

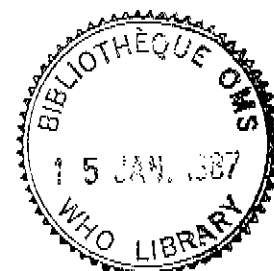
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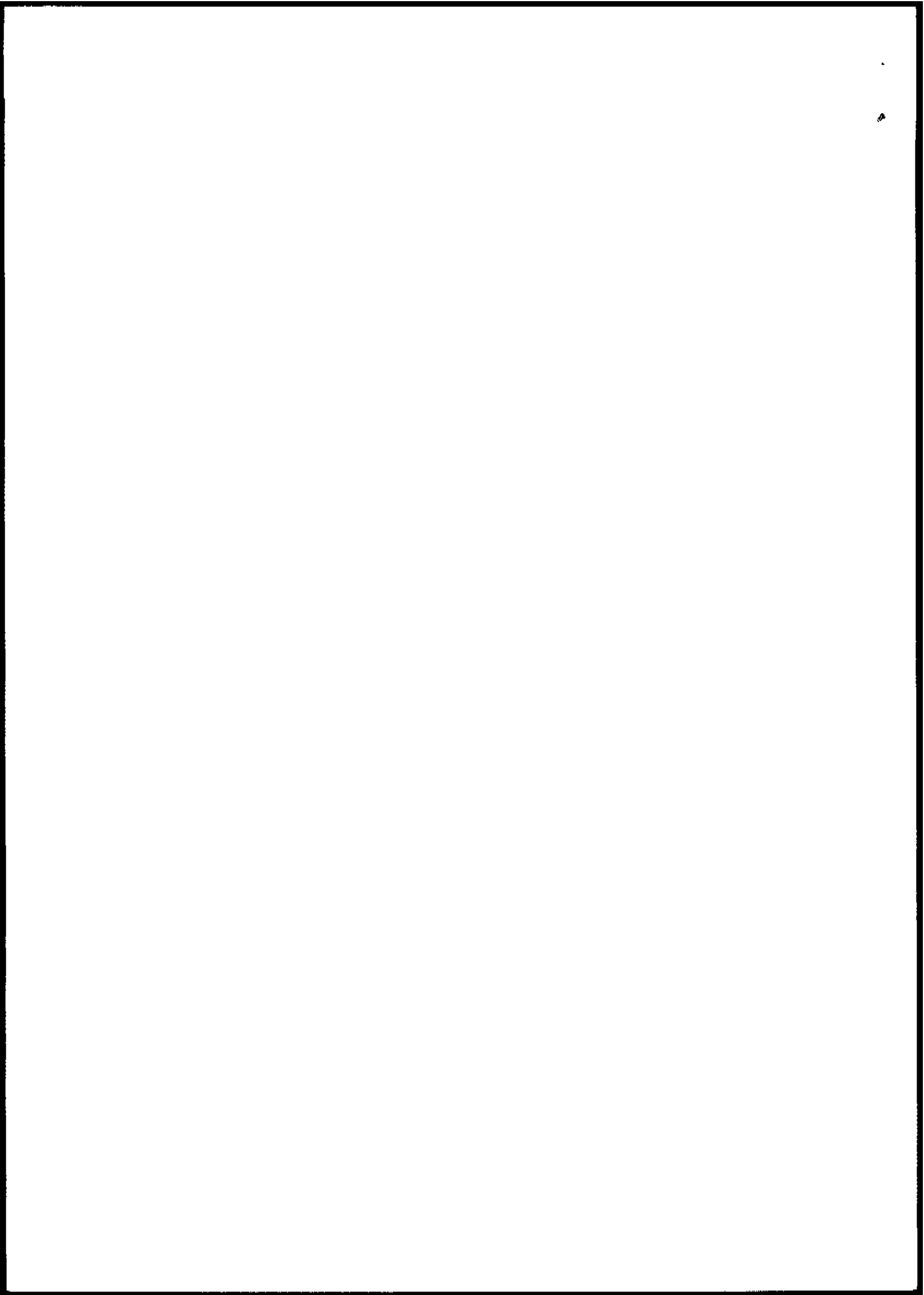
BCG VACCINATION OF THE NEWBORN

Rationale and guidelines for country programmes

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BCG VACCINATION OF THE NEWBORN

Rationale and guidelines for country programmes

Tuberculosis control programmes in developing countries rely on case-finding and domiciliary chemotherapy and on BCG vaccination. Case-finding followed by adequate treatment reduces not only human suffering but also transmission of tuberculosis in the community. But case-finding in developing countries is largely limited to microscopic examination of sputum from persons presenting with symptoms of pulmonary tuberculosis, and treatment is often not completed.

