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FREEZE-DRIED BCG VACCINE

At the thirteenth session of the WHO Regional Committee for South-East Asia, the question of freeze-dried BCG vaccine for use in countries in the South-East Asia Region was discussed, and the Regional Committee adopted a resolution requesting the Regional Director to urge the Director-General to ensure that WHO's study of freeze-dried vaccine be completed as quickly as possible and, further, to find ways and means of assisting the governments to obtain it at a reasonable cost.

The Director-General has been consulted in this matter, and the position of WHO's investigations is described in the attached memorandum. There is no question but that freeze-dried BCG vaccine offers many advantages for use in the countries of South-East Asia, and it is hoped that very shortly it will be possible for assistance to be given towards its procurement for use in national BCG campaigns.

Introduction

Production of freeze-dried BCG vaccine on an industrial scale has now been established in several countries, and freeze-dried BCG vaccine is being more and more widely used. WHO has long taken an active interest in this field, realizing that the introduction of freeze-dried vaccine in BCG vaccination programmes would be a step forward in several respects. One advantage of the freeze-dried vaccine is that it can be subjected to laboratory control tests of innocuity, sterility and potency while it is still in storage, and unsuitable batches can be rejected before use. Also because of its superior keeping qualities, the freeze-dried product needs to be supplied far less frequently than liquid vaccine - a considerable advantage, for instance, in countries with integrated BCG vaccination schemes where the vaccine has to be distributed to a large number of often remote health centres, each with a relatively low consumption. Most important, however, is that at least one freeze-dried BCG product appears to possess considerable resistance against heat. The use of a heat-stable vaccine would obviate the need for constant refrigeration, which is one of the more serious difficulties in BCG programmes, particularly in the tropics.

In view of the great potential importance of freeze-dried BCG vaccine, WHO, five years ago, started a long series of studies in human beings of the allergenic potency of such vaccines and especially of the duration of the post-vaccination allergy produced. In addition, the Organization has sponsored several experimental studies which are being conducted in co-operation with laboratories in Czechoslovakia, Denmark, France, Japan, Poland and the United Kingdom. This work of WHO has been concerned mainly with the Japanese freeze-dried glutamate BCG vaccine, which seemed most promising for use in tropical countries because of its stability at high temperatures. At the same time, however, numerous studies on other freeze-dried vaccine products have been undertaken, mainly under the aegis of national research institutions, and much experience with the various products has accumulated. A short review of the present status of freeze-dried BCG vaccine is given.

Present Knowledge

The most widely used freeze-dried BCG products are manufactured in Japan, France, the USSR and the United Kingdom, and for the sake of brevity the present review has been limited to these four products. However, freeze-dried BCG vaccines are also being produced in many other countries, e.g. Canada, the Federal Republic of Germany and Poland.

As regards the freeze-dried glutamate vaccine produced in Japan, it was shown in a preliminary study by WHO that this product had a satisfactory allergenic potency not only after cold storage but also after storage up to one month at 37°C, and even at 42°C. One month's exposure to 50°C, however, markedly reduced its allergenic potency. In a second study, recently completed, the allergy produced by this vaccine after storage at 2.4°C was found to remain constant over a period of five

years. Another finding was that the vaccine appeared to produce as much or more allergy for the same size of local lesion at the vaccination site as Danish liquid vaccine. Further studies are under way to determine the duration of the allergy induced by glutamate vaccine after several weeks' storage at high temperatures. In these studies, which are expected to be completed by the beginning of 1964, the conditions of reconstitution of the glutamate vaccine have been varied, as have the conditions of storage after reconstitution.

Laboratory studies conducted under the auspices of WHO have revealed that the glutamate vaccine has a remarkably high viable count as compared with different liquid vaccines and that the viable count is only moderately reduced after several weeks', and even after two to four months', storage at 37°C.

Mice protection tests carried out with large doses of vaccine at the Tuberculosis Research Institute, Prague, showed a clear and comparable immunizing effect for the glutamate vaccine (0.25 mg) and Danish liquid vaccine (0.375 mg). The results of immunization in mice obtained at the same time in the International Children's Centre in Paris, however, gave an indication - though far from conclusive - that glutamate vaccine in small doses (0.002 - 0.0002 mg) is less protective than the Danish liquid vaccine. Further laboratory studies of the immunogenic effect of the glutamate vaccine are under way.

Controlled trials of the immunizing effect of this vaccine in humans have not been reported so far. The corresponding liquid vaccine prepared from the same sub-strain, however, has been subject to several trials designed to assess its protective value. Thus, in a controlled trial in Japanese railroad workers in 1940-1943, vaccination with the liquid product was found to reduce the incidence of tuberculosis by about 70 per cent.

