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Outbreak of paralytic poliomyelitis in Oman: evidence for widespread transmission among fully vaccinated children

ROLAND W. SUTTER PETER A. PATRIARCA SHAUN BROGAN
PRADEEP G. MALANKAR MARK A. PALLANSCH OLEN M. KEW
ALLAN G. BASS STEPHEN L. COCHI JAMES P. ALEXANDER
DAVID B. HALL ALI JAFFER M. SULEIMAN
AHMED A. K. AL-GHASSANY MUSALLAM S. EL-BUALY

From January, 1988, to March, 1989, a widespread outbreak (118 cases) of poliomyelitis type 1 occurred in Oman. Incidence of paralytic disease was highest in children younger than 2 years (87/100 000) despite an immunisation programme that recently had raised coverage with 3 doses of oral poliovirus vaccine (OPV) among 12-month-old children from 67% to 87%. We did a case-control study (70 case-patients, 692 age-matched controls) to estimate the clinical efficacy of OPV, assessed the immunogenicity of OPV and extent of poliovirus spread by serology, retrospectively evaluated the cold chain and vaccine potency, and sought the origin of the outbreak strain by genomic sequencing. 3 doses of OPV reduced the risk of paralysis by 91%; vaccine failures could not be explained by failures in the cold chain nor on suboptimum vaccine potency. Cases and controls had virtually identical type 1 neutralising antibody profiles, suggesting that poliovirus type 1 circulation was widespread. Genomic sequencing indicated that the outbreak strain had been recently imported from South Asia and was distinguishable from isolates indigenous to the Middle East. Accumulation of enough children to sustain the outbreak seems to have been due to previous success of the immunisation programme in reducing spread of endemic strains, suboptimum efficacy of OPV, and delay in completing the primary immunisation series until 7 months of age. Additionally, the estimated attack rate of infection among children aged 9–23 months exceeded 25% in some regions, suggesting that a substantial proportion of fully vaccinated children had been involved in the chain of transmission.

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Introduction

Widespread use of oral poliovirus vaccine (OPV) has led to the virtual elimination of paralytic poliomyelitis in industrialised countries, in addition to substantial reductions in the incidence of the disease in the developing world.[1,2] However, the efficacy of OPV in inducing humoral immunity against poliovirus types 1 and 3 in some countries has been lower than expected.[3–5] Recent outbreaks in vaccinated populations in The Gambia,[6,7] Brazil,[8] and Taiwan[9] have also raised concern that primary reliance on routine immunisation may be inadequate to achieve the goal of eradicating wild poliovirus infection globally by the year 2000. We here report the results of an outbreak investigation in Oman.

Background

The Expanded Programme on Immunisation (EPI) in Oman began in 1981; administration of OPV was recommended at 3, 5, and 7 months of age at specific health centres, with a reinforcing dose at 19 months. Because coverage with 3 or more doses had only reached 67% by 1985, a more extensive infrastructure was gradually developed in 1986; this used outreach and recall activities by mobile teams, and required that every contact with curative care institutions should be used as an opportunity to vaccinate children who were behind schedule. Immunisation coverage among children aged 12 months

ADDRESSES: **Divisions of Immunization** (R. W. Sutter, MD, P. A. Patriarca, MD, S. L. Cochi, MD), **and Viral and Rickettsial Diseases,** (M. A. Pallansch, PhD, O. M. Kew, PhD, D. B. Hall, PhD) **Centers for Disease Control, Atlanta, Georgia, USA; Ministry of Health** (S. Brogan, MA, P. G. Malankar, MB, A A. K Al-Ghassany, MD, A. J. M. Suleiman, MB, Prof M. S. El-Bualy, MB), **and UNICEF, Muscat, Sultanate of Oman** (A. G Bass); **and Expanded Programme on Immunisation, World Health Organisation, Geneva, Switzerland** (J. P. Alexander, MD). Correspondence to Dr R. Sutter, Division of Immunisation (E05), Centers for Disease Control, Atlanta, Georgia 30333, USA.

increased rapidly to 83% within a few months, with a concomitant decline in the reported number of poliomyelitis cases. Coverage increased further to 88% in 1987.