Children scarcely benefit from the current case-finding and treatment programmes, directly or indirectly. If they develop tuberculosis they rarely produce sputum and even if a sample can be obtained it is seldom positive on microscopy. On the other hand they are prone to developing serious acute forms, such as meningitis and miliary disease, which are often fatal, even when treated. Transmission to young children is almost always intrafamilial and frequently takes place before the source of infection is detected. The control of childhood tuberculosis therefore rests almost entirely on BCG vaccination, especially when systematic examination of child contacts is not feasible.

EFFICACY AND EFFECTIVENESS

The protective effect of BCG vaccination is easily demonstrated in animal models, but the efficacy of BCG vaccination in man could not be determined. Controlled field trials gave widely different results. Initially these differences were explained from the fact that the vaccines used differed in many aspects (strains, viability, dosage), but it appeared that also environmental and possibly other factors could play a role. The latest trial confirmed this. Although vaccines were used that had been selected because of their efficacy in experimental models, there was no protective effect at all against the adult type of pulmonary tuberculosis; the various types of childhood tuberculosis were not studied.

Since trials in children are expensive and difficult to carry out, not in the least because of ethical objections to having an unvaccinated control group, and many known and unknown variables are involved, it appeared totally impractical to solve the question of efficacy for BCG vaccine. Therefore, WHO, with financial support from UNICEF and several member states, initiated evaluation of the effectiveness of routine BCG vaccination programmes.

This evaluation is based on case-control and contact studies, which are far simpler than controlled trials because they are retrospective as regards the vaccinations and, for the case-control studies, also as regards case-finding. For a long time studies with a retrospective element were considered technically much inferior to controlled trials, mainly because of possible incomparability of study groups. In case-control studies this problem is solved to some extent; for the contact studies a method to deal with it was worked out.

So far five studies have been completed. All showed that BCG vaccination conferred protection against childhood tuberculosis. The level of protection varied from study to study and in each study it varied with the type of disease. Invariably protection was highest against the more serious types of disease. This observation confirms experimental evidence that BCG vaccination does not prevent infection but haemotogenous dissemination from the site of infection to other parts of the body.

One case control study, on meningitis alone, showed over 90% protection and another case-control study as well as a contact study showed similarly high levels against meningitis and miliary disease. In a further contact study serious forms were not observed (children were given treatment on the slightest suspicion) and a case-control study showed 80% protection against miliary disease but only 50% against meningitis. In all studies the effectiveness was relatively low as regards unilateral hilar and paratracheal lymphadenitis and primary complex.

Observations of the local BCG scars and of tuberculin sensitivity in the contact studies suggest that the children not always had received an adequate dose of BCG; unfortunately it was not possible technically to establish the relationship between the quality of the vaccinations and the protective effect: the scars were very small in almost all children and tuberculin sensitivity was barely higher than in non-vaccinated children.

That the quality of the vaccinations does play a role was demonstrated in a comparative trial of two vaccines. Children vaccinated with a vaccine produced by the Japan BCG Laboratory from the French strain had a significantly lower risk of developing tuberculosis than children vaccinated with Glaxo vaccine. On the other hand in the former there were complaints about lymphadenitis, but not in the latter. It appeared that children given the Glaxo vaccine who developed a scar were at a far lower risk than those who did not. Since there were no unvaccinated controls, however, the absolute levels of protection could not be determined.

PRACTICAL IMPLICATIONS

The results observed confirm that BCG vaccination has an important role to play in the control of childhood tuberculosis. But they also show that a varying proportion of the vaccinated children fail to become immunized. This proportion no doubt can be reduced by taking a number of precautions.

