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Poliomyelitis in the Netherlands before and after vaccination with inactivated poliovaccine

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INTRODUCTION

In most countries, where poliomyelitis was a major problem about 15 years ago, the disease has been reduced to negligible proportions by vaccination. Within a short period two effective vaccines became available, the live attenuated virus (o.p.v.) only a few years later than the inactivated poliovaccine (i.p.v.). The former vaccine is used nowadays in most parts of the world because of the ease of oral administration, the effective individual protection offered and the strong interference with the natural spread of the poliovirus. The latter type of vaccine, which must be administered parenterally, provides the immunized with a protection which as a rule equals that produced by the live vaccine. Depending on the amount of antigen it may even provoke a higher level of antibody (Henry *et al.* 1966). There are many observations (Henry *et al.* 1966; Dick *et al.* 1961) which show that i.p.v. interferes with alimentary infection but to a less extent than the live avirulent viruses.

The administration of i.p.v. can be simplified by combining it with diphtheria, tetanus and pertussis antigens, as a quadruple vaccine, which can easily be incorporated into a nationwide infant immunization schedule. Inactivated poliovaccine either alone or in such a combined vaccine has been used in the Netherlands since 1957 in the Government sponsored vaccination programme, which started in the autumn of 1957.

We decided to compare the poliomyelitis morbidity before and after vaccination began, in order to determine the degree of protection conferred on individuals and the community by this i.p.v. vaccination programme.

The figures for the incidence of poliomyelitis in the period 1924–65 were derived from reports of the Office of the Chief Medical Officer, as were the details, vaccination history, virus isolations etc., of the poliomyelitis cases occurring in the 1958–65 period. The number of vaccinated subjects in each age group was calculated from the acceptance rates taken from reports of the Office of the Chief Medical Officer and from population statistics (C.B.S. 1963, 1953–65). In this way the morbidity rates for vaccinated and non-vaccinated persons in each age group, and the percentage of morbidity reductions, were calculated.

METHODS AND MATERIALS

Vaccines

At first poliovaccine was imported from the U.S.A. (1957–59) and Belgium (1958–61). From 1961 formalin-inactivated poliovaccine produced in the Netherlands by the Rijks Instituut voor de Volksgezondheid (National Institute of Public Health) was used.

The Dutch formalin-inactivated poliovaccine is prepared from the Mahoney type 1, M.E.F.1 type 2 and Saukett type 3 strains of poliovirus. The potency of the vaccine lots was determined in monkeys according to the regulations of the U.S. National Institute of Health and is shown in Fig. 1. From 1962 the poliovaccine

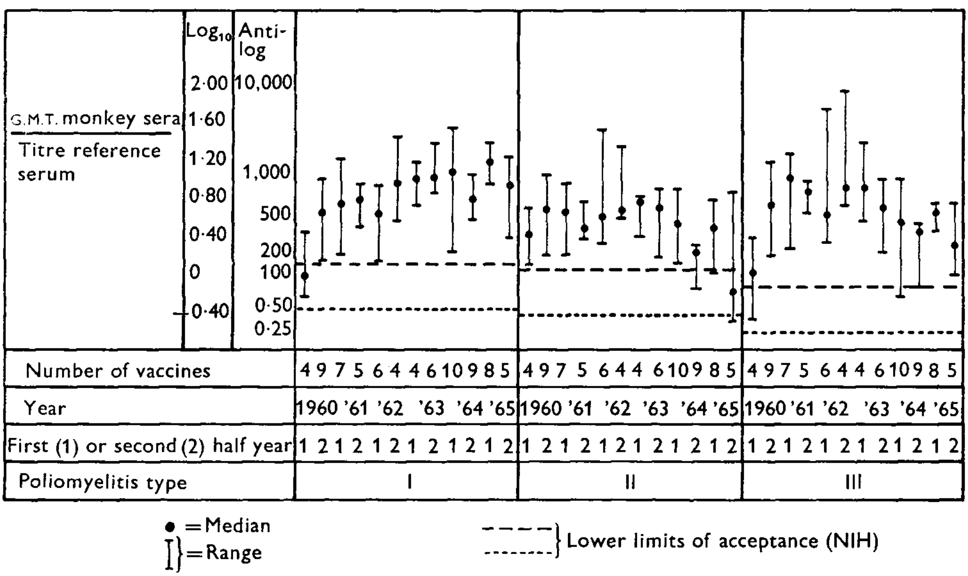

Fig. 1. Monkey potency test of poliomyelitis vaccine (NIH-test). Results of 77 lots produced from 1960 to 1965.

has been incorporated with diphtheria and tetanus toxoids and killed *Bordetella pertussis*. This quadruple vaccine contains 15 Lf diphtheria toxoid, 5 Lf tetanus toxoid and 16×10^9 *B. pertussis* organisms in a 1 ml. dose, and 1·5 mg. aluminium phosphate per dose is added as an adjuvant.

