



Use of unlicensed BCG vaccine to protect against TB

Use of unlicensed BCG vaccine to protect against tuberculosis (TB): information for healthcare professionals and prescribers

Since 2015, stock of the only UK-licensed BCG vaccine has been interrupted. In April 2016, PHE issued advice on [prioritisation of BCG vaccine stock](#) for neonates and infants of recognized high-risk groups for tuberculosis (TB) or to tuberculin negative children under 6 years of age. In addition, PHE managed to secure an interim supply of BCG vaccine, from Intervax Ltd of Canada. Intervax BCG vaccine is a WHO prequalified vaccine and has been used extensively across the globe, but is unlicensed in the UK and is presented in glass ampoules rather than vials. **This document provides general information on the use of unlicensed medicines and specific guidance on how Intervax BCG vaccine should be reconstituted and administered.**

UNICEF have issued an [update on the global BCG vaccine market](#) noting that global supply is no longer constrained and is considered sufficient to meet country requirements. In July 2017 PHE [published an update on BCG vaccine availability](#) in the UK noting that there was sufficient stock of Intervax vaccine to extend the offer of vaccination to all eligible groups as described [here](#). BCG vaccine availability continues to be monitored closely as future supply (licensed and unlicensed) remains uncertain.

What is the difference between a licensed and unlicensed medicine?

Before a medicine can be placed on the market in the UK, it must first be granted a licence, also known as a marketing authorisation. While no medicine is completely risk free, a licence indicates that clinical trials of the medicines safety and efficacy have been carried out and the benefits of a medicine are believed to outweigh the risks. In the UK, licences can be granted by the Medicines and Healthcare Products Regulatory Agency (MHRA) for the UK and the European Medicines Agency (EMA) for the European Union (EU).

Some unlicensed medicines may not have a licence anywhere and may be specially prepared for individual patients. Other medicines may have a valid licence in other countries, but no current licence in the UK because the manufacturer has not applied for one.

In certain areas of medicine, for example in paediatrics, difficulties in the development of age-appropriate formulations means that many medicines used in children are off-label or unlicensed. So, not having a UK licence does not mean the medicine is unsafe or untested.

What assurances are there about the efficacy, quality and safety of BCG vaccine supplied by InterVax?

The vaccine has been a World Health Organization (WHO) prequalified vaccine for 25 years, meaning it can be used by United Nations organizations for immunisation against TB. InterVax BCG vaccine is supplied to over 100 countries world-wide including the Netherlands, France, Belgium, Norway and Sweden. In 2015, over 51 million doses were distributed globally. The vaccine has a good safety record.

Studies have shown InterVax BCG vaccine to be highly potent (WHO, Expert Committee on Biological Standardization, Geneva, 19-23 September 2009, WHO/BS/09.2114).

Whilst there is a different BCG strain in the InterVax vaccine compared to the UK licensed BCG vaccine, it is not anticipated that there would be a major difference in adverse events or any new serious adverse events.

Why isn't there a licensed BCG vaccine to administer to patients?

There has been a global shortage of BCG vaccine. In addition, the PHE contracted supplier of BCG vaccine for the UK has experienced manufacturing issues that have severely affected the availability of vaccine for the national immunisation programme. It is not known when supplies of UK licensed BCG vaccine will return to normal.

In 2016, PHE successfully secured an alternative supply of BCG vaccine from a different manufacturer (InterVax, Canada) which does not hold a UK Marketing Authorisation and is therefore supplied on an unlicensed basis. This vaccine has been used extensively around the world for many years, but a UK licence has never been applied for, as a consequence this product does not have a UK licence. This vaccine is the only suitable alternative vaccine currently available to the UK.

Should parents wait until BCG vaccine with a UK licence is available to immunise their babies?

No. Waiting for a licensed vaccine may mean that babies and children remain unprotected and at risk of severe forms of TB. InterVax BCG vaccine has been imported to the UK as an unlicensed product to ensure that babies and infants at highest risk of TB and with the greatest ability to benefit from the vaccine are protected.

The most effective use of BCG vaccination is to give it as soon as possible after birth to prevent infants at increased risk of exposure to TB, from becoming infected. These infants are at increased risk of developing severe disease, such as miliary tuberculosis and TB

meningitis. BCG is less effective at protecting against adult-type disease in older age groups.

Who should receive BCG vaccine?

During the recent period of constrained vaccine supply, PHE issued advice on the prioritisation and use of BCG vaccination in the UK. This was to ensure that babies and infants at highest risk of TB and with the greatest ability to benefit from the vaccine were protected.

