Current Practice

CHILD CARE IN GENERAL PRACTICE

Immunization in General Practice

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Immunization programmes differ in each country according to the prevalence and severity of each infection. Every practitioner concerned with immunization regimes should study current recommendations. Details of international immunization regimes are published by W.H.O. (1961) and those for Great Britain by the Ministry of Health (1963). The subject is also discussed by individual authorities (for example, Parish and Cannon, 1962; Symposium on Immunology, 1963). In Great Britain widespread immunization against poliomyelitis, diphtheria, tetanus, pertussis, and smallpox is carried out in early childhood. B.C.G. inoculation is sometimes carried out in the newborn period to protect children of tuberculous families, but is more usually deferred until later childhood.

Useful measures in the preparation of vaccines include the mixing of several antigens in a combined prophylactic and the incorporation of "mineral carriers" such as aluminium phosphate. They allow a course of immunization to be completed in fewer attendances and improve antibody response. However, it is important to review the safety of these two measures which in 1956 were suspected of predisposing to "provocation poliomyelitis." More recently the Ministry of Health (1962) considered that it was reasonable to assume that poliovaccine given before or with other prophylactics would diminish the risk of this complication. Moreover as control of poliomyelitis has improved so much in recent years the risk has come to be regarded as very small indeed. Combined and alum-precipitated vaccines are now widely accepted. The administration of oral poliovaccine and subcutaneous triple prophylactic (DTP/Vac) simultaneously is not yet accepted officially, but it has been shown to be effective and reduces immunization attendances considerably (see Table).

Regular re-evaluation of the safety and efficacy of all vaccines is essential, as none is entirely without risk of complications. General contraindications to any immunization procedure include intercurrent illness, and—particularly in the case of live-virus vaccines—convalescence from specific fevers, concurrent steroid therapy, or the first trimester of pregnancy. If any doubt exists about the safety of an individual procedure consultation with the medical officer of health or with the consultant paediatrician will usually provide a solution. Specific contraindications are described under individual diseases in this short review.

Poliomyelitis

Live attenuated Sabin poliovaccine (OPV), which is now recommended and issued officially in Great Britain (Ministry of Health, 1962), gives effective immunity against all three virus types from the age of 3 months onwards. This is achieved by three feeds of a trivalent OPV of approximately 0.1 ml. each at

four- to eight-week intervals. "Gut immunity" ensues within two or three weeks and produces resistance of long duration to intestinal invasion by virulent poliovirus. If trivalent OPV is given in infancy, a further dose can be given concurrently with other measures during the second year of life and also at school entry. A child who has been fully immunized with Salk vaccine can have his immunity reinforced with a single dose of trivalent OPV, but a full course of three doses is prudent when OPV follows an incomplete course of Salk vaccine.

Gut infection with OPV may produce additional beneficial effects. The distribution of vaccine virus to susceptible contacts by vaccinees may help to eliminate the wild poliovirus from the community. In addition, this may be a useful measure in times of epidemics in limiting the spread of wild poliovirus.

Specific contraindications to oral poliovaccine are few. It is considered inadvisable to vaccinate patients who have diarrhoea, since this may be a manifestation of infection with other enteroviruses which may interfere with successful vaccination.

World-wide experience of OPV has shown complications to be remarkably few. Very rarely, vaccine-associated paralytic disease has been reported after administration of Type III monovalent vaccine in the U.S.A. and Canada (*Brit. med. J.*, 1964a). The incidence has been assessed as less than one case per million vaccinees. In England and Wales the incidence of paralytic disease reported after trivalent OPV has been no greater than would be expected from coincidence.

Inactivated poliovaccine (Salk) injected in two doses at monthly intervals with a third dose seven to 12 months later is a satisfactory alternative method for polio vaccination. However, it suffers from the disadvantage that, though it provides protection against paralysis, it does not usually prevent gut infection. Salk vaccine may be incorporated into DTP/Vac as "quadruple" prophylactic. This may be given in three doses at intervals of four to six weeks from the third month of life onwards, with a reinforcing dose at 15 months of age.