Transport and storage

Freeze-dried vaccines gradually lose their potency (viability). This loss strongly depends on the temperature at which the vaccine is kept. During refrigerated storage the vaccines are extremely stable, but at 37 °C a 50% loss in the number of culturable particles will occur within 20 - 60 days, depending on the vaccine. The deleterious effects are cumulative. Freeze-dried vaccines, therefore, should be kept in cold storage except for short periods carefully accounted for, e.g. during transport. The expiry date stamped on the pack is valid only on condition that the vaccine has been kept all the time at 2 - 8 °C.

Dosage

The response to BCG vaccination is dose-dependent. Since it has not been possible to determine a threshold dose for any vaccine, the rational procedure is to give the highest dose that is acceptable. Acceptability is determined by the local vaccination reaction (ulcer, scar) but in young children especially by the incidence of suppurative axillary lymphadenitis. The frequency of this unpleasant reaction is related linearly to the dosage, but varies with the kind of vaccine used. Experience has shown that the risk is low for vaccines from the Glaxo and Japan strains and much higher for vaccines prepared from the French and Danish strains. On the other hand the very occurrence of lymphadenitis forms part of the (artificial) primary complex and may be relevant

to induction of immunity. Vaccines that cause a high incidence of lymphadenitis, therefore, could be effective at a relatively low dosage. Each programme should therefore check that the dose of vaccine administered is appropriate for the vaccine used. Special caution is required when a particular vaccine is replaced with another. In practice switching vaccines is best avoided, also because often there are differences in physical characteristics that require special precautions during reconstitution. All complaints from country programmes about "outbreaks" of suppurative lymphadenitis in the last twenty years were connected with a change of vaccine.

Reconstitution

Some vaccines are in the form of a powder, others in the form of a cake in the ampoule. In the former case one must ensure that the vaccine is in the ampoule body and not in the neck when opening the ampoule. To prevent the vaccine powder from being blown out upon the implosion (the ampoules are sealed under vacuum) the neck of the ampoule is filed at its base and a plastic sheet is wrapped tightly around the filed site before the neck is broken off. The ampoule of reconstituting fluid is opened and, with a dry, sterile, 5 ml syringe and a long needle the amount of fluid required is taken from the ampoule. About half of this amount is transferred to the ampoule with the vaccine. After gently shaking the rest of the fluid is transferred. If the vaccine is in the form of a cake, no particular precautions are needed to prevent the vaccine from being blown out, but sufficient time should be allowed for obtaining a homogeneous suspension, which is facilitated by drawing the vaccine a few times into the syringe used for reconstitution. The reconstituted vaccine should be protected from light. It can be used for several hours but it should not be stored: vaccine remaining at the end of vaccination session should be discarded.

Administration

The programme should have taken an informed decision on the dose to be given and specified the volume to be injected. It now matters to see that each dose reaches entirely its strictly intradermal destination.

The recommended site for injection is half way down the lateral aspect of the arm, over the insertion of the deltoid muscle. In some populations vaccination nearer to the shoulder, and especially over the acromion, is associated with an increased risk of keloid formation. A clean skin need not be sterilized with ether or alcohol. Syringes and needles for BCG vaccination should be carefully washed and sterilized by steaming, boiling, or dry heat. Detergents and disinfectants should not be used; care should be taken to use distilled or demineralized water, to avoid calcium deposits. Before washing a fine wire should be passed through the needle to make sure it is not obstructed. The pistons should be taken out of the barrels and the piston rings inspected and replaced if damaged. The syringes are reassembled after sterilization when cooled off.

Before vaccination the needle is firmly fitted to the syringe with sturdy sterile forceps. The syringe is filled with the right amount of vaccine; it is held vertically towards the light to see that there is no air in it. If there are air bubbles it may be wise to empty the syringe into the ampoule and fill it again. A single bubble may be moved to the top, by tapping the barrel, and slowly expelled. If this is done care should be taken that no BCG is spilled on the hands and, especially, that no BCG is squirted in someone's eyes.

The upper arm of the child is firmly held with one hand, the thumb slightly stretching the skin of the injection site. The syringe is held by the barrel and the needle is inserted, bevel upwards, some 5 mm into the dermal tissue.