Vaccine schedules

In the early years two primary injections of plain poliovaccine given 1 month apart were followed by a booster dose about 6 months later. In the 3 years after the vaccination campaigns began late in 1957, all children born between 1945 and 1958 were offered the vaccine.

In 1960 the schedule was altered (Brandwijk *et al.* 1961). The children born in that year and later were given three primary injections at monthly intervals and a booster about 6 months later.

From 1962 onwards diphtheria, tetanus, pertussis and poliomyelitis were com-

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bined in one vaccine. A primary series of three injections was given at the age of 3, 4 and 5 months respectively, followed by a booster injection at 11 months of age.

In 1964 and 1965 children born in the years 1952–9 were revaccinated with one dose of diphtheria–tetanus–poliomyelitis vaccine. Those born in 1960 and 1961 were offered revaccination in 1965 with either diphtheria–tetanus–poliomyelitis vaccine or diphtheria–tetanus–pertussis–poliomyelitis vaccine. From that year on this procedure became routine for revaccination at the age of 4–5 years against these diseases.

RESULTS

Incidence of poliomyelitis in the Netherlands

Since 1924, when poliomyelitis became notifiable, the disease has developed as is shown in Fig. 2. A distinction between paralytic and non-paralytic cases was made after 1951. In the 34 years from 1924 to 1957 the average annual number of

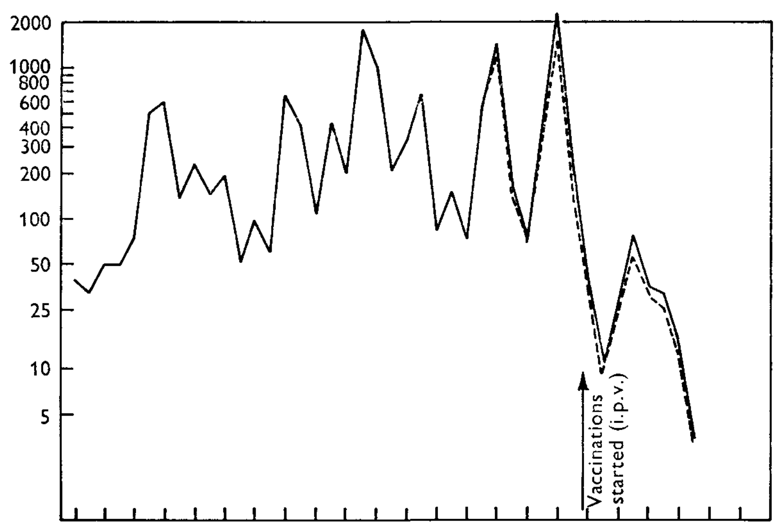

Fig. 2. Poliomyelitis anterior acuta. Notified cases in the Netherlands, 1924–65. —, All cases (paralytic and non-paralytic); - - -, paralytic cases.

all cases was 419 and the average morbidity rate per 100,000 inhabitants was 4·5. In the eight years from 1958 to 1965, covering the period in which polio vaccination became established, the average annual number of all cases was 31 and the morbidity rate 0·27 per 100,000, a reduction in morbidity of 94 %.

The lowest number of cases for any 8-year period between 1924 and 1957 was 1491 (1924–31), whereas 249 cases were reported between 1958 and 1965.

Table 1 shows the age distribution of poliomyelitis from 1950 to 1965. It is apparent that those most affected were the 1–4-year-old children, closely followed by those under 1 year of age. The 5–9-year children, particularly those of age 5 and 6, also showed a high rate. In the older age groups morbidity was less.

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Effect of polio vaccinations

We compared the poliomyelitis morbidity in two 4-year periods (1950–3, 1954-7) before vaccinations began and in the 8 years after. Both 4-year periods included a pre-epidemic year (1951 and 1955), an epidemic (1952 and 1956) and a post-epidemic one (1953 and 1957).