In France a freeze-dried glucose vaccine is produced by the Institut Pasteur, Paris. According to results from a long-term comparative study in Danish school-children, this vaccine produces relatively strong and durable allergy. No marked waning of the post-vaccination allergy was observed over a period of five years. Controlled studies conducted by the International Children's Centre indicate that the vaccine can be stored at refrigeration temperature for up to one year without any marked loss of allergenic potency (as measured by tuberculin retesting twelve months after vaccination) or lesion-producing capacity. These studies have further shown that the vaccine can be exposed to 30°C for one month without any substantial reduction in its allergenic potency or local activity. Limited field trials carried out by WHO also suggest that the freeze-dried Pasteur vaccine can tolerate one month's exposure to 30°C. Similar exposure to higher temperatures, for instance 42°C, was, however, found to cause a substantial reduction in its potency. No controlled trials of the immunizing effect of this product in humans have been reported. However, the corresponding liquid vaccine prepared from the same sub-strain has been shown, in a long-term trial in school-children, including control groups, to provide protection against primary and post-primary tuberculosis.

In the USSR, freeze-dried BCG vaccine has been used exclusively since 1952. This vaccine is prepared with 10 per cent saccharose and one per cent gelatin. It is issued for vaccination by scarification, oral and intradermal routes. It is reported that it can be stored for one year if kept at 4-8°C and protected from light. It has been found in several studies to show good allergenic potency in humans and a sufficient immunizing effect in guinea-pigs.

In the United Kingdom, a freeze-dried dextran-glucose BCG vaccine is produced by the Glaxo Laboratories Ltd. In a controlled study in school-children conducted by the Medical Research Council's Committee on the Standardization of Freeze-Dried BCG Vaccines, the allergenic potency of this vaccine has been compared with that of Danish liquid vaccine. Batches stored for ten to nineteen months at refrigeration temperature produced, on the average, slightly weaker allergy than the Danish liquid vaccine, and slightly smaller vaccinal lesion. There was no waning of the allergy during the twelve months' post-vaccination follow-up. The effect of exposure to room temperature (averaging 23°C) for one to twelve months was also investigated. Two of the four batches included showed a definite reduction in allergenic potency (after twelve and seven months at room temperature respectively). Storage at room temperature for periods exceeding one week is not recommended. The study did not include vaccinations with batches exposed to temperatures exceeding 23°C. However, laboratory tests (viable counts) included in the study suggest that the vaccine is extremely unstable at 37°C. In its second report, the Medical Research Council's Committee on the Standardization of Freeze-Dried BCG Vaccine concluded that: "It is evident from the results of this and the previous investigation that the British freeze-dried BCG vaccine may be regarded as satisfactory for use as a successful prophylactic agent against tuberculosis, since it was shown to produce, in strictly controlled trials in tuberculin-negative adolescent children, a high degree of tuberculin sensitivity which developed at a similar rate and was maintained to the same extent as that produced by the Danish liquid vaccine".

It should be added that the British freeze-dried vaccine is prepared from the same sub-strain as the Danish liquid vaccine, which has been shown, in a carefully controlled trial in school-children, to confer substantial protection against the development of tuberculous disease.

Conclusions

At present, a heat stable freeze-dried vaccine would seem to recommend itself for use in BCG programmes in areas where the fragile liquid vaccine, because of adverse storage conditions, is likely to suffer an appreciable reduction in viability before use. Such adverse storage conditions may obtain in countries with a hot climate when facilities for refrigeration of the vaccine are limited. In such cases the liquid vaccine is often likely to be inferior to the glutamate vaccine in respect of its content of undamaged live organisms.

Under good conditions of transport and storage, permitting constant refrigeration and frequent supplies, there is much to be said for the liquid vaccine. When fresh, it tends to contain a far higher proportion of live organisms than do the freeze-dried preparations. Also, liquid vaccine of reasonable quality is easier and cheaper to produce. Its potency cannot be investigated thoroughly before use as can that of freeze-dried vaccine; however, a continuous laboratory and field assessment of the batches used will permit the detection of possible defects in the vaccine. As such defects usually are due to recurring technical deficiencies in the production laboratory, it is generally possible, by remedying these deficiencies, eventually to obtain a liquid vaccine of fairly uniform quality. Another consideration is that liquid vaccine does not require reconstitution before use. Although the reconstitution of freeze-dried vaccine is a reasonably simple procedure, which can be carried out by any intelligent and conscientious person, it may represent a source of unsatisfactory vaccination results if sufficient care is not taken.

To summarize, the use of freeze-dried BCG vaccine of satisfactory biological activity is recommended where the liquid vaccine is likely to suffer appreciable reduction in viability due to adverse storage and transport conditions, especially in a hot climate. As regards the provision of freeze-dried BCG vaccine for use in WHO-assisted BCG programmes, it is not recommended that a large number of laboratories be encouraged to produce freeze-dried vaccine. As shown by long experience, not all BCG laboratories have been able to produce a liquid vaccine of satisfactory and reasonably uniform quality; the large-scale production of a freeze-dried vaccine fulfilling these requirements is far more difficult. Only relatively few laboratories have succeeded in this undertaking and only after several years' intensive effort. Governments wanting to introduce freeze-dried vaccine would be well advised, therefore, to obtain it from one of the centres that have mastered the problems of mass producing freeze-dried vaccine of high and uniform allergenic potency. At the present stage, it cannot be considered that any one produce is superior to all others. However, a freeze-dried product of proved heat stability, such as the glutamate BCG vaccine, would seem most suitable in that it will meet the problem of improper transport and storage, which is one of the most serious obstacles in internationally-assisted BCG programmes.