The thumb of the hand holding the arm may be put on the barrel to hold it in place. The vaccine is then injected very slowly so that it infiltrates the tissue. If this is not done the vaccine will ooze out again when the needle is withdrawn. If the vaccine is inadvertently injected under the skin a subcutaneous abscess will develop which may leave an ugly retracted scar. The injection should leave a wheal of some 5 - 8 mm with an orange peel aspect. If it does not, and the entire dose has been expelled from the syringe, the injection has not been intradermally. In that case the injection should not be repeated. The vaccinator should therefore watch for the appearance of the characteristic wheal during the injection, but he should read the exact dose from the scale of the syringe.

Age for vaccination

The newborn not only are more likely to develop suppurative lymphadenitis than older children, they also show a diminished response in terms of post-vaccination tuberculin sensitivity. Yet, vaccination at birth is highly advisable. In most countries this is a unique opportunity to reach the children and thus to attain a high vaccination coverage early in life. Furthermore, a child not only may become infected because someone in the family develops infectious tuberculosis, it also may occur that an undetected source of infection already exists in the family when the child is born. In this case even a short delay might result in vaccination coming after infection, i.e. too late.

Reactions and complications

BCG vaccination normally produces a local skin lesion, usually with ulceration, which heals spontaneously in 2 - 3 months. Abnormal reactions are rare. If they are observed frequently they probably are due to a faulty technique. Even large local lesions are best left untreated; secondary infections at the site of injection are most unlikely. It has been suggested that in extreme cases systemic treatment with erythromycin (daily, up to one month) is helpful.

Axillary or cervical lymphadenitis will be observed in a small proportion of the vaccinated infants. It will heal spontaneously and it is best not to treat the lesion if it remains unadherent to the skin. An adherent or fistulated lymph gland, however, may be drained and an anti-tuberculosis drug may be instilled locally. Systemic treatment with anti-tuberculosis drugs is ineffective.

Keloid is difficult to treat. Simple surgical removal is likely to make it worse. A combination of surgery, irradiation, and drug treatment may be effective, but should be undertaken by a specialized practitioner.

Rare complications include lupus vulgaris, erythema nodosum, iritis, osteomyelitis and generalized progressive BCG-itis. The latter complication, which is often fatal, has been observed in cases of severe immunodeficiency; systemic antituberculosis treatment is indicated.

Contraindications

Acquired immunodeficiency syndrome and known hypogammaglobulinaemia are absolute contraindications to BCG vaccination. Relative contraindications are treatment with corticoids and with cytostatics, and serious skin disorders. In cases of prematurity and neonatal disorders vaccination is delayed until the child leaves the maternity clinic. Minor illnesses such as mild respiratory infections and diarrhoea should not be considered as contraindications.

Monitoring and evaluation

The easiest way to check whether a child has been vaccinated is to see whether it has a lesion or scar. A small percentage of children do not develop a scar, most often because the dose was insufficient. It is therefore practical to verify, at any occasion that may present itself, whether a child has a BCG lesion or scar and to vaccinate if not. BCG vaccination can be given safely at the same time as any other vaccination.

The quality of the administration can be monitored by measuring the scar sizes in groups of some 100 children known to have been vaccinated. The distribution of the sizes, when entered into a histogram, should appear normal (in the statistical sense) and have a small variance and an appropriate mean. If this is observed it may be assumed that the vaccinations were adequate as far as the injection technique is concerned.

To obtain a measure of the quality of the entire vaccination procedure, groups of some 100 children may be given a tuberculin test 3 - 5 months after vaccination. If the distribution of tuberculin reactions shows a normal distribution and the variance and mean are characteristic for the vaccine used (e.g. as established by an expert team), the entire procedure, from transport to injection, has been adequate.

It is difficult to monitor the occurrence of suppurative lymphadenitis, since this would require multiple examinations of a large group of infants. A practical alternative is to record the number of cases presented (as well as the number of vaccinations) at certain "sentinel" maternity clinics.

The actual effectiveness of the vaccinations may be evaluated by carrying out follow-up studies in child contacts of newly detected cases, or case-control studies. The former have the advantage of showing the incidence of childhood tuberculosis, the latter that of showing the spectrum of clinical forms. Systematic recording of the vaccination status of diagnosed cases, possibly in certain "sentinel" hospitals, is highly indicated in this connection.

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