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Investigation into a cluster of infant deaths following immunization: evidence for methanol intoxication

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Abstract

A cluster of infant deaths due to severe metabolic acidosis following immunization was reported in a prosperous farming village in Egypt. Fears that more deaths might occur, and of a deleterious effect on national immunization programs prompted an urgent investigation by national and international partners. The deaths, and other previously unrecognized illness following immunization, were associated with excessive topical application of methanol. Methanol was employed as an anti-pyretic and anti-inflammatory agent following injections. Fear of adverse reactions to vaccine had encouraged increasing use of methanol for these purposes. Local physicians and nurses were unaware of the toxicity of methanol and did not consider it in the differential diagnosis, and thus did not offer appropriate life-saving therapy. The interaction of traditional practices and modern medical interventions can have clinically important consequences, and should be considered when programs are introduced and as they are monitored.

1. Background

A cluster of three deaths among infants 2 months of age was reported on 1 December 1999 to the Ministry of Health and Population (MOHP), Expanded Program on Immunization (EPI) program in Egypt. All three deaths had occurred in infants aged 2 months who had received their first scheduled immunizations with diphtheria, pertussis and tetanus (DPT), oral poliovirus (OPV) and hepatitis B virus (HBV) vaccines in an agricultural village (Village A) in the Nile delta, in a health district of the Gharbiya Governorate. The immunizations had been administered in the same session on 29 November 1999, at the village health center. Thirty children received immunizations at this session, and none of the other 27 children were known to have presented to health care practitioners, nor were any other untoward events reported to local public health officials following immunization. All three affected infants had been healthy prior to immunization, developed severe symptoms at approximately the same time, and died within 40 h of immunization. All three had been managed in the intensive care unit of a nearby University Hospital where laboratory tests had demonstrated a severe metabolic acidosis which proved unresponsive to conventional therapy.

During the previous 2 months three older infants from a neighboring village (Village B) had died in the district General Hospital, and these deaths were also suspected to be connected to immunization. Vague rumors emerged of other, similar, incidents over the previous year and in different geographical locations. The news media devoted much attention to these incidents, publishing inaccurate and inflammatory information which potentially could have damaged the immunization program, and in particular, the second round of National Immunization Days (vaccination with oral polio vaccine as part of the global polio eradication effort) scheduled to start on 5 December 1999. Fortunately, the National Immunization Days were well attended and passed without incident.

Mounting concern amongst public health officials and the general public about the safety of the vaccines being used in the immunization programs in Egypt prompted the MOHP

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to assemble a joint team of investigators from the MOHP, the US Naval Medical Research Unit No. 3 (NAMRU-3) and the World Health Organization, to determine the causes of this cluster of deaths and the nature of the association with immunization. We report the findings of this investigation which took place on 14–15 December 1999.

2. Methods

2.1. Clinical record review of fatal cases

Hospital records of the six fatal cases from Villages B and A were reviewed, and the physicians who had cared for these children during their admission were interviewed.

2.2. Epidemiological studies

2.2.1. Case finding

Interviews were conducted with staff at the Health Center in Village A and reports of unexplained illness and deaths were solicited. In addition, medical records at four nearby hospitals were reviewed for infants meeting a standard case definition based on the information initially available. The case definition encompassed any child 9 months of age or less hospitalized in 1999 with convulsions, alteration in level of consciousness or a diagnosis of encephalitis/encephalopathy, unexplained death, or death due to pneumonia. Children with only febrile convulsions and/or bacterial meningitis were excluded.

2.2.2. Cohort study

A retrospective cohort study of all children vaccinated in the 29 November session at the Village A Health Center was designed. A questionnaire was administered to parents collecting information about the child's health, and about health and social events preceding and following the immunization. Questions were asked about feeds, medicines and traditional remedies administered, carers for the child during the peri-immunization period, and the nature of the water supply to the home. Families of the three children who had died during September and October in the neighboring Village B were also interviewed; this data was excluded from the statistical analysis.

2.3. Procedural investigations

Details of the vaccines used in the immunization clinic were compiled, and general vaccine storage, handling and administration practices at the health center were reviewed.

2.4. Laboratory investigations

Parents submitted topical and oral medications which had been given to their children in the post-vaccination period for toxicological analysis by the Central Public Health Laboratory, MOHP, Cairo.