Table 1. *Age distribution of poliomyelitis cases before* (1950–3, 1954–7) *and after* (1958–65) *vaccinations began*

	1950–3		1954–7		1958–65	
Age (years)	All cases	%	Paralytic cases	%	Paralytic cases	%
< 1	167	6·6	183	7·4	16	7·5
1–4	1314	52·0	1324	53·7	89	42·0
5–9	490	19·4	587	23·8	53	25·0
10–14	160	6·3	90	3·7	19	9·0
15–19	99	3·9	54	2·2	6	2·8
⩾ 20	295	11·8	227	9·2	29	13·7
All	2525	100·0	2465	100·0	212	100·0

Table 2. *Reduction of poliomyelitis morbidity rates in different age groups before* (1950–3 *and* 1954–7) *and after* (1958–65) *vaccinations began*

	Morbidity rate per 100,000			1958–65 % reduction compared with	
Age (years)	1950–3 (all cases)	1954–7 (paralytic cases)	1958–5 (paralytic cases)	1950–3	1954–7
< 1	18·5	20·3	0·84	95·5	95·9
1–4	35·3	37·3	1·20	96·6	96·8
5–9	11·3	12·9	0·59	94·8	95·4
10–14	4·7	2·2	0·21	95·5	90·5
15–19	3·1	1·6	0·07	97·7	95·6
⩾ 20	1·1	0·8	0·05	95·4	93·7
All	6·1	5·6	0·23	96·3	95·9

Table 2 shows the morbidity by age in the three periods and the reduction in morbidity rate expressed as a percentage. The over-all reduction is about 96 % and there are only small differences between age groups. The low incidence in the older age groups may reflect the influence of the epidemics in 1952 and 1956. Despite the vaccine being confined to those under 15 years there was no increase in morbidity in the older age groups.

From Table 3 the influence of the number of injections of poliovaccine can be seen. Of the 212 paralytic cases notified in the post-vaccination period (1958–65) 207 were considered and five were omitted. In two of these five patients the vaccination history was unknown, two more were vaccinated in other countries and could not, therefore, be compared with those vaccinated in the Netherlands; and the fifth showed signs of the disease upon arrival in this country.

The morbidity rates in three groups (non-vaccinated, 1 or 2 doses and 3 or more doses), are compared for three age groups from 1 to 14 years. In those under 1 year of age a comparison is not meaningful, because the main part of the vaccination schedule is performed in this group. Few above the age of 15 were vaccinated over this 8-year period, since vaccination was offered only to those born in 1945 and later. From table 3 it can be seen that there is a major reduction in morbidity after 1 or 2 doses of vaccine. The reduction for the three age groups is 85·7, 83·5 and 88·2 respectively. After completion of the vaccination schedule with three or more injections the reduction in morbidity in the children of 1–4 years is 95·7 %, in those of 5–9 years, 93·4 % and in the 10–14-year-olds 89·7 %. As the 1–4-year-old children include the most recently vaccinated, this may account for the difference in the fall of morbidity.

Table 3. *Vaccination history and age distribution of* 207 *paralytic poliomyelitis cases* (1958–65); *reduction of morbidity rate by vaccination*

	Non-vaccinated		1 or 2 doses		3 or more doses		% reduction in morbidity in vaccinated compared with non-vaccinated	
Age (years)	Cases	Rate per 100,000	Cases	Rate per 100,000	Cases	Rate per 100,000	1 or 2 doses	3 or more doses
< 1	14	< 2·0	1	—	0	—	—	—
1–4	53	8·75	13	1·25	22	0·38	85·7	95·7
5–9	32	3·33	6	0·55	15	0·22	83·5	93·4
10–14	12	0·68	1	0·08	4	0·07	88·2	89·7
15–19	6	0·15	0	—	0	—	—	—
⩾ 20	28	0·05	0	—	0	—	—	—

Table 4. *Reduction of morbidity rate* (1958–65) *in relation to age and vaccination history*

	Non-vaccinated: % reduction in morbidity compared with		3 or more doses: % reduction in morbidity compared with	
Age (years)	1950–3	1954–7	1950–3	1954–7
< 1	> 89	> 90	—	—
1–4	75	77	98·9	99·0
5–9	71	74	98·1	98·3
10–14	86	69	98·5	96·8
15–19	95	91	—	—
⩾ 20	95	94	—	—

Table 4 gives information about the degree of protection attained in non-vaccinated persons by the immunity of vaccinated individuals. For this purpose we compared the morbidity rates in such subjects over the years 1958–65 with the two preceding 4-year periods. We found a clear reduction in incidence of polio-

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myelitis, but the reduction was different in the various age groups. In the children under 14 years it is about 70%, but in those over 15 years it is more than 90%. In the fully vaccinated subjects the morbidity fell by about 98–99% compared with the unvaccinated.

