PAPERS AND ORIGINALS

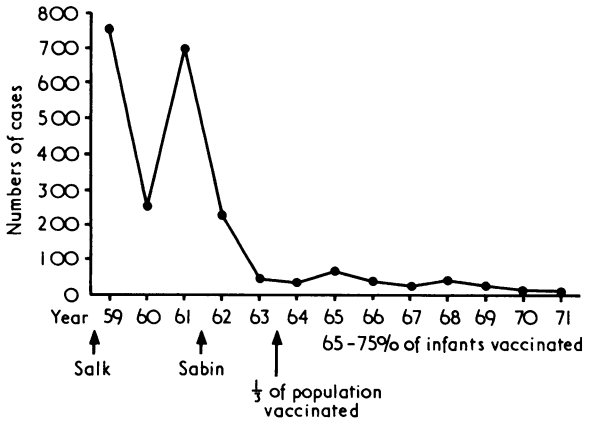
Evolution of poliovirus since introduction of attenuated vaccine

YVONNE E COSSART

British Medical Journal, 1977, **1**, 1621-1623

Summary

Genetic marker tests were performed on 997 strains of poliovirus isolated from patients with neurological disease and from healthy people in England and Wales. Before the introduction of live attenuated vaccine most strains could multiply at raised temperatures. Now, however, many strains isolated from cases of poliomyelitis or from healthy persons with no known contact with vaccine cannot grow above 37°C, and in this respect resemble the vaccine strains. The three serotypes are also much more evenly represented. Hence probably to a limited extent the vaccine-like strains have established themselves in the community.



Yearly incidence of paralytic poliomyelitis in England and Wales since introduction of live attenuated polio vaccine.

Virus Reference Laboratory, Central Public Health Laboratory, London NW9 5HT

YVONNE E COSSART, MB, FRCPATH, bacteriologist (now at Department of Bacteriology, University of Sydney, NSW 2006, Australia)

Introduction

Since live attenuated polio vaccine became available in 1962 the yearly numbers of cases of paralytic poliomyelitis in England and Wales have fallen to low levels (see figure). Many strains of poliovirus, however, are still isolated from patients who have had no known contact with vaccine or with a recently vaccinated person. Few of these patients have neurological symptoms and it is important to know whether vaccine-derived polioviruses have displaced the naturally occurring strains in the community. I have tried to answer this by comparing the genetic marker characteristics of strains isolated before and after the introduction of vaccination.

Materials and methods

Virus strains were kindly provided by many virologists in public health laboratories in England and Wales. Cultures containing mixtures of different serotypes were not studied but otherwise no selection was made. Half of all the isolates reported to the Epidemiological Research Laboratory between 1965 and 1972 were tested (see table I). About 11% of the strains were isolated from cases of suspected poliomyelitis, and most of the remainder from normal children during enterovirus surveys.

The reproductive capacity temperature (RCT) marker test[1] was used. In this test the titre attained by the strain in cultures maintained at a raised temperature (39·8°C for types 1 and 2, and 40·3°C for type 3)

TABLE I—*Proportion of poliovirus isolates available for study*

Period	No of strains reported in CDR*	No tested	Distribution of serotypes (%)		
			Type 1	Type 2	Type 3
1965–8	1167	502	49	24	27
1969–72	885	495	32	39	29

**Communicable Disease Reports* of Public Health Laboratory Service.

is compared with that at the permissive temperature of 36°C. Vaccine strains grow poorly if at all at the higher temperatures, while the wild strains are little affected. Conventionally strains are classified as "wild" if their titre is reduced by less than 10^2 TCD_{50}/0·1 ml, and as "vaccine-like" if the titre is reduced by 10^5 TCD_{50}/0·1 ml or more. A few "intermediate" strains also occur.

Serum samples for the antibody survey were from healthy young adults. Polio neutralisation tests were performed in roller cultures of primary monkey kidney cells, a virus dose of 100 TCD_{50} being used and the serum virus mixtures being incubated for three hours at 37°C before inoculation.

Results

Table I shows the number of strains tested and the prevalence of each serotype. The results for strains isolated between 1965-8 and 1969-72 are given separately in all tables so that progressive alteration in the character of the isolates may be assessed.

TABLE II—*Prevalence of poliovirus serotypes during different periods*

Period	No of strains	Distribution of serotypes (%)		
		Type 1	Type 2	Type 3
Strains isolated from poliomyelitis cases				
1956–64*	4851	89	4	7
1965–8	84	52	19	28
1969–72	32	22	50	28
Strains isolated during enterovirus surveys				
1957[8]	209	67	12	21
1961 (pre-Sabin)[9]	86	59	9	31
1962 (recent Sabin)	662	27	31	43
1965–8	401	49	24	27
1969–72	405	32	39	29

*Figures from *Communicable Disease Reports* of Public Health Laboratory Service.