Since the improvement in global supplies of BCG vaccine, PHE has advised that the offer of vaccination should be extended to all eligible groups (see below) ensuring that delivery of vaccine is optimised first for those in the highest priority group.

Groups eligible for BCG 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 living in areas of the UK where the annual incidence of TB is 40/100,000 or greater or 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.

Moderate priority

- D.** Previously unvaccinated, tuberculin-negative children aged from six to under 16 years of age 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, tuberculin tested and vaccinated if negative as per the **Green Book** section on tuberculin testing prior to BCG vaccination,
- E.** Previously unvaccinated tuberculin-negative individuals under 16 years of age who are contacts of cases of respiratory TB (following **NICE recommended contact management advice**).

F. Previously unvaccinated, tuberculin-negative individuals under 16 years of age who were born in or who have lived for a prolonged period (at least three months) in a country with an annual TB incidence of 40/100,000 or greater.

G. Previously unvaccinated, tuberculin-negative individuals under 16 years of age who are going to live or work with local people for more than three months in a country where the annual incidence of TB is 40/100,000 or greater.

Lowest priority

H. Individuals at occupational risk.

Use of BCG for occupational health purposes remains the lowest priority; however those at especially high risk of occupational exposure may require special consideration and should be assessed on an individual basis. Occupational health providers are able to order InterVax BCG vaccine through ImmForm.

What about babies and children who have missed BCG vaccine?

A significant cohort of children have missed out on their BCG vaccine and local NHS England teams have put plans in place to maximise the use of available vaccine and where possible catch up children who are still able to benefit. For specific information on local programme delivery and plans for catch-up please contact your NHS England Screening and Immunisation Team.

Parents should be reassured that the overall risk of TB in unvaccinated children in the UK is low, and that the main way to stop TB from spreading is to make sure that people with TB are diagnosed early and treated correctly.

What reaction is likely to occur after successful immunisation with InterVax BCG vaccine?

The usual reaction to successful BCG vaccination is induration at the injection site, followed by a local lesion which starts as a papule two or more weeks after vaccination. It may ulcerate and then slowly subside over several weeks or months, leaving a small, flat scar when it heals. It may also include enlargement of a regional lymph node (e.g. the axillary lymph nodes) to less than 1 cm.

Are there any other side effects?

Enlargement of the axillary lymph-nodes may occasionally develop after vaccination but spontaneous resolution usually occurs after a few months. In rare cases perforation and persistent suppuration can accompany the lymph-node enlargement and anti-tuberculosis

treatment may be indicated. Keloid and lupoid reactions may also occur at the site of injection.

Severe injection site reactions, large, local discharging ulcers, abscesses and keloid scarring are most commonly caused by faulty injection technique, excessive dosage or vaccinating individuals who are tuberculin positive.

Other adverse reactions to the vaccine include headache, fever and enlargement of a regional lymph node to greater than 1cm and which may ulcerate.

Allergic reactions (including anaphylactic reactions), more severe local reactions such as abscess formation, and disseminated BCG complications (such as osteitis or osteomyelitis) are rare.

Who has PHE consulted with over the importation of unlicensed BCG vaccine?

Before securing supplies of BCG vaccine without a UK marketing authorisation, PHE consulted with the Medicines and Healthcare Products Regulatory Agency (MHRA), the National Institute for Biological Standards and Control (NIBSC), the Joint Committee on Vaccination and Immunisation (JCVI) and the Department of Health (DH).

Unlicensed BCG vaccine is being imported into the UK in accordance with medicines legislation, which is permitted when there are shortages of a suitable licensed product. The MHRA has not objected to the importation of the InterVax vaccine.

PHE has also consulted with WHO and other European countries where the vaccine is in use.

Where does liability rest when prescribing and using InterVax BCG vaccine?

Liability for clinically appropriate prescribing and administration of InterVax BCG vaccine lies with the prescriber and immuniser respectively, as it would for any licensed product. For example, if the wrong dose was prescribed or administered, liability lies with the responsible healthcare professional.

Can I use a Patient Group Direction (PGD) to administer unlicensed BCG?

No. Medicines legislation states that PGDs can only be used for medicines that have a current UK licence.

How should InterVax BCG be prescribed?

Unlicensed BCG vaccine has to be individually prescribed using a Patient Specific Direction (PSD), a prescription or patient medicines administration chart. A PSD is the traditional written instruction, signed by a doctor, dentist, or non-medical prescriber for medicines to be supplied and/or administered to a named patient after the prescriber has assessed the patient on an individual basis. More information about PSDs can be found here:

<http://webarchive.nationalarchives.gov.uk/20141205150130/http://www.mhra.gov.uk/Howweregulate/Medicines/Availabilityprescribingsellingandsupplyingofmedicines/Frequentlyraisedissues/PatientSpecificDirections/index.htm>

Taking into account the practicalities of the requirement for prescribers to individually assess each patient, use of PSDs will need prior local agreement through local governance processes.