Table 5. *Isolation of poliomyelitis virus in* 166 *cases of paralytic poliomyelitis* (1959–65)

Year	Poliomyelitis type I	II	III	Negative	Total tested
1959	0	0	1	7	8
1960	4	3	4	8	19
1961	55	0	5	7	67
1962	25	0	1	4	30
1963	17	0	2	8	27
1964	2	0	8	3	13
1965	0	0	2	0	2
Total	103	3	23	37	166

Table 6. *Virus isolations according to age and vaccination history in* 166 *patients* (1959–65)

Age group (years)	Vaccination history 0 (−) Pos. No.	%	Neg. No.	%	1 or 2 (±) Pos. No.	%	Neg. No.	%	3 or more (+) Pos. No.	%	Neg. No.	%
< 1	11	92	1	8	0	—	1	—	0	—	0	—
1–14	72	90	8	10	10	91	1	9	19	53	17	47
15–19	3	75	1	25	0	—	0	—	0	—	0	—
⩾ 20	14	64	8	36	0	—	0	—	0	—	0	—
All	100	85	18	15	10	83	2	17	19	53	17	47

Table 5 shows the results of poliovirus isolations in 166 paralytic poliomyelitis patients in the 7-year period 1959–65. Insufficient isolation results were available from the cases recorded in 1958. It can be seen that type II was isolated from polio patients in 1960 only. In 1961, 1962 and 1963 type I prevailed, but in 1964 and 1965 the picture changed and type III was more frequently isolated.

In Table 6 the results of virus isolations in the 166 patients in the period 1959–65 are shown by vaccination history and age. The percentage of those with positive virus isolations was reduced by about 40% in the three or more times vaccinated compared with the non-vaccinated subjects. This probably indicates a relative decrease in virus excretion, but it may be due to paralytic disease not caused by poliovirus. Type III virus was relatively more frequently encountered than type I in vaccinated subjects. Thus in the 1–14-year-olds the ratio between the number of cases with virus isolations in the unvaccinated and vaccinated groups was 60:13 for type I and 9:6 for type III.

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Because the coverage with poliovaccine in the Netherlands is slightly irregular, it appeared interesting to establish the relation between the morbidity of paralytic poliomyelitis in different municipalities and the acceptance rate. Figure 3 shows the results of our calculations. On the abscissa the municipalities are arranged in

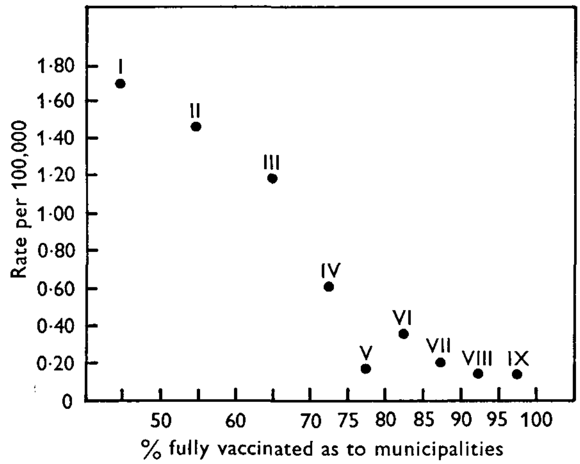

Fig. 3. 1958–65. Paralytic poliomyelitis. Relation between average yearly morbidity rate per 100,000 and the estimated percentage of children under 16 who had had three or more doses of polio vaccine, in different municipalities. I, 50 %; II, 51–60 %; III, 61–70 %; IV, 71–75 %; V, 76–80 %; VI, 81–85 %; VII, 86–90 %; VIII, 91–95 %; IX, 96–100 %.