TABLE III—*Vaccination history of patients yielding poliovirus isolate*

Serotype	Period	% recently vaccinated	% with uncertain history	% not recently vaccinated
Type 1	1965–8	57	5	38
	1969–72	55	9	36
Type 2	1965–8	31	26	42
	1969–72	42	8	50
Type 3	1965–8	46	24	30
	1969–72	57	12	31

TABLE IV—*Clinical features of poliomyelitis during different periods*

Serotype	Period	Total No of patients with neurological disease	% paralysed
Type 1	1965–8	75	41
	1969–72	11	36
Type 2	1965–8	27	40
	1969–72	18	11
Type 3	1965–8	33	27
	1969–72	14	36

TABLE V—*Results of genetic marker tests on poliovirus strains isolated during different periods*

Serotype	Period	No of strains tested	% vaccine-like	% intermediate	% wild
Type 1	1957 (outbreak)	34	12	38	50
	1965–8 (all strains)	245	76	6	18
	1969–72 (all strains)	126	89	6	4
Type 2	1953 (outbreak)	18	16	28	55
	1965–8 (all strains)	120	70	22	8
	1969–72 (all strains)	153	73	26	1
Type 3	1953–5 (all strains)	5	20	80	
	1965–8 (all strains)	137	43	43	14
	1969–72 (all strains)	116	60	33	7

The changing prevalences of the three serotypes is evident from table II. The dominance of type 1 both as a cause of paralytic poliomyelitis and as an isolate from asymptomatic excretors has been lost. Type 2 strains are now more common than either type 1 or type 2.

Table III shows the vaccination histories of the patients yielding poliovirus isolates. Over a third of the strains studied came from those with no history of recent vaccination or contact with a vaccinated person.

The clinical features of the disease have also changed. Whereas in 1957 66% of all patients with poliomyelitis had classical paralytic polio,[2] less than half of the patients with neurological disease in the present study were paralysed (table IV).

Table V summarises the results of all marker tests carried out, and for comparison gives the results of an earlier study[3] of strains isolated before the introduction of vaccine. There has been a noticeable decline in the overall number and proportions of wild strains of all three serotypes, and vaccine-like strains now predominate. This change is evident in strains isolated from patients with neurological disease (table VI) as well as in isolates from asymptomatic excretors with no known contact with vaccine or with a recently vaccinated person (table VII).

TABLE VI—*Results of genetic marker tests on strains associated with neurological disease*

Serotype	Period	No of strains tested	% vaccine-like	% intermediate	% wild
Type 1	1965–8	44	39	18	43
	1969–72	5	80		20
Type 2	1965–8	16	75	25	
	1969–72	18	66	33	
Type 3	1965–8	24	25	46	29
	1969–72	9	66	11	22

TABLE VII—*Results of genetic marker tests on strains of polioviruses from persons known not to have personal or household contact with vaccine*

Serotype	Period	No of strains tested	% vaccine-like	% intermediate	% wild
Type 1	1965–8	93	45	11	44
	1969–72	45	87	11	2
Type 2	1965–8	51	73	18	10
	1969–72	77	69	30	1
Type 3	1965–8	41	36	41	22
	1969–72	36	58	36	6

TABLE VIII—*Results of genetic marker tests on asymptomatic patients with history of recent vaccination or household contact with vaccinated person*

Serotype	Period	No of strains tested	% vaccine-like	% intermediate	% wild
Type 1	1965–8	140	93	4	2
	1969–72	70	91	3	6
Type 2	1965–8	37	81	16	3
	1969–72	64	83	17	
Type 3	1965–8	63	43	46	11
	1969–72	66	57	33	9

Almost all the type 1 strains isolated from vaccinated persons and their household contacts failed to grow at the higher temperature in the genetic marker test (table VIII), but many of the type 2 and type 3 strains had intermediate characteristics.

The effect of the vaccination campaign on the proportion of young adults with immunity is seen even in the small sample of sera tested, fewer lacking antibody in later years. There has also, however, been a qualitative change in the ability to neutralise the vaccine-like and wild prototype strains. In 1961 the vaccine-like strains were less readily neutralised than the wild strains, whereas by 1967 they were equally or better neutralised (table IX).

TABLE IX—*Comparison of ability of sera obtained from young adults in different years to neutralise wild and vaccine-like polioviruses*

Serotype	Strain	No (%) of patients without antibody		
		1961	1967	1972
Type 1	Mahoney*	7/18 (39)	7/23 (30)	7/20 (35)
	Sabin 1	10/18 (56)	5/23 (22)	6/20 (30)
Type 2	YSK*	4/18 (22)	2/23 (9)	2/20 (10)
	Sabin 2	6/18 (33)	2/23 (9)	2/20 (10)
Type 3	Saukett*	3/18 (17)	4/23 (17)	1/20 (5)
	Sabin 3	4/18 (22)	4/23 (17)	1/20 (5)

*Wild prototype strains.