For how long will the unlicensed BCG be prescribed?

Guidance from MHRA states an unlicensed medicinal product should not be supplied where an available equivalent licensed medicinal product can meet the needs of the patient. Therefore, if a supply of a UK licensed BCG vaccine is available; the licensed product should always be used instead of the unlicensed BCG vaccine. However, PHE is only recommending that InterVax BCG is used until licensed BCG vaccine becomes available again.

Who can prescribe unlicensed medicines?

Any registered doctor, nurse, midwife or pharmacist independent prescriber can prescribe unlicensed medicinal products. Supplementary prescribers can prescribe unlicensed medicinal products where this is in accordance with an agreed clinical management plan.

Can a nurse/midwife supplementary prescriber prescribe unlicensed BCG vaccine?

Although supplementary prescribers can legally prescribe unlicensed medicines in accordance with a patient's clinical management plan (CMP), obtaining a PSD from an independent prescriber for BCG vaccine is likely to be less onerous than implementing a CMP particularly when dealing with a significant volume of patients in a routine immunisation clinic.

When seeking consent, what should I explain to the parents or carers about using InterVax BCG vaccine?

The responsibility that falls on healthcare professionals when prescribing an unlicensed medicine is greater than when prescribing a licensed medicine. It is good practice to give as much relevant information as parents or carers require.

As part of the normal consent process, you should give the parent, or those authorising immunisation on the individual's behalf, sufficient information about the proposed immunisation, including known serious or common adverse reactions, to enable them to make an informed decision.

You should explain the reasons for prescribing an unlicensed medicine. For example, there has been a global shortage of BCG vaccine and there is no licensed product currently available in the UK. Data from the manufacturer has been assessed and indicates satisfactory quality and safety and use of unlicensed BCG vaccine is currently the only way to offer immunisation against TB.

Further information for prescribers can be found here: <https://www.gov.uk/drug-safety-update/off-label-or-unlicensed-use-of-medicines-prescribers-responsibilities>

Depending on individual parental needs, two leaflets about the use of BCG vaccine in new babies are available. A general information leaflet on TB and the BCG vaccine is available here: <https://www.gov.uk/government/publications/tb-bcg-and-your-baby-leaflet>

A leaflet for parents explaining the use of unlicensed BCG vaccine is available here: <https://www.gov.uk/government/publications/unlicensed-bcg-vaccine-guide-for-parents-and-carers>

What training materials are available to staff administering InterVax BCG vaccine?

In addition to reading all of this factsheet, immunisers should refer to the slide set on the use of InterVax BCG vaccine and the advice sheet supplied with packs of the vaccine. The training slide set is available here: <https://www.gov.uk/government/publications/intervax-bcg-vaccine-training-slideset-for-healthcare-professionals>

Should I ask the parent or person with parental responsibility to give written consent or sign a waiver?

Consent must be obtained before starting any treatment or physical investigation or before

providing personal care for a patient. This includes the administration of all vaccines. There is no legal requirement for consent to immunisation to be in writing and a signature on a consent form is not conclusive proof that consent has been given. There is no requirement for patients or the person with parental responsibility, to sign a waiver to receive unlicensed BCG vaccine.

I am a nurse/midwife independent prescriber, where can I find more information from my regulator on prescribing unlicensed medicines?

The Nursing and Midwifery Council (NMC) circular linked below provides more information for nurse/midwife independent prescribers and the prescribing of unlicensed vaccines. Please note, this should be read in conjunction with the NMC Code and NMC Standards for Medicines Management, also linked below:

NMC circular on nurse/midwife independent prescribing:

https://www.nmc.org.uk/globalassets/sitedocuments/circulars/2010circulars/nmccircular04_2010.pdf

NMC code: <https://www.nmc.org.uk/standards/code/>

NMC Standards for Medicines Management: <https://www.nmc.org.uk/standards/additional-standards/standards-for-medicines-management/>

I am a doctor, where can I find more information from my regulator on prescribing unlicensed medicines?

The General Medical Council (GMC) has guidance for doctors here

<http://www.gmc-uk.org/guidance/28349.asp>

How is InterVax BCG vaccine presented?

InterVax BCG vaccine is a freeze-dried preparation in ampoules containing a maximum of 10 adult (or 20 infant) doses per ampoule, sealed under vacuum.

