed until 34 weeks post-conceptual age.[24]
- Avoid or defer immunisation in a child born with a condition that may require immunosuppressive therapy in future.

20.7 Expected responses and AEFIs

20.7.1 Expected responses

Following the BCG injection, a white weal should appear. This should subside in approximately 30 minutes. The site requires no swabbing or dressing.

Ninety to ninety-five percent of people vaccinated with BCG develop a local reaction, which may include shallow ulceration, followed by healing and scar formation within three months. A minor degree of adenitis developing in the weeks following immunisation should be regarded as normal, not a complication. It may take months to resolve. Suppurative adenitis may also take months to resolve; usually no treatment is required.

20.7.2 AEFIs

AEFIs with BCG vary with age and vaccine strain and are summarised in Table 20.2.

Table 20.2: Age-specific estimated risks for complications after administration of BCG vaccine

Complication	Incidence per 1 million vaccinations	
	Age <1 year	Age 1–20 years
Local subcutaneous abscess; regional lymphadenopathy	387	25
Musculoskeletal lesions	0.39–0.89	0.06
Multiple lymphadenitis; non-fatal disseminated lesions	0.31–0.39	0.36
Fatal disseminated lesions	0.19–1.56	0.06–0.72

 Lotte A, Wasz-Hockert O, Poisson N, et al. 1988. Second IUATLD study on complications induced by intradermal BCG-vaccination. *Bulletin of the International Union against Tuberculosis and Lung Disease* 63: 47–59.

The risk of BCG adverse reactions depends on many factors, including strain type, route of administration and the underlying immune state of the patient. Severe injection site reactions, large ulcers and abscesses can occur in individuals who are tuberculin positive. Special care is needed both in interpreting initial tuberculin skin results and in delivering the BCG vaccine.

Rarely, osteitis and osteomyelitis, lupoid and other types of skin disorders, and neurological disorders have been reported following BCG vaccination. Although rare, disseminated BCG disease is the most severe BCG vaccine complication occurring in immunocompromised people, such as children with primary immune deficiency. This needs rapid and aggressive treatment and has a high mortality.

Keloid scars at the injection site, although not uncommon, are largely avoidable. Some sites are more prone to keloid formation than others and vaccinators should adhere to the site recommended (mid-upper arm). Most experience has been with the upper arm site, and it is known that the risk of keloid formation increases greatly if the injection is given higher than the insertion of the deltoid muscle into the humerus.

Every effort should be made to recover and identify the causative organism from any lesions that constitute a serious complication.

Most local and regional adenopathy resulting from BCG vaccination will resolve spontaneously, and there is rarely a need for medical or surgical intervention. Treatment recommendations for local abscess formation and suppurative lymphadenitis remain controversial.[30] If suppurative adenitis reactions persist for longer than three months, seek specialist opinion. However, anyone presenting with more widespread or distant disease needs referral to a specialist.

Abscesses and more serious complications should be reported to CARM (see 'AEFI reporting process – notifying CARM' in section 1.6.3), and also reported to the local medical officer of health in the interests of quality control of the BCG vaccination technique.

20.8 Public health measures

It is a legal requirement that all cases of active TB be notified to the local medical officer of health. While there is no legal requirement to notify cases of latent TB infection that are being treated, for surveillance purposes and with the patient's consent they should be reported to the local medical officer of health.

Under the Health (Protection) Amendment Act 2016, the medical officer of health is given wide powers to investigate and control all TB cases and their contacts, while DHBs are required to make provision for the treatment and supervision of patients and their contacts.

The primary purpose of neonatal BCG vaccination is to protect child case contacts from TB disease and its most devastating consequences. Screening of certain risk groups and case contact management are other elements of TB control in New Zealand. These programmes do not obviate the need for BCG vaccination, as screening coverage is partial and contact tracing may not occur in time to prevent illness in child contacts. The local medical officer of health can advise on local TB control policies, including issues in BCG immunisation.

Both TB infection and BCG immunisation lead to the development of a cellular immune response, which can be detected by measuring dermal induration after the injection of tuberculin-purified protein derivative (eg, via the tuberculin skin test). A positive response to a tuberculin skin test may be an indication of current infection, previous natural infection or prior BCG immunisation. However, the false positive effect after vaccination will wane, rapidly in all individuals who receive the vaccine in the neonatal period and more slowly in those who are vaccinated at an older age such as during the primary-school years.[31]

In vitro tests have been developed to measure the release of interferon-gamma from host lymphocytes in response to well-defined antigens. The antigens used are not present in BCG strains of *M. bovis* or most non-tuberculous mycobacteria. Interferon gamma release assay has the advantage of greater specificity and convenience, but it is more expensive.[32] For more information, refer to the 'Tuberculosis' page of the Ministry of Health website (www.health.govt.nz/our-work/diseases-and-conditions/tuberculosis) and the 'Tuberculosis' chapter of the *Communicable Disease Control Manual 2012*.[33]

20.9 Variations from the vaccine data sheet

The data sheet states that BCG vaccine should not be given to infants born to HIV-positive mothers. The Ministry of Health recommends that BCG may be given to HIV-negative infants born to HIV-positive mothers – providing that the infant is confirmed to be HIV negative by appropriately-timed PCR tests before the vaccine is given.[28, 34] Seek specialist advice.

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