Discussion

When live attenuated polio vaccine was first introduced the spread of Sabin strains among household contacts was found to be limited.[1] The RCT marker characteristic of polioviruses isolated from children at intervals after vaccination, however, tended to revert towards that of the wild strain. This was most noticeable for type 3, and the change was accompanied by increased neurovirulence for monkeys.[5] Controversy arose about using the attenuated vaccine when there was uncertainty about the stability of the strain after intestinal passage in man. Continued surveillance of poliomyelitis cases in Britain has shown that few cases (less than one per million doses[6]) can be attributed directly to vaccination. Little attention, however, has been given to the more remote effects of releasing large amounts of the attenuated strains into the community. About six million doses each containing 10^6 TCD_{50} of each serotype are given yearly in England and Wales.

In this study the results of RCT marker tests on strains from patients with a definite history of recent vaccination showed a little evidence of reversion towards virulence. Even so, 90% of the type 1 strains, 80% of the type 2 strains, and more than half of the type 3 strains remained unaltered so far as this characteristic was concerned.

About one-third of all the strains studied came from persons without any definite contact with vaccine, so it is clear that, far from being eliminated, polioviruses are still circulating widely. Since all three serotypes are about equally represented and the RCT marker test results for these viruses were on the whole similar to those for strains from known vaccines, these "naturally occurring" strains must originally have been derived from the vaccine. It also seems that wild strains introduced by travellers from countries where polio is still endemic are failing to become established. Few strains with the classical wild RCT marker characteristic were isolated from asymptomatic excretors or even from patients with neurological disease.

Before vaccine was introduced only a few cases of paralytic polio were caused by strains that failed to grow at raised temperatures, but such strains were well recognised.[3] The RCT marker test used here cannot differentiate "reverted" vaccine strains from atypical wild strains, so that the origin of viruses with a vaccine-like RCT characteristic from patients with neurological disease is uncertain. The predominance of types 2 and 3 rather than type 1 suggests that they have probably originated from vaccine but have been modified by many passages in man. Few such strains have emerged, even a decade after the introduction of the vaccine, but continued surveillance is needed, particularly if the general level of immunity is allowed to wane.

Most people now reaching adolescence and young adult life have acquired immunity to polio from vaccination in infancy, followed perhaps by boosting due to asymptomatic infection. The naturally occurring strains now seem to be of vaccine origin, and since the wild and vaccine-like strains differ slightly in their antigenic composition[7] it is important to confirm that satisfactory immunity to the wild strains is being maintained. The small pilot study of sera obtained from young adults in different years showed that there are measurable differences in the ability to neutralise vaccine-like and wild strains of the same serotype. When these differences were observed in 1961 the wild strains were better neutralised. The reverse is now found, and sera from some people with measurable anti-Sabin titres fail to neutralise the prototype wild strains at a concentration (titre of 1/10 or more) that would be regarded as protective. This trend needs to be confirmed by a much larger survey.

The remarkable success of polio vaccine has encouraged the introduction of other live attenuated vaccines against common virus infections, but only for polio is there any information on the effect of vaccination on the natural history of the agent. Laboratory marker tests for distinguishing vaccine-like strains from wild prototypes are not available for any of these newer attenuated virus vaccines.

This study shows that the poliovirus has adapted to the changed situation and remains a ubiquitous human parasite. Although the strains currently circulating are much less likely to cause neurological disease than earlier wild strains, the level of immunity in young adults is now closely similar to that which prevailed before vaccination began.

A high price is likely to be paid by future generations if the present dearth of paralytic cases is taken to mean that universal polio vaccination is no longer needed in infancy.

References

1 Lwoff, A, *Bacteriological Reviews*, 1959, **23**, 109.
2 Chief Medical Officer, *Annual Report, 1957*. London, HMSO, 1958.
3 Cossart, Y E, *Journal of Hygiene*, 1967, **65**, 67.
4 Fox, J P, *et al*, in *Poliomyelitis, Proceedings of V International Polio Conference, Copenhagen, 1960*, p 368. London, Pitman, 1961.
5 Melnick, J L, in *Poliomyelitis, Proceedings of V International Polio Conference, 1960*, p 384. London, Pitman, 1961.
6 *Bulletin of the World Health Organisation*, 1976, **53**, 319.
7 McBride, W D, *Virology*, 1959, **7**, 45.
8 Spicer, C C, *Journal of Hygiene*, 1961, **59**, 143.
9 Galbraith, N S, *Journal of Hygiene*, 1965, **63**, 441.

(*Accepted 1 April 1977*)