Diphtheria

In practice, diphtheria immunization is usually given in the form of a combined vaccine with pertussis and tetanus antigens. The weak diphtheria formol-toxoid (Dip/Vac/FT), which is unsuitable for primary immunization by itself (Medical Research Council Committee on Diphtheria Toxoid, 1962), can thus be incorporated in a triple vaccine (DTP/Vac) in which *B. pertussis* organisms reinforce the effect of toxoids. This is given in three doses at monthly intervals from 2 months, with a reinforcing dose in the second year of life. For further reinforcing doses, at school entry and at five-year intervals thereafter, a fluid toxoid (Dip/Vac/FT) is effective, either alone or in combination with tetanus toxoid (DT/Vac). It is sometimes desirable in individual cases to give diphtheria

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antigen without the other components. For primary immunization this is best achieved by giving purified toxoid aluminium phosphate (Dip/Vac/PTAP) in two doses at monthly intervals with a third dose six to 12 months later. Usually it is more usefully combined with tetanus toxoid as in adsorbed diphtheria-tetanus vaccine (DT/Vac/PTAH). This vaccine is indicated for infants in whom pertussis vaccine is unnecessary or contra-indicated, and in older children for primary immunization. In the latter, a preliminary Schick test will reveal those at risk of severe reactions. Such children may be given Toxoid Antitoxin Floccules (Dip/Vac/TAF) in three doses spaced four to six weeks apart. However, this prophylactic must be used cautiously since it contains horse serum.

Pertussis

Pertussis vaccination can reduce the incidence of the disease by 80%. In Britain vaccination is most needed in early infancy and childhood, when encephalopathy, pulmonary sequelae, and fatalities are most likely to occur. It is sometimes considered justified in older children in households where there are younger and unvaccinated infants at risk who cannot themselves be vaccinated because of contraindications. In some developing countries pertussis carries high morbidity and fatality rates throughout childhood. In these communities vaccination is clearly desirable in all susceptible children. Three doses of 20,000 million killed *B. pertussis* organisms may be administered at intervals of four to six weeks. Usually this prophylactic is incorporated in DTP/Vac (see Schedule P in Table).

The most serious complication of pertussis vaccination is true encephalopathy. This should be distinguished from the occasional febrile convulsion. This complication was not encountered among 50,000 vaccinees in an M.R.C. trial, (Medical Research Council Whooping Cough Immunization Committee, 1959), and was estimated by W.H.O. (1961) as occurring in less than one in a million cases. Nevertheless, until a controlled investigation has been carried out strict caution should be observed in giving pertussis vaccine. It is contraindicated in children with brain damage or a history of convulsions, in those who have had a systemic reaction to a previous pertussis immunization, and perhaps also in those with a history of infantile eczema or asthma.

Tetanus

Active immunization should be universal, especially as the highly effective tetanus toxoid can easily be combined with other antigens in childhood. The use of tetanus antitoxin (ATS) is unsatisfactory and may be dangerous—first, because it is frequently not given after trivial injuries which may, however, lead to the disease, and, secondly, because it may produce dangerous hypersensitivity reactions in certain individuals.

Subsequent doses of ATS may be rapidly eliminated, so that it becomes less efficient when used more than once. Hyperimmune antitetanus human gamma-globulin may be a definite improvement on ATS, but it is still not generally available.

In practice, tetanus toxoid is usually given as part of DTP/Vac (see Schedule P). Protection may be assumed to last three to five years after the primary course or a reinforcing dose. Separate immunization with plain fluid toxoid (Tet/Vac) may be given in two intramuscular injections, at six-week intervals, followed by a third dose 12 months later; reinforcing doses should be given five and 10 years later. An alternative and slightly stronger preparation is adsorbed tetanus toxoid (Tet/Vac/PTAH), which may be administered in the same way. This preparation is indicated when combined active-passive tetanus immunization is given after a wound. Adsorbed diphtheria-tetanus toxoid (DT/Vac/PTAH) is indicated for primary immunization against these two diseases, especially in older children who have already been immunized against whooping cough.