The ampoules containing the freeze dried BCG powder are presented in a box containing 20 ampoules, i.e. each box contains a maximum of 200 doses (or 400 doses for infants less than 12 months of age). The diluent is presented in another box containing 20 ampoules of sodium chloride 0.9%. Please note that although the product information suggests that the number of doses available from 1ml of reconstituted BCG vaccine is 20, this expresses the number of declared doses per ampoule and not the actual number of doses of reconstituted vaccine that can be extracted. In practice, experience from its use so far has shown that the maximum extractable number of doses of reconstituted vaccine is approximately 10 for infants less than 12 months of age.



Figure 1 InterVax packaging & ampoules

How should I store InterVax BCG vaccine?

The vaccine should be protected from light and stored in a fridge at a temperature between 2° and 8°C. More information about the storage and handling of vaccines can be found here: <https://www.gov.uk/government/publications/storage-distribution-and-disposal-of-vaccines-the-green-book-chapter-3>

How should I reconstitute InterVax BCG vaccine?

Clean your hands using soap and water or alcohol hand gel. Wear a pair of non-sterile disposable gloves.

Before reconstituting the vaccine, write the date and time on the side of the ampoule containing the freeze dried BCG powder.

The freeze dried powder preparation in the ampoule is sealed under vacuum so care is required when opening the ampoule to avoid the powder being accidentally expelled. Prior to use, the ampoule should be tapped gently so that the freeze dried powder falls to the bottom of the ampoule.

Special care should be taken when opening the ampoules and the square of plastic provided with the pack should be used to wrap around the ampoule, after which the neck can be broken off carefully to avoid escape of the dry powder. Each pack of 20 ampoules is routinely supplied with one plastic square. This should be retained for use in opening the 20 ampoules of freeze dried powder.

As a temporary measure, each pack of 20 ampoules of InterVax BCG will be supplied with additional plastic squares as a safeguard, to cover inadvertent disposal of the supplied single sheet. This temporary measure is in place to enable staff to become accustomed to using and preparing this vaccine. These additional squares should be **retained** if unused as future vaccine supplies are unlikely to come with additional plastic squares.

In the event that you do not have a plastic square to aid the safe opening of the ampoule

containing the freeze dried BCG powder, do NOT attempt to open it without a protective film. An alternative to the plastic square should be used, for example a film such as Parafilm (available via NHS Supply Chain) or any other similar product can be used.

Ensure good aseptic technique. Draw up the entire content of the diluent ampoule supplied by InterVax into a syringe using a long needle, PHE recommend you use a 21G needle. Reconstitute the vaccine by slowly and very gently adding the entire content of the syringe containing the diluent to the freeze dried powder. In **order to prevent aerosolisation** of the powder, the diluent is best added by angling the ampoule containing the freeze dried powder slightly, so that the diluent slowly trickles down the inside of the glass, into the powder. Once all the diluent has been added to the powder, mix by slowly drawing up and down in the syringe several times.

Two to three minutes later a homogeneous slightly opalescent colourless suspension should



appear. The vaccine powder should be completely dissolved in diluent. The reconstituted vaccine should be inspected for any particulate matter, if there is any the vaccine should be discarded.

Following reconstitution, remove and safely dispose of gloves and wash hands using soap and water (not alcohol hand gel).

Ideally, the reconstituted vaccine should be used immediately or within a short period of time. However, if not used immediately, the reconstituted vaccine should be stored away from light, at between 2° and 8°C and must be discarded after 6 hours. Routine storage at temperatures

outside this of this range is not supported by information provided by Intervax Ltd or by PHE guidance on the vaccine cold chain. Whilst this may not be normal practice, this is an exceptional circumstance for the use of this vaccine. Staff should consider the need to clearly label opened ampoules with a time of reconstitution label and to ensure time and date are recorded separately. To facilitate this, it may be considered appropriate to provide locally printed labels stating "Do not use six hours after reconstitution" or similar. Intervax Ltd have been unable to supply any data regarding the stability of reconstituted BCG vaccine stored in syringes prior to its administration.

Care should be taken when storing the ampoule containing the reconstituted vaccine to ensure it remains upright. A blood or test tube tray can be used for this purpose but is not absolutely necessary.

N.B. As an added precaution, it is recommended that healthcare workers who are severely immunocompromised, should not reconstitute or administer InterVax BCG vaccine (note this advice is specific to InterVax BCG only and not other live vaccines).