After a five-month period in which no cases of poliomyelitis were identified, an outbreak became apparent during the early months of 1988. A total of 118 cases were identified by March, 1989 (overall attack rate 6/100 000 population). Cases were reported from 6 of the 7 administrative regions of Oman, including remote villages with total populations of up to 1000. The age distribution of case-patients was typical of that reported for countries with endemic poliovirus transmission and low rates of vaccination, even though most infants and young children in Oman had received at least 3 doses of OPV by 12 months of age. Similarly, although most reported outbreaks of this magnitude have mainly involved unvaccinated children,[9] 87% of case-patients in Oman had received at least 1 dose of OPV and 50% had received at least 3 doses. After confirmation that the outbreak was caused by wild type 1 poliovirus (isolated from 17 of the 29 patients from whom stool specimens had been obtained), mass vaccination campaigns were carried out successively for children aged 0–5 and 6–18 years between October and December, 1988, first in the two most affected regions (Batinah and Eastern) and then nationwide.

Because the outbreak was confined almost entirely to the target population for the EPI, our studies centred mainly on the efficacy of OPV in preventing infection and paralysis.

Patients and methods

Case ascertainment

All hospitals and health centres reporting cases during the outbreak were contacted again to ensure that all reports had been received and that there were no new cases. Additionally, village-to-village searches were done in the catchment areas of 16 randomly selected health centres that had not reported cases during the outbreak; these centres served an estimated population of 6749 children under 24 months of age. Based on the attack rate in the catchment areas of the health centres that had reported cases during the outbreak (1·4/1000 children 0–23 months of age), a population of at least 5000 children from unaffected catchment areas needed to be searched. If no more than 2 unreported case-children could be detected in these areas, we would be 99% sure (by the Poisson distribution) that the number of unreported cases in presumed unaffected areas of Oman was close to zero. We tested this method in two health centre catchment areas in which cases had been identified previously; 6 of the 7 case-patients who had been reported during the outbreak were detected.

Case-control study

All patients aged 5–24 months were enrolled retrospectively into the study if they had acute flaccid paralysis clinically compatible with poliomyelitis and (1) had wild-type poliovirus isolated from stool samples (n = 16); or (2) had a residual neurological deficit 60 days after onset (standardised examinations) (n = 50); or (3) had died from complications associated with poliomyelitis (n = 4). These criteria increased the likelihood of including only genuine cases of poliomyelitis in the analysis. Birthdate and vaccination dates were obtained from health centre registries for each case, as were up to 10 controls matched for age and village of residence (or nearest village when a sufficient number of such controls was not available) of the corresponding case. Date of onset of paralysis was used as the reference date for assessing vaccination status of corresponding controls.

Because variables such as chronological age, age at vaccination, and interval between OPV doses were not normally distributed, non-parametric methods (Wilcoxon rank sum test) were used to detect statistically significant differences between case-patients and controls. Vaccine efficacy estimates (and 95% confidence intervals) were calculated with conditional logistic regression appropriate for case-control studies with variable matching[10] and with an adjusted conditional logistic regression model, which controlled for doses of OPV/DTP (diphtheria, tetanus, pertussis) received within 30 days before either onset of paralysis (case) or reference date (control). The adjusted model was used to account for partial efficacy of OPV doses received during this period, for the provocation effect of DTP injections in inducing paralysis,[11] and for visits to health facilities in which there may have been exposure to another (unrecognised) risk factor.