The procedure after exposure to a risk of tetanus from a cut or wound differs for *immune* and *non-immune* subjects. It is important, therefore, that an accurate record of previous active immunization should be readily available. *Immune* subjects need receive only a reinforcing dose of tetanus toxoid (Tet/Vac), except where the wound is deep, heavily contaminated, or long-standing (over three days). Under these conditions the administration of a concurrent dose of antitoxin (ATS) should be considered. A *non-immune* person is usually given tetanus antitoxin 1,500 units, preferably with a first dose of active immunization of Tet/Vac/PTAH. The active course is completed six weeks later. The strict medico-legal obligation for prophylactic antitoxin is discussed in a recent statement from the Ministry of Health (1964). It is apparent that the danger of serum reactions allows a greater degree of latitude for the individual practitioner in deciding whether antitoxin should be given. A preliminary subcutaneous test dose of 0.2 ml. of ATS—or 0.02 ml. with a history of asthma or other allergy—may allow warning of reaction, such as anaphylaxis, within 10 minutes of administration. If a general reaction occurs, epinephrine 1/1,000 subcutaneously should be given at once, and no further serum administered.

Smallpox

In Great Britain routine smallpox vaccination is not compulsory and has recently come under criticism in view of the rarity of the disease and the possibility of severe reactions (*Brit. med. J.*, 1964b). However, it still has a place in the immunization programme, because it diminishes the hazards of primary vaccination later in life and provides a reservoir of immunity which may limit the spread of smallpox during epidemics. The present modified variola virus-vaccine, treated with glycerol

Immunization Regimes

Ministry of Health Schedule P (Modified)				Recent Unofficial Modifications A and B.					
Age	Visit	Vaccine	Interval (Wks.)	Age	Visit	A		B	
						Vaccine	Interval (Wks.)	Vaccine	Interval (Wks.)
1-6 months	1	DTP/Vac*	4-6	2-6 months	1	DTP/Vac + OPV	4-6	Quadruple†	4-6
	2	DTP/Vac	4-6		2	DTP/Vac + OPV	4-6	Quadruple	4-6
7-11 months	3	DTP/Vac			3	DTP/Vac + OPV		Quadruple	
	4	OPV†	4-8						
	5	OPV	4-8						
	6	OPV							
18-21 months		Diphtheria, tetanus, pertussis (DTP/Vac)							
School entry		Smallpox vaccination during the first two years, preferably in the second year							
8-12 years		Diphtheria and tetanus (DT/Vac) + OPV							
Over 12 years		Diphtheria and tetanus (DT/Vac) + OPV							
		Smallpox re-vaccination							
		B.C.G.							

* DTP/Vac = diphtheria, tetanus, pertussis vaccine;

† OPV = oral poliovaccine;

‡ Quadruple = diphtheria, tetanus, pertussis, polio (killed) vaccine.

and phenol, carries a small though definite risk of producing generalized vaccinia or vaccinal encephalopathy. Wynne-Griffith (1960) has studied the reported cases of post-vaccinal encephalopathy and of generalized vaccinia occurring after primary vaccination in England and Wales between 1951 and 1957. The incidence was highest during the first year of life (15.8 per million with a mortality of 8.7 per million), lowest in the age group 1 to 4 years (incidence 2.1 per million, no deaths), and rose again over 15 years of age (28.7 per million, deaths 2.9 per million). A similar pattern was evident for generalized vaccinia. Primary vaccination is therefore best postponed to the second year of life. Contraindications include active infantile eczema (either in the vaccinee or in any household contact), hypogammaglobulinaemia, concurrent steroid therapy, and pregnancy.

After primary vaccination in early childhood revaccination can be given conveniently at 8 to 10 years of age at school. However, for those who are in occupations exposed to risk it should be repeated every one to three years, depending on the degree of risk. Apart from ensuring continued protection, revaccination at short intervals carries a lower risk of severe reactions than revaccination at long intervals, which has the same risk as primary vaccination.

In times of epidemic, vaccination or revaccination is urgently indicated for primary, secondary, or tertiary contacts within two or three days of exposure. Hyperimmune anti-vaccinal gamma-globulin should be given concurrently in the other arm where contraindications to vaccination would exist in non-epidemic times. Widespread vaccination of a population during a limited smallpox epidemic should not be undertaken lightly since more harm than good may result from neurological and other complications.