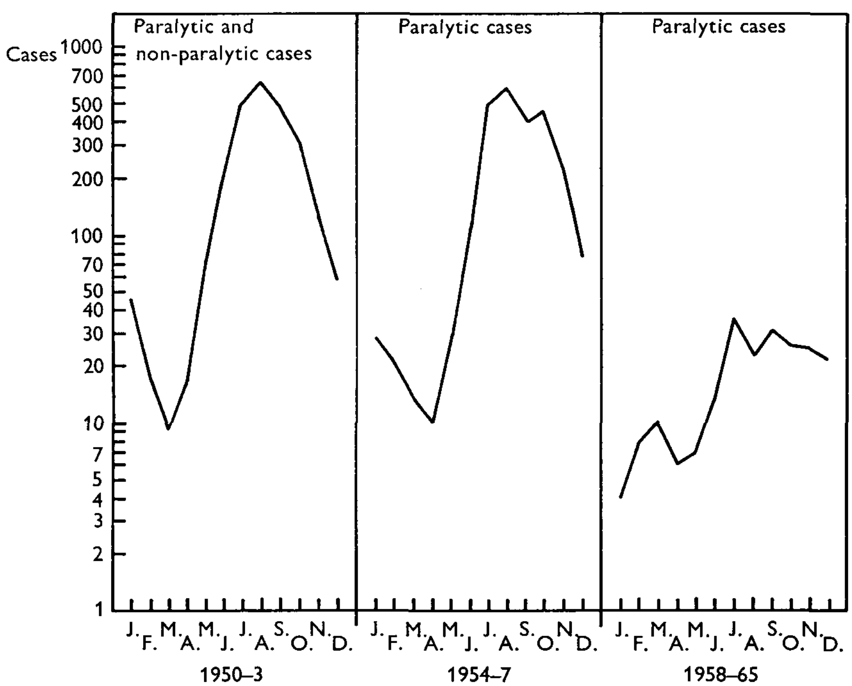

Fig. 4. Monthly distribution of poliomyelitis in the Netherlands in the periods 1950–3, 1954–7 and 1958–65.

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nine groups according to the estimated percentage of three or more times vaccinated children under 16 years. This estimation was derived from the acceptance rate in September 1964 of the children born from 1959 to 1963.

The municipalities with the lowest percentages of fully vaccinated children showed the highest morbidity figures. The morbidity reached a relatively low, but constant level in the municipalities where the percentage of fully vaccinated was 75 % or more.

Finally Fig. 4 shows the monthly distribution of notified polio cases in the years 1950–3, 1954–7 and 1958–65. It is apparent that the seasonal curve is levelling off, despite the fact that in the post-vaccination period the highest number of cases still occurs in July.

DISCUSSION

From the beginning the vaccination campaign was directed particularly to the most vulnerable age groups, which are the most important disseminators of the infection, i.e. the children of 1–4-years and 5–9 years (Table 1). The decision to adopt the routine schedule, which starts at the age of 3 months and is completed before the end of the first year was a compromise. It was realized, that in the early months of life the response to the antigens would not be maximal (Perkins, Yetts & Gaisford, 1958, 1959), but in view of the higher risks associated with pertussis in very young infants it was thought that administration of this component could not be postponed. Moreover, for reasons of organization it was desirable to complete the schedule within the first year of life. By this procedure a high acceptance rate in those eligible for vaccination was reached. In 1964 for the 1–4-year-old children the overall acceptance rate for three or more doses was about 89 % and for those born from 1945 to 1959 it was 87–89 %.

The importance of the acceptance rate is shown in Fig. 3, from which it might be concluded that, under the conditions prevailing in the Netherlands, at least 75 % of the children, evenly distributed in a community, must be fully vaccinated to obtain a satisfactory reduction of poliomyelitis.

Against this background of good coverage, especially in the most susceptible age group (1–4 years) the results presented here must be considered. They make it clear that the reduction of paralytic poliomyelitis in the Netherlands is due to at least two factors; immunity in vaccinated people and a 'herd-immunity' as shown in Table 4. This latter phenomenon most probably is due to the decreased capacity of the vaccinated to spread poliovirus. The outcome of the virus isolations as presented in Table 6 and results from other investigators (Henry *et al.* 1966; Dick *et al.* 1961) support this explanation.

However, it might be useful in this respect to remark that in the adjacent countries, Belgium and the German Federal Republic, the circulation of wild polio viruses may have been reduced considerably by the use of o.p.v.

From Table 4 it can be seen that the highest level of polio reduction is reached in persons of 15 years and older. The decreased possibilities for shedding poliomyelitis virus by young children and the lower susceptibility with increasing age might have been responsible for these high figures.