Serology

Sera were obtained from the following groups of children: (1) 52 case-patients 60 or more days after onset of paralysis, 15 of whom had received 3 or more doses of OPV (fully vaccinated) at least 30 days before onset of paralysis, and 37 of whom had not (unvaccinated and partly vaccinated); (2) 35 control children from Rustaq (located in Batinah, the region with the highest poliomyelitis attack rate) who were potentially exposed to wild poliovirus during the outbreak (bled at the end of the outbreak January–February, 1989) (Rustaq I); (3) an additional 35 control children from Rustaq who were bled 7 months or more after the outbreak had ended (Rustaq II); and (4) 70 control children from Khasab (located in the Musandam region, which did not report cases during the outbreak), half of whom were enrolled and bled January–February, 1989 (Khasab I), and the other half January–February, 1990 (Khasab II). All 140 control children were a convenience sample selected according to age (9–18 months) and a history of having received a minimum of 3 doses of routinely administered OPV at least 30 days before serum collection (as documented by written record); many of these children had also received a fourth dose during the mass OPV campaign from October to December, 1988.

All 192 sera were tested in triplicate with a modified microneutralisation technique at the Centers for Disease Control (CDC), Atlanta,[12] in dilutions ranging from 1/8 to 1/1024. Statistically significant differences in type-specific antibody titres among the various groups of children were assessed with a non-parametric test (Wilcoxon rank sum test).

Evaluation of the cold chain

All OPV shipments received and stored in Oman during 1987 and 1988 were tracked from the point of arrival at Seeb International Airport, Muscat, to their final destination (usually a peripheral health centre) to see whether storage temperatures and length of storage complied with recommendations of the World Health Organisation (WHO).[13] Additionally, 27 EPI vaccination sites (usually peripheral health centres) were visited to observe current OPV storage, transport, and administration techniques. Because vials of OPV distributed in Oman during 1987 and 1988 had been used up or destroyed (due to expiration) by the time of this review, 138 vials currently in use were collected from regional vaccine stores, hospitals, and health centres on unannounced visits, and submitted to their respective manufacturers and to an independent laboratory (Bureau of Biologics, Ottawa, Canada) for potency testing.[14]

Retrospective evaluation of vaccine potency

All lots used during 1987 and 1988 were traced to three manufacturers. Each manufacturer was asked to provide the results of potency testing before the release of each lot, in addition to current test results from any samples that had been retained. A WHO reference standard was included with all titrations.

Poliovirus transmission among vaccinated children

The incidence of poliovirus infection among vaccinated and unvaccinated children aged 9–23 months was estimated for each region of Oman, based on assumed infection-to-paralytic case ratios ranging from 100/1 to 300/1.[15] The number of children in each region who had received 1, 2, or 3 or more doses of OPV was based on a retrospective review of immunisation records of 9438 children

who were born in 1987, the results of which were extrapolated to all children of 9–23 months. The number of children who remained susceptible to wild poliovirus infection during the outbreak was based on estimates of vaccine efficacy obtained in the case-control study, with the assumption that all unvaccinated children were susceptible to infection and that none had been exposed to wild poliovirus before the outbreak. To obtain the most conservative estimate of infections among vaccinated children, we also assumed that such infections would occur only after all susceptible children had been infected.

Genomic sequencing

To determine the source of the wild type 1 polioviruses from the Oman epidemic, we analysed 3 of the 17 case isolates by partial genomic sequencing. Contiguous nucleotide sequences encoding the carboxy-terminal residues of a capsid protein VP1 (90 nucleotides) and the amino-terminal residues of a non-capsid protein 2A (60 nucleotides) were determined. Sequences were compared by means of a database containing the corresponding nucleotide sequences of more than 150 wildtype polioviruses isolated since 1975 from Asia, Africa, Europe, and the Americas, with techniques described elsewhere.[16]

Results

Case ascertainment

No additional cases of paralytic poliomyelitis were identified retrospectively in health centres and hospitals. Searches in the 167 villages which comprised the catchment areas of 16 randomly selected health centres also failed to detect additional cases. The 118 patients reported previously were thus regarded as the total number of paralytic cases, and were assumed to be representative of all cases that had actually occurred.