Tuberculosis

In communities where tuberculosis is well controlled, such as the United Kingdom, only certain groups of the population need be vaccinated. These include tuberculin-negative school-children over the age of 12, students, hospital personnel, and those who will be in contact with known cases of tuberculosis at all ages. B.C.G. vaccination of newborn infants is at present confined to tuberculous households, but widespread vaccination of the newborn is thought desirable by some.

The vaccine contains a non-virulent strain of attenuated *Mycobacterium tuberculosis* and is given intradermally to tuberculin-negative susceptible individuals. The papule which follows three to six weeks later is accompanied by tuberculin conversion. Protection at an 80% level lasts for about five to seven years. Rare local reactions, such as abscesses or glandular involvement, respond to anti-tuberculosis drugs.

Measles

Killed and living attenuated measles vaccines have been prepared, but are still under trial. The justification for protection against measles in economically advanced countries like Britain lies in the high complication rate of the disease during childhood. Widespread vaccination is needed urgently in developing areas such as certain parts of Africa, where the mortality is still high.

Pyrexia or rash are still occasional complications of an otherwise effective regime of a single intramuscular dose of attenuated vaccine, given from 9 months onwards. Measures to reduce reactions include further attenuation, simultaneous administration of gamma-globulin, or the preliminary use of two doses of killed vaccine.

A single dose of formalin-inactivated saline vaccine can give protection against types A and B and Asian virus. The short duration (three to six months) of the immunity it confers limits its usefulness to "at risk" cases, especially those with chronic lung or heart disease.

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Typhoid and Paratyphoid Fevers

Vaccination for those who travel to countries at risk can be achieved intradermally with two doses at monthly intervals of heat-killed, phenol-preserved TAB vaccine; a third dose is indicated six to 12 months later. For older children and adults tetanus toxoid can be incorporated with TAB/Vac. Transient local and general reactions must be anticipated.

Yellow Fever

A single injection of living attenuated vaccine is obligatory for those entering or leaving areas where the infection is endemic. It is contraindicated under 9 months of age, because of the occasional cases of encephalopathy. A list is available of centres where yellow-fever vaccination is carried out (Ministry of Health and Department of Health for Scotland, 1960). It should not be performed for four days before, or 21 days after, a smallpox vaccination.

Rubella

At present there is no effective prophylactic for rubella embryopathy, but the recent isolation of rubella virus in tissue culture makes the preparation of a vaccine feasible in the future.

Schedule of Immunization

Any immunization schedule must offer the highest possible protection against each disease before the age of greatest risk, a low-reaction rate, and administrative simplicity with the fewest number of visits and maximal acceptance rate. It is desirable to complete all primary immunization against diphtheria, pertussis, and tetanus within the first six months of life. Ideally, polio immunization should be performed at the same time. However, the youngest age for establishing effective primary immunity depends mainly on the persistence of inherited maternal antibody. High levels may blanket active immunization in the early months of life, particularly when weak antigens are used, such as plain vaccines or fluid toxoids. Plain DTP/Vac can be started at 1 or 2 months of age, as pertussis organisms enhance the antigenic effect of fluid diphtheria toxoid. However, a reinforcing dose should be given during the second year of life. This is the basis of the modified Schedule P recommended by the Ministry of Health (see Table), in which three doses of OPV given between 7 and 11 months of age follow the primary course of DTP/Vac. Six attendances are necessary in the first year of life. Attendances can be cut to three if the OPV is given simultaneously with the DTP/Vac (Butler *et al.*, 1964). A further alternative consists of three doses of quadruple prophylactic at four- to six-week intervals, starting after 2 months of age. There is some evidence that insufficient lasting active immunity may be produced before 6 months of age, so an alternative immunization scheme (Schedule Q modified, Ministry of Health, 1963) is also recognized officially. By the age of 6 months, nearly all inherited antibodies should have disappeared and any immaturity of antibody response may be more easily overcome. In this schedule OPV at 6 to 10 months in three doses is followed by two injections of DTP/Vac between 11 and 13 months. The disadvantage of this procedure is that it is of no value in reducing the peak mortality or morbidity of pertussis, which occurs in the first year of life.