Table 3 gives a good insight into the individual protection reached during the period under study (1958–65), for all children considered in this table profited by the herd immunity, caused by the substantial vaccine coverage. The lower reduction rate for the fully vaccinated 10–14-year-old children could be an argument in favour of a revaccination between 4 and 10 years. The reduction rates, which are presented in Table 3, compare well with results published from other countries. For the U.S.A. a percentage of 91 in the age group 0–4 years and of 93 in the 5–14-year-old children was calculated (Langmuir, 1960). In Canada the 0–4-year group showed 87·4 % reduction, the 5–19-year group 97·1 % and the over-all percentage was 95·6 % (Kubryk, 1960). Data from a few outbreaks in Australia show the same general picture (Duxbury, Goulding & Graydon, 1963). In Sweden the reduction for all ages was 97·4 % (Olin, 1960). All these figures are based on the decrease of poliomyelitis in a comparatively short period after vaccination campaigns were completed. The reduction rates found by these investigators are higher than the first published results in the U.S.A. after the extensive 1954 field trial (Francis *et al.* 1955). The differences between the results mentioned above may be due to the quality of the vaccines, the vaccination schedule, the age groups covered and the acceptance rates.

The best estimate for the over-all protection against paralytic poliomyelitis in fully vaccinated children in the Netherlands can be made from the last two columns of Table 4. The morbidity has fallen by 97–99 % with slight differences for the age groups considered. These children have an individual protection and are further protected by the 'herd' immunity mentioned.

Finally, it may be of interest to compare the results of vaccinations in the Netherlands and in the four Scandinavian countries Denmark, Norway, Sweden and Finland. In Denmark o.p.v. type I was only used in a mass-campaign in 1963. For the rest i.p.v. was offered in these four countries.

In the Netherlands o.p.v. was used twice on a small scale to suppress local outbreaks. For this purpose in the summer of 1962 a few hundred doses of o.p.v. type I were used in Amsterdam and in December 1963 a few thousand doses of o.p.v. of the same type went to the island Tholen in the province Zeeland, a pocket with low acceptance rate, where some polio cases occurred.

Considering the situation in the Scandinavian countries in 1962–3 (Gard, 1964) we see a reduction of 90–95 % in Norway. In Denmark and Finland there are still a few cases but the reduction is more than 94 % and in Sweden poliomyelitis has virtually disappeared (Gard, 1966).

In the Netherlands the favourable picture which is so evident in Sweden is developing more slowly. After the rise in 1961, the number of paralytic cases steadily decreased to 3 in 1965, of which one was imported from Nigeria. Unfortunately 1966 brought a slight rise to 10 paralytic cases, mainly occuring in a region badly covered by vaccination. The different results in the Netherlands and Sweden may be due to several factors: population density, family size, housing conditions, pattern of coverage by vaccine, vaccination schedule and vaccine quality. The first three conditions are more favourable for virus dissemination in the Netherlands. Probably in Sweden the regions with a low acceptance rate are lacking. No comparison of vaccine potency has been made.

From the figures presented here, we may conclude that with inactivated polio-vaccine a good protection can be obtained provided that a vaccine of good quality is used and a high rate of acceptance is reached.

SUMMARY

Formalin-inactivated polio vaccine has been used in the Netherlands since 1957. Within 3 years all children born in 1945 and later were offered vaccine. In the first years poliovaccine from different manufacturers were used. In 1961 a vaccine produced in the Netherlands by the 'Rijks Instituut voor de Volksgezondheid' (National Institute of Public Health) became available and in 1962 the poliomyelitis components were incorporated in a quadruple vaccine, which contains 15 Lf diphtheria, 5 Lf tetanus toxoid and 16×10^9 *Bordetella pertussis* organisms in addition to the three polio components. As an adjuvant this quadruple vaccine contains 1·5 mg. aluminium phosphate per 1 ml. dose. For infants the schedule became three doses at ages 3, 4 and 5 months respectively, followed by a booster dose at the end of the first year. The over-all acceptance rate can be estimated at almost 90 % of those eligible, but there were pockets in the population with lower rates.

Since 1924 poliomyelitis has been a notifiable disease. During and after the last World War major epidemics occurred.