Case-control study

Of the 86 case-patients aged 5–24 months reported during the outbreak, 70 (81%) met the case definition for paralytic poliomyelitis and were enrolled into the study. Reasons for exclusion of the other cases included lack of clear-cut neurological deficit at 60 days (10 children); not found (5); and not found in health centre registry (1).

The 70 case-patients were closely matched for age with their 692 controls (median 267 *vs* 260 days); 79% of controls lived in the same village as the corresponding case. Likewise, there were no significant differences in vaccination status between the two groups: 94%, 79%, and 51% of case-patients had received at least 1, 2, or 3 doses of OPV, respectively, compared with 97%, 80%, and 55% of controls. Because the third dose of OPV was not routinely given until 7 months of age, the vaccination rate in the study

TABLE I—AGE, AGE AT OPV ADMINISTRATION, AND INTERVAL BETWEEN OPV DOSES AMONG CASE-PATIENTS AND CONTROLS, OMAN, 1988

Variable	Case	Control	Median difference	p value*
Median age†	267 (70)	260 (692)	7	0·85
Median age† *at*				
OPV1	100 (66)	98 (668)	2	0·04
OPV2	171 (55)	163 (553)	8	0·07
OPV3	247 (36)	228 (375)	19	0·06
OPV4	NA	580 (18)	NA	NA
Median interval†				
OPV2–OPV1	63 (55)	64 (553)	1	0·31
OPV3–OPV2	70 (36)	63 (375)	7	0·21

NA = Not applicable
*Wilcoxon rank sum test †In days
No of cases/controls in parentheses

TABLE II—CLINICAL EFFICACY OF OPV IN PREVENTING PARALYTIC DISEASE, OMAN, 1988

No of OPV doses	Statistical model	Discordant sets: No cases	Discordant sets: No controls	Clinical efficacy*	95% CI
0	..	..	..	Referent	..
1	Unadjusted	11	24	−21%	−389%, 70%
1	Adjusted†	11	24	30%	−234%, 85%
2	Unadjusted	7	15	62%	−80%, 92%
2	Adjusted	7	15	80%	−30%, 97%
3	Unadjusted	5	18	87%	12%, 98%
3‡	Adjusted	5	18	91%	36%, 99%

Data for calculating vaccine efficacy are available upon request from the authors.
*Compared with 0 doses, based on conditional logistic regression appropriate for case-control studies with variable matching
†Controlled for OPV/DTP received within 30 days before date of onset of paralysis in case-patients (or reference date in corresponding controls)
‡18 control children who had received 4 doses of OPV were excluded from analysis, no case-patients were excluded
CI = confidence interval.

population was lower than the national rate at 12 months of age (87%). However, case-patients were more likely to have received each dose of OPV at an older age than controls, with delays ranging from 2 to 19 days (table I).

Estimates of vaccine efficacy are shown in table II. A primary series of OPV (3 doses) reduced the risk of paralysis by 91% (adjusted estimate); two doses reduced the risk by 80%. Because these estimates were based on discordance (dissimilarity) between the vaccination status of case-patients and their controls, and because most case-patients and controls in this analysis had received the same number of doses of OPV (and were therefore concordant), 95% confidence intervals were wide (table II). However, the prevalence of antibodies to poliovirus type 1 was 89% among control children bled 7–12 months (see below) after the end of the outbreak, providing additional support for the validity of the vaccine efficacy point estimate of 91% after 3 doses of OPV. The efficacy estimates hardly changed when the 10 patients without clear-cut neurological deficits at 60 days were included in the analysis.