3. Results

3.1. Clinical record review of fatal cases

Table 1 summarizes the six cases in the health district from September to December 1999. The available history of the clinical events both before and after admission to the district General Hospital is less detailed for cases 1–3 from Village B than for the cluster in Village A. Two of the three children from Village B were reported to have had a temperature of 38 °C on admission. For these three infants, the medical notes do not record any examination findings, imaging or laboratory studies to support the diagnosis applied. The cluster which prompted the investigation, cases 4–6, were all managed in the intensive care unit of a nearby University Hospital, where they all exhibited a diminished level of consciousness. Laboratory tests revealed a severe metabolic acidosis (pH 7.2, 6.9, and 6.9, respectively on admission). Three of the children (cases 3, 4 and 6) were reported to have had convulsions. Respiratory depression or other severe respiratory abnormality were explicitly recorded for cases 4–6. Case 1 was believed to have pneumonia, and case three received therapy appropriate for respiratory depression. All six children lapsed into coma soon after admission and died, despite intensive supportive therapy.

Table 1
Summary of fatal cases

Case ID	Age (months)	Date of immunization	Interval to onset of symptoms (h)	Interval to death (h)	Reported diagnosis
1	3	20 September 1999	~48[a]	~48–51[a]	Pneumonia
2	6	11 October 1999	33	34	Encephalitis
3	4.5	11 October 1999	57	>61[b]	Encephalopathy
4	2	29 November 1999	21	31	Post-DPT encephalopathy
5	2	29 November 1999	21	31	Post-DPT encephalopathy
6	2	29 November 1999	8	37	Post-DPT encephalopathy

[a] Little detailed information on timing of events available for this case. Reported to have had onset of symptoms, hospital admission and death on 22 September 1999.
[b] Exact time of death not recorded.

3.2. Epidemiological studies

3.2.1. Case finding

Four local hospitals (a University Hospital, a city Fever Hospital, a district Fever Hospital, and the district General Hospital) were surveyed for additional suspect cases using the case definition given above. The survey revealed a total of 16 additional suspect cases. There were peaks in the number of cases in the age groups 1–3 and 7 months, suggesting a higher risk for these age groups.

3.2.2. Cohort study

Complete data was obtained on 24/30 children in the cohort from Village A. Partial data was obtained on 5/30, but did not include detailed information on use of compresses in the post-vaccination period. One child was out of the village with his family; this child was said to be in good health. The cohort study revealed previously unrecorded illness among vaccines following the 29 November clinic session. In addition to the three children who died, it was discovered that another four children were reported to have experienced drowsiness/unresponsiveness after immunization, and that they recovered without obvious sequelae. The early manifestation of illness in the children who died was elucidated; all first gave cause for concern by cessation of suckling. Following this, they all slept for several hours, before waking up grunting and with an altered, weak cry. Two of the deaths occurred in cousins living in the same household, but these had no close geographical relation to the other dead child's house. None of the three earlier fatal cases from Village B had any close geographical or social contact with each others' households. No obvious common environmental factor could be detected. Oral medication administered after vaccination was not associated with illness or death. Only one child had received paracetamol, and this child had remained well. No child had received aspirin.

Despite careful exploration of other substances and/or medications which might have been concurrently administered to the children, no common factor could be detected for cases resulting in death with the exception of the application of "red alcohol" impregnated compresses to both DPT and HBV injection sites; compresses were applied for long periods of time. All four children who became drowsy or unresponsive had received "red alcohol" impregnated compresses. The association between illness (defined as death or drowsiness/unresponsiveness) and exposure to "red alcohol" was statistically significant ($P \leq 0.005$, one-tailed Fisher's exact test; RR = 2.17). Moreover, the relative risk of illness or death associated with exposure of more than one hour when compared to no exposure or exposure of less than 1 h was 10. All three children from Village A who died were exposed to alcohol compresses for 12 h. The three infants from Village B also experienced prolonged exposure to "red alcohol" compresses. The association between death and exposure to at least one-half bottle (250 ml) of "red alcohol" was also statistically significant ($P = 0.014$ one-tailed Fisher's exact test).

In addition to children who received "red alcohol" impregnated compresses, a number of other children received compresses soaked with water or with medicinal (clear) alcohol. None of these children became unwell. The use of compresses at an injection site as an anti-inflammatory measure appeared to be prevalent in this community. "Red alcohol" was also reported to be used in the community for topical disinfection, and as an anti-pyretic by topical application.

3.2.3. Laboratory results

Samples of "red alcohol" collected from households where children had died, three of which were the remnants of the bottles used after immunization, and one bottle of the same brand which was purchased as a replacement, were submitted for analysis to the MOHP Central Public Health Laboratory in Cairo on 15 December. The bottle labels indicated that the liquid contained therein was 90% alcohol. Methanol was not mentioned in the labeling. All were found to contain 70–90% methanol. Parents of children who had been unwell but survived, or who had remained well, also provided similar bottles which had been used for compresses or rubs on their children. All these bottles of "red alcohol" had been purchased at village groceries.