For details of regarding the immunocompromised, see pages 43 to 45 in the link below:
https://www.gov.uk/government/uploads/system/uploads/attachment_data/file/147824/Green-Book-Chapter-6-v2_0.pdf

Pregnant healthcare workers may reconstitute and administer the vaccine ensuring full compliance with the measures outlined above to prevent escape of the freeze dried powder. Care should be taken to avoid accidental self-administration through needlestick injury.

How do I administer InterVax BCG vaccine?

The vaccine should be administered through intradermal injection with use of a sterile 1.0 ml syringe fitted with a short beveled 26G 10mm (0.45mm x 10mm) needle for each individual. The needle should be primed before administering the intradermal injection. Other needles are not suitable and should not be used. For all age groups the recommended site of injection is into the lateral aspect of the left upper arm at the level of the insertion of the deltoid muscle. Only those trained in intradermal injection technique should administer BCG vaccine.

What dosage should be used?

Once reconstituted, the vaccination dose

- for infants less than one year of age is 0.05ml.
- adults and children over the age of one year, the dose is 0.1ml.

Please note that although the product information declares that the 1ml of BCG vaccine that can be reconstituted from each ampoule is enough to vaccinate 20 infants, experience from

its use so far has shown that, in practice the maximum number of doses that can be extracted is sufficient to vaccinate approximately 10 infants less than 12 months of age.

Can I administer InterVax BCG at the same time as other vaccines, including live ones?

To ensure timely protection InterVax BCG can be given at the same time or at any time before or after other vaccines such as DTaP/IPV+Hib and hepatitis B vaccines. Other vaccines to be given at the same time as Intervax BCG should not be given into the same arm. It is advisable not to give further vaccination in the arm used for BCG vaccination for 3 months because of the risk of regional lymphadenitis

BCG can be administered at the same time as other live vaccines including rotavirus, live attenuated influenza vaccine (LAIV), oral typhoid vaccine, yellow fever, varicella, zoster and MMR.

For further information, see this link: <https://www.gov.uk/government/publications/updated-recommendations-for-administering-more-than-1-live-vaccine>

How do I dispose of unused InterVax BCG vaccine and any used needles and syringes?

Unused vaccine along with used needles and syringes should be disposed of in a purple lidded (cytotoxic) sharps bin.

How should I optimise available stocks of BCG vaccine and reduce wastage?

There is currently sufficient stock of Intervax vaccine to offer vaccination to all eligible groups (see pages 3 and 4). However BCG vaccine availability continues to be monitored closely as future supply (licensed and unlicensed) remains uncertain.

As the ampoules containing reconstituted vaccine have a 6-hour shelf life after opening, local commissioners and providers should consider how best to optimise the use of the available BCG stock, in order to avoid any wastage.

It is important to ensure that the delivery of the neonatal programme is optimised to improve access for all eligible neonates, for example by immunising babies in maternity units prior to discharge. This may lead to an increase in wastage of doses in some areas. Specific plans will depend on local BCG programme delivery which varies across the country so please liaise with your NHS England Screening and Immunisation Team.

How should I record the administration of InterVax BCG vaccine?

Record the administration of InterVax BCG vaccine in the usual way in the clinical record, including name, dose, date and site of intradermal injection, batch number and expiry date. There is no legal requirement for a list of patients who received unlicensed BCG to be kept, however individual providers may choose to do so if they wish.

What product information is supplied with InterVax BCG vaccine?

The product information sheet supplied with the vaccine should be discarded. Instead please use the PHE supplied leaflets with InterVax BCG vaccine. One is for parents (similar to a Patient Information Leaflet) and one for healthcare workers (similar to a Summary of Product Characteristics).

Does InterVax BCG vaccine contain any animal products?

The BCG vaccine supplied by InterVax does not contain animal products. The medium for the production of BCG also does not contain animal products.

Where should I report adverse incidents?

As with any vaccine, suspected adverse reactions to InterVax BCG should be reported to the MHRA using the Yellow Card scheme. More information about the Yellow Card scheme can be found here: <https://yellowcard.mhra.gov.uk/>

There has been a spillage of either un-reconstituted or reconstituted BCG vaccine. What should I do?

Deal with the spillage promptly following local procedures for the management of medicines spillages. Universal standard precautions should be applied including wearing non-sterile gloves, apron and face-mask.

After removing and safely disposing of all PPE, wash hands using soap and water (not alcohol hand gel)

There has been an accidental exposure to the vaccine, e.g. needlestick injury or splash onto mucous membranes, what should I do?

In addition to following local procedures for the management of needle stick injury, refer to a TB specialist for assessment of risk and possible anti-TB medication.

First published: June 2016

Revised: March 2018

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Withdrawn October 2018