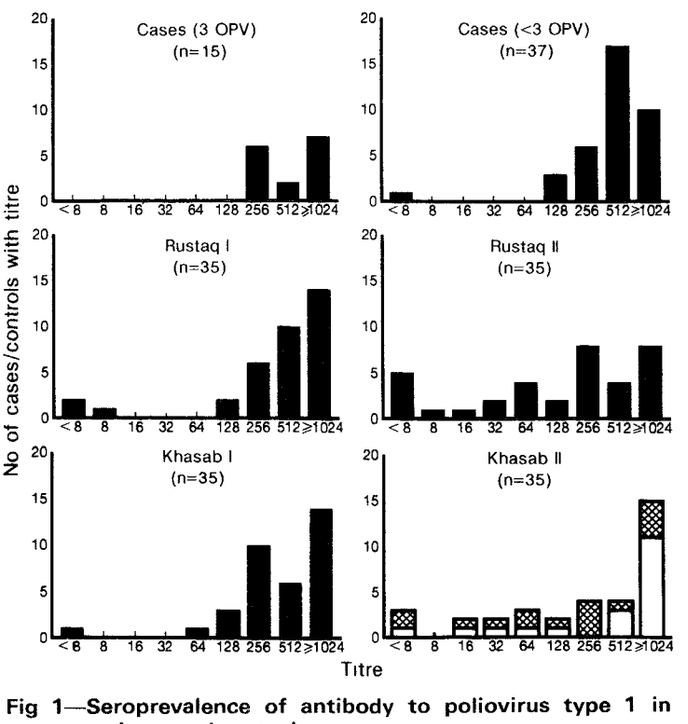

Fig 1—Seroprevalence of antibody to poliovirus type 1 in case-patients and controls.

Born during □ and after ▩ outbreak.

Serology

Unvaccinated and partly vaccinated case-patients, fully vaccinated case-patients, and fully vaccinated controls bled shortly after the outbreak (Rustaq I and Khasab I) had virtually identical neutralising antibody titre profiles to type 1 (fig 1). Although seroprevalence to type 1 was similar in all four control groups (mean 92%, range 86–97%, fig 1), titres were significantly lower in vaccinated controls bled 7–12 months after the outbreak (Rustaq II and Khasab II) than in those bled earlier (geometric mean titres [GMTs] 617 *vs* 243; Wilcoxon rank sum test, $p = 0{\cdot}002$). The association between higher type 1 titres and early specimen collection was maintained for Rustaq ($p = 0{\cdot}003$) and Khasab ($p = 0{\cdot}02$) when children in Khasab who were born during the outbreak (fig 1, open bars) were excluded from analysis.

Analysis of antibody seroprevalence, median titres, and GMTs to poliovirus type 3 provided additional evidence of suboptimum antibody responses to type 3 virus in Omani children who had received 3 or more doses of OPV. As shown in table III, only 43–83% of such children had detectable neutralising antibody to type 3, with GMTs ranging from 15 to 100. Reasons for higher responses in the control groups from Khasab (Musandum region) could not be determined.

TABLE III—SEROPREVALENCE OF ANTIBODY AGAINST POLIOVIRUS TYPE 3 IN CASE-PATIENTS AND VACCINATED CONTROLS, OMAN

Patient/conrol group	No (%) with detectable neutralising Ab*	Geometric titre	
		Median	Mean (95% CI)
Case			
(≥3 doses OPV)	8/15 *(53%)*	9	14 (7,25)
(<3 doses OPV)	12/37 *(32%)*	<8	13 (8,22)
Control†			
Rustaq I	15//35 *(43%)*	<8	15 (8,29)
Rustaq II	18/35 *(51%)*	9	15 (9,25)
Khasab I	26/35 *(74%)*	72‡	54 (28,104)
Khasab II	29/35 *(83%)*	114‡	100 (51,194)

*Based on a screening titre of 8
†All children had received at least 3 doses of OPV more than 30 days before serum collection.
‡Significantly higher compared with other groups ($p < 0{\cdot}01$, Kruskal-Wallis test).