The methanol is a by-product of the sugar industry, and is produced by one company in Egypt and subsequently supplied in bulk to a number of other companies for bottling and distribution. Red dye is added to distinguish the toxic methanol from medicinal alcohol, but the toxic potential of methanol is not indicated on the label, and many people are unaware of this danger.

3.2.4. Vaccines employed; storage, handling and administration practices

The six children who died had been immunized at three different vaccination sessions: on 20 September 1999 in Village B (one death), on 11 October 1999 in Village B (two deaths) and on 29 November 1999 in Village A (three cases). Vaccines from three manufacturers were administered in the two health clinics. No single lot of vaccine was used in all three sessions or on all children who died. All lots had been distributed to other clinics around Egypt, and no other similar incidents or adverse events have been reported in conjunction with their use. One lot of DTP utilized in the 11 October and 29 November clinic sessions has been tested for toxicity, but no abnormality was demonstrated. No other vaccine lot was used in more than one session. All lots of vaccines from the most recent session were also sent for safety testing which has not revealed any problems. A stringent review of vaccine production protocols for the implicated batches concluded that they were acceptable, and found no indication of any practice which would have deleteriously affected vaccine quality.

Vaccine storage, handling and administration practices were found to be good, and adhered closely to the EPI program guidelines. The refrigerators in which vaccines are stored did not contain any other products, so administration of an incorrect substance or medication was ruled out. The vaccines did not require reconstitution, so the possibility of contamination through an erroneous choice of diluent was also excluded. In all three clinic sessions, other children who remained well had been immunized with vaccines from the same vials used for children who later died. It is the practice of the physicians to examine patients prior to vaccination and to delay immunization for children considered to be unhealthy, including children with minor colds. On average, around 25% of children have their immunization delayed until they have recovered.

Post-immunization care advice offered to parents included the use of paracetamol to treat mild fever, and the instruction to bring the child back to the clinic in the event of any more serious illness. This advice also conforms to EPI guidelines. The nursing staff of the clinics recommended prophylactic application of alcohol compresses at injection sites to minimize local reactions. This advice is not derived from accepted guidelines, and appears to have resulted from a well-intentioned attempt to incorporate local practices to reduce the risk of adverse outcomes following vaccination.

4. Discussion

Considering the two incidents, the number of deaths (six) for the period of time and for any week post-vaccination was far in excess of what would have been expected based on routine mortality data. For the birth cohort which is around 350 in the two neighboring villages totaling 10,000 inhabitants, only nine deaths per year from all causes for children aged 1–11 months would be expected, and only one death every 2 years would be expected to occur coincidentally within 1 week after vaccination. There were no other registered deaths among children under 1 year of age from Village A or Village B between 20 September and 13 December 1999.

In the absence of both post-mortem examinations and retained blood specimens from hospital laboratory tests, the retrieval of methanol and the finding of the its use on the children in case households provide the most direct evidence available to implicate methanol as the cause of death in the affected children.

Although methanol ingestion has been the most frequently encountered route of poisoning, percutaneous absorption of methanol or inhalation of methanol vapor are equally effective in producing acute methanol toxicity in adult and pediatric exposures [1–6]. Percutaneous exposure with fatal outcome has been reported previously. The largest series involved 48 children intoxicated with percutaneously applied alcohol, 21 of whom were intoxicated with methanol. The alcohol compresses were a local treatment for abdominal pain. In this series, 12/21 children receiving methanol compresses died, compared to 2/27 receiving only ethanol compresses. Thirteen of the children receiving methanol had severe respiratory depression, 14 went into coma, 11 had seizures, 7 had anuria or severe oliguria [3].

Pure methanol has an anomalously high diffusion rate through the epidermis, compared to ethanol and isopropanol, because of the more severe damage it causes in the stratum corneum. Pure methanol permeates the epidermis at a rate of 10.4 mg/cm^2 h [7]. In this investigation, households were questioned about the size of the compresses and the duration of application. Wide inter-individual variability of the toxic dose is a prominent feature in acute methanol poisoning [1,2,10], thus, the minimum lethal dose of methanol for humans in the absence of medical treatment is not known for certain. However, on the basis of available human case reports it is between 0.3 and 1 g/kg [8,9].

Young infants are particularly at risk of rapid accumulation of a toxic dose because of their high surface area to volume ratio. The youngest cases could have received a lethal dose with a 10 cm × 10 cm compress in as little as 2