There is almost complete agreement about procedures after the age of 1 year (see Table). Thus smallpox vaccination is recommended during the second year of life. It is recommended that DTP/Vac should not be given during the two weeks before, or three weeks after, smallpox vaccination. In practice, both procedures are often carried out simultaneously without any increase in the rates of reactions. Some prefer also

to give a reinforcing dose of OPV during the second year, but it is probably safe to leave this until school entry at 5 years, when a reinforcing dose of DT/Vac or DT/Vac/PTAH can be given. At 8 to 12 years the latter is repeated and smallpox revaccination is also undertaken. The schedule is completed with the administration of B.C.G. to tuberculin-negative school children over 12 years of age.

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TO-DAY'S DRUGS

Deoxyribonuclease, Chymotrypsin, and Amylase

In "To-day's Drugs" last week (p. 775) an account was given of fibrinolytic enzymes suitable for intravascular use in the treatment of thrombosis and embolism. The present article presents an account of a heterogeneous group of enzyme preparations which are commercially available for the treatment of thick purulent exudates, and as anti-inflammatory agents.

Deoxyribonuclease

This is a generic name of a group of enzymes which catalyse the breakdown of deoxyribonucleic acids and hence produce a rapid fall in the viscosity of solutions containing such acids. Deoxyribonucleic acid-protein complexes are present in abundance in purulent exudates, and deoxyribonuclease has been used to reduce the viscosity of thick exudates in empyema, sinuses, and meningitis; it has also been used for the debridement of infected wounds and burns.

Streptococcal Deoxyribonuclease (Streptodornase)

Streptodornase is commercially available, combined with streptokinase (Varidase) as a preparation of local use in the treatment of empyema, haemothorax, purulent meningitis, and a variety of other suppurative conditions. The viscosity of thick pus is rapidly reduced, with improved drainage and accelerated healing. If fibrin is present it is also lysed by the streptokinase content of the Varidase. Varidase may increase the volume of secretion as well as reducing viscosity, and adequate and frequent drainage is therefore necessary if it is introduced into closed cavities.

Toxicity.—The main toxic effect is fever, probably due to an impurity. Acute allergic reactions occur rarely. The preparation is sometimes locally irritant.

Varidase Oral

This preparation is a mixture of streptokinase and streptodornase, and has been used in the treatment of inflammatory states and vascular occlusion. Even if its streptokinase content were fully absorbed, many patients would show no plasma fibrinolytic response because of neutralization of the streptokinase by antibody. Further, the absorption of such a preparation, and the consequent biochemical effects if any, are almost

certain to be variable and unpredictable. Oral Varidase would appear to be an entirely unacceptable way of administering streptokinase to produce a fibrinolytic state. The contention that orally administered streptokinase produces a clinical anti-inflammatory effect without any of the biochemical changes associated with the specific action of streptokinase as a plasminogen activator appears improbable, and would require unequivocal demonstration in an adequately designed double-blind trial. If oral Varidase is given for its streptodornase content, the streptokinase is unnecessary, and the streptodornase would probably be much more effective given locally or parenterally.

Pancreatic Deoxyribonuclease

A preparation of bovine pancreatic deoxyribonuclease is available for intravenous, intramuscular, and intrathecal use (Deanase). When given systemically it passes into serous cavities, abscess cavities, and bronchial secretions; significant amounts are also excreted in the urine. It appears to be free from side-effects when given for a short period of time, though because of its bovine origin sensitization is possible with prolonged or repeated courses.

Its use in aerosols has also been suggested in the treatment of respiratory diseases with much thick and viscid secretion in the bronchial tree.

Adequate appraisal of deoxyribonuclease given systemically has not been carried out. The evidence at present available suggests that the therapy may be of benefit, but proof from well-designed, double-blind trials is lacking.

Chymotrypsin

Intramuscular

A preparation of the proteolytic enzyme chymotrypsin is available for intramuscular injection (Chymar). The manufacturers claim that it reduces and prevents inflammation and traumatic oedema, hastens absorption of effusions, restores circulation, promotes healing, and liquefies thick viscid secretions. They recommend it for the treatment of all conditions in which inflammation and oedema (except oedema of renal and cardiac origin) retard healing or present a danger to the involved organ. Unequivocal evidence to support these sweeping claims has not been published and in the meantime there must be reservations about the place of this remedy in therapeutics.