Vaccine potency

All OPV used in Oman during 1987 and 1988 had been supplied from three manufacturers (Smith-Kline RIT, Rixensart, Belgium; Sclavo, Siena, Italy; and Torlak, Beograd, Yugoslavia). Potency testing before release indicated that all 14 lots shipped to Oman had met or exceeded minimum potency requirements set by WHO—ie, $\geq 10^6$, $\geq 10^5$, and $\geq 10^{5\cdot5}$ mean tissue culture infective doses of poliovirus types 1, 2, and 3, respectively.[14]

Cold chain evaluation

Manually maintained temperature records, recording thermometer charts, and WHO vaccine monitor cards for 1987 and 1988 were available from 36 (88%) of the 41 vaccine storage facilities that were evaluated retrospectively, including the central facility in Muscat, 7 of 8 regional stores, 3 of 5 subregional stores, and 25 of 27 peripheral EPI vaccination sites. These and other indicators of vaccine handling and storage procedures failed to reveal any deficiencies that could implicate cold chain failure as a major contributing factor for the outbreak.[17] Apart from a single event lasting 32 hours in one of the regional vaccine stores in 1987, there was no indication that any vaccine vials had been exposed to temperatures above 8°C before distribution or that any had been used beyond the expiration date. Potency testing of vaccine samples collected from central, regional, and peripheral vaccine stores showed no significant decrease in potency compared with samples of the same lots retained by each manufacturer.

Poliovirus transmission among vaccinated children

Vaccination coverage with 3 doses of OPV at the time of the outbreak was 87% for children aged 12 months. Based on the number of reported cases, the overall attack rate of paralytic disease in children 9–23 months was 57/100 000. There was no correlation between vaccination coverage and attack rates by region; the region with the highest attack rate (Batinah, 117/100 000) had one of the highest coverage rates (88%), whereas the region with the lowest coverage (Capital, 71%) had a low attack rate (6/100 000) (fig 2).

As shown in table IV, the outbreak could have theoretically been sustained among susceptible children alone if 1 paralytic case had occurred for every 100 infections. However, based on a higher infection-to-paralytic case ratio of 300/1, which has been seen in various settings,[15] thousands of fully vaccinated children—although protected from paralysis—became infected during the outbreak, in addition to those who became infected as a result of primary vaccine failure. If this estimate is applied to

TABLE IV—ESTIMATED NUMBER OF POLIOVIRUS INFECTIONS IN SUSCEPTIBLE AND VACCINATED CHILDREN, OMAN, 1988

Region	Estimated population 9–23 mo	Estimated no of susceptible children*	No of paralytic cases†	Poliovirus infections‡		Estimated no of infections in fully vaccinated children§	
				100/1	300/1	100/1	300/1
Capital	15 850	3958	1	100	300	−3858	−3658
Batinah	22 314	2933	26	2600	7800	−333	+4867
Dahirah	7194	1253	2	200	600	−1053	−653
Interior	9386	1005	1	100	300	−905	−705
Eastern	10 061	1483	8	800	2400	−683	+917
Dhofar	6126	831	3	300	900	−532	+69
Musandam	1068	111	0	0	0	−111	−111

*Based on review of immunisation records of 9438 children born in 1987 and extrapolating results to all children aged 9–23 mo All unvaccinated children were assumed to be susceptible, along with 70%, 20%, and 9% of children who had received 1, 2, and 3 doses of OPV, respectively (see table II). Data assume that all infections would first take place in susceptible children, infections in fully vaccinated children would take place only after total no of infections exceeded total no of susceptible children
†Confirmed cases aged 9–23 mo. Probable cases (patients with no clear-cut neurological deficit 60 days after onset of paralysis) were excluded from analysis
‡Assuming an infection-to-paralytic disease ratio of 100/1 or 300/1
§Over and above the no of fully vaccinated children (9%) who remained susceptible as a consequence of primary vaccine failure (table II). Regions with a positive balance indicate that other fully vaccinated children, although protected against paralysis, were involved in the chain of transmission. Negative numbers indicate that susceptible children would theoretically remain in the region