The poliomyelitis morbidity rates in the 8 post-vaccination years 1958–65 were compared with those from two preceding 4-year periods 1950–3 and 1954–7. In the 1–4-year-old children, who presented the most vulnerable age group, paralytic poliomyelitis was reduced by about 97 % and in the other age groups this percentage was slightly less. The over-all reduction was 96 %. Comparison of the morbidity rates of non-vaccinated persons in 1958–65 with the rates from 1950–3 and 1954–7 gave an impression of the extent of the herd immunity. These rates were reduced 70–80 % in the children under 15 years and 90–95 % in those over this age. The individual protection given to the vaccinated was calculated from the morbidity rates in non-vaccinated, incompletely and fully vaccinated persons in the 1958–65 period. The reduction of morbidity was 90–95 % for children of 1–14 years who got three doses or more and about 85 % for those who had only 1 or 2 doses. Fully vaccinated children, who are profiting from both individual protection and herd immunity, showed a reduction of 97–99 %.

From the data presented it is concluded that vaccination with inactivated poliomyelitis vaccine can provide very effective protection for the individual and the community provided that a vaccine of good quality is used and the rate of acceptance is 75 % or better.

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REFERENCES

BRANDWIJK, A. C., COHEN, H., HEKKER, A. C., HOFMAN, B., VAN RAMSHORST, J. D., TASMAN, A., VAN DRIEL, C. B., SCHAAPMAN-TILMA, B. & DE VRIES, J. A. (1961). Een gecombineerd difterie–kinkhoest–tetanus–poliomyelitis vaccin (DKTP) ter immunisatie van de zuigeling. *Ned. Tijdschr. Geneesk* **105**, 1331.

CENTRAAL BUREAU VOOR DE STATISTIEK (1953–65). *Maandstatistiek van de bevolking en de Volksgezondheid*. Ed. de Haan-Utrecht.

CENTRAAL BUREAU VOOR DE STATISTIEK (1963). *Bevolking van Nederland. Leeftijd en geslacht* 1900–1952. Ed. de Haan-Utrecht.

DICK, G. W. A., DANE, D. S., MCALISTER, J., BRIGGS, M., NELSON, R. & FIELD, C. M. B. (1961). Vaccination against poliomyelitis with live virus vaccines. 7. Effect of previous Salk vaccination on virus excretion. *Br. med. J.* ii, 266.

DUXBURY, A. E., GOULDING, G. & GRAYDON, J. J. (1963). Vaccination against poliomyelitis; The present position in Australia. *Lancet* i, 377.

FRANCIS, T., JR, KORNS, R. F., VOIGHT, R. B., BOISEN, M., HEMPHILL, F. M., NAPIER, J. A. & TOLCHINSKY, E. (1955). An evaluation of the 1954 poliomyelitis vaccine trials. Summary report. *Am. J. publ. Hth* **45**, part 2 (suppl).

GARD, S. (1964). Polio virus vaccination and epidemiologic situation in Scandinavia. *Proc. Xth Symposium Europ. Ass. Poliomyelitis and Allied Diseases*. Warsaw.

GARD, S. (1966). Aspects of polio virus epidemiology and surveillance in Sweden. *Proc. XIth Symposium Europ. Ass. Poliomyelitis and Allied Diseases*, Rome. (In preparation.)

HENRY, J. L., JAIKARAN, E. S., DAVIES, J. R., TOMLINSON, A. J. H., MASON, P. J., BARNES, J. M. & BEALE, A. J. (1966). A study of polio vaccination in infancy: excretion following challenge with live virus by children given killed or living poliovaccine. *J. Hyg., Camb.* **64**, 105.

KUBRYK, D. (1960). Paralytic poliomyelitis in Canada, 1959. *Can. J. publ. Hlth* **51**, 389.

LANGMUIR, A. D. (1960). Inactivated virus vaccines: protective efficacy. *Int. Polio Conf.* no. 5. Copenhagen, 1960.

OLIN, G. (1960). Protective efficacy of inactivated polio virus vaccines: Swedish experiences. *Int. Polio. Conf.* no. 5. Copenhagen, 1960.

PERKINS, F. T., YETTS, R. & GAISFORD, W. (1958). Serological response of infants to poliomyelitis vaccine. *Br. med. J.* ii, 68.

PERKINS, F. T., YETTS, R. & GAISFORD, W. (1959). Response of infants to a third dose of poliomyelitis vaccine given 10 to 12 months after primary immunization. *Br. med. J.* i, 680.

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