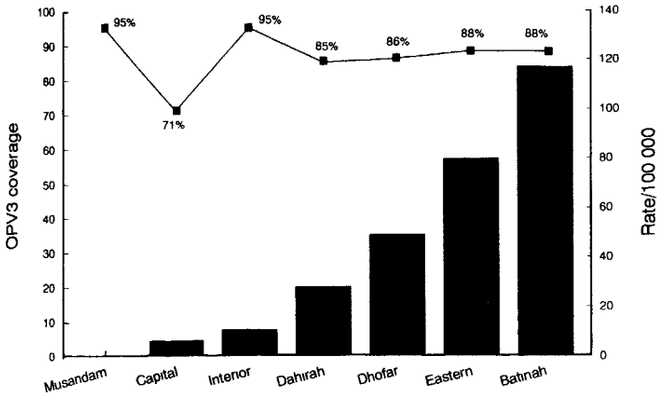

Fig 2—Vaccination coverage (%) and attack rates of paralytic poliomyelitis among children aged 9–23 mo by region, Oman.

the attack rates of paralytic disease shown in fig 2, more than 25% of fully vaccinated children may have been infected in the Batinah and Eastern regions.

Genomic sequencing

The three epidemic isolates analysed by partial genomic sequencing of the VP1/2A region were very closely related to each other (99–100% nucleotide sequence homology); this finding is consistent with the existence of a recent source infection. The isolates from Oman were genetically distinct (78% sequence homology) from wild type 1 polioviruses isolated during the 1988 outbreak in Israel, and from earlier isolates obtained in the Middle East (77–84% homology).[16] The sequence did match (92–97% homology) those of recent type 1 polioviruses from southern Asia,[16] where an epidemic occurred in 1987.

Discussion

Our findings confirm that the outbreak of poliomyelitis in Oman had one of the highest attack rates of paralytic disease that has been reported during the vaccine era, with transmission lasting for more than 12 months. Among the most disturbing features of the outbreak was that it occurred in the face of a model immunisation programme and that widespread transmission had occurred in a sparsely populated, predominantly rural setting. Whether the mass vaccination campaigns were effective in reducing further spread of the outbreak could not be determined because the incidence of disease had already begun to decline.

Although we may never know the causes of the outbreak, several factors seemed to be important in the build-up of susceptible children less than 2 years old. First, rapid increases in vaccination coverage before the outbreak may have reduced or interrupted endemic circulation of indigenous strains, diminishing the contribution of natural infection to overall immunity levels in the general population. Secondly, the number of susceptible infants was further increased by delays in completing the primary immunisation series until 7 months of age, rather than 3·5 months of age as currently recommended by the EPI; the importance of this delay was underscored in the case-control study, which showed significant differences in age at vaccination between case-patients and age-matched controls. Thirdly, the clinical efficacy of 3 doses of OPV (91%) was lower than that observed in industrialised countries, which contributed to a further reduction in the effective levels of immunity in the target population. Sub-optimum performance of OPV was also suggested by our serological studies of case-patients and controls, nearly 50% of whom had no detectable antibody against poliovirus type 3. Additionally, we did not find any deficiencies in the cold chain that could account for these findings. Although our methods may not have been sensitive enough to detect minor fluctuations in freezer or refrigerator temperatures at peripheral health centres, one previous study in the tropics showed that OPV samples left at ambient temperatures for up to 7 days had negligible loss in potency.[7]

Our investigations also raise questions about adequate levels of secretory immunity after OPV, which is believed to confer significant advantages over inactivated poliovirus vaccine in preventing intestinal infection and subsequent excretion.[18,19] Although conservative estimates of the number of infections suggest that transmission could have been sustained among unvaccinated and partly vaccinated susceptible children in at least some regions of Oman, the wide geographic extent of disease, the high estimated attack rates of infection in the Batinah and Eastern regions, unusually high GMTs to poliovirus type 1 among the 70 control children who were bled shortly after the outbreak, and the lack of clustering of unvaccinated infants based on immunisation record reviews suggest that a substantial proportion of fully vaccinated children may have been involved in the chain of transmission. Whether this finding is (or will be) typical of the experience in other developing countries is uncertain. Because sanitation and hygienic practices in rural areas of Oman were relatively poor, the inoculum of wild poliovirus may have been large enough to overcome the usual levels of secretory antibody that would otherwise protect vaccinated children from infection.

Genomic analysis indicated that the poliovirus type 1 strain responsible for the outbreak had been introduced to Oman only recently. To our knowledge, this is the first recorded importation of polioviruses into a developing country that led to an outbreak of this magnitude. Thus, maintenance of high immunisation levels and surveillance for poliomyelitis is essential, even in countries that have substantially reduced or eliminated wild poliovirus infection.

These findings have important implications for the World Health Organisation's initiative to eradicate poliomyelitis globally by the year 2000.[20] The most important strategy to achieve this goal is to raise OPV coverage to greater than 80% by 1 year of age, adhering to the recommended schedule of four doses at 0 (birth dose), 6, 10, and 14 weeks of age to provide protection as early in life as possible. However, our investigation suggests that this strategy alone may be insufficient to achieve eradication, and that supplementary strategies such as changes in OPV formulation,[8] expanding the routine vaccination schedule to include additional doses at birth[21] and at the time of measles vaccination,[7] mass vaccination campaigns,[18,22,23] combined administration of inactivated and live vaccines,[24] or new generation poliovirus vaccines may be required.

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Neutrophil apoptosis and clearance from neonatal lungs

J. M. GRIGG J. S. SAVILL C. SARRAF C. HASLETT M. SILVERMAN

8 newborn babies with airways inflammation, who were mechanically ventilated, underwent bronchoalveolar lavage to examine the fate of neutrophils in the inflamed airways. Light microscopy and electronmicroscopy showed evidence of neutrophil apoptosis and ingestion of intact neutrophils by macrophages in specimens from all 8 infants. Neutrophil apoptosis, without the local release of intracellular contents that promote inflammation, might represent a mechanism by which tissue injury is reduced during the resolution of neonatal pulmonary inflammation.

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Introduction

Severe neonatal respiratory distress syndrome is characterised by alveolar neutrophil infiltration. Neutrophils disappear as the condition resolves, but persist in the airways of infants who develop chronic bronchopulmonary dysplasia.[1] The factors which determine whether neutrophil influx ceases or persists, and the mechanisms by which neutrophils are cleared from inflamed neonatal lungs, are not known. Disintegration of effete neutrophils within the airways might be one mechanism by which neutrophils are cleared, but the cell contents released can injure tissues directly and cleave matrix components into fragments which are chemotactic for leucocytes, thereby amplifying inflammation;[2] such neutrophil disintegration would therefore be likely to lead to persistence rather than resolution of pulmonary inflammation. Indeed, persistently high concentrations of neutrophil elastase in bronchoalveolar lavage fluid are associated with progression to chronic lung disease in newborn babies.[3] Are there other mechanisms by which neutrophils can be removed from the airways without releasing their contents? An alternative fate, observed in vitro and within inflamed joints, is programmed cell death or apoptosis; apoptotic neutrophils are recognised and engulfed by macrophages without release of their contents.[4] We sought evidence for this phenomenon in the lungs of newborn babies who had airways inflammation.

ADDRESSES: **Departments of Paediatrics** (J M. Grigg, MRCP, M. Silverman, FRCP), **Medicine** (J. S. Savill, MRCP), and **Histopathology** (C Sarraf, PhD), **Royal Postgraduate Medical School, Hammersmith Hospital, London, and Department of Respiratory Medicine, City Hospital, Edinburgh, UK** (Prof C Haslett, FRCPE) Correspondence to Dr J M Grigg, Department of Paediatrics, Royal Postgraduate Medical School, Hammersmith Hospital, Du Cane Road, London W12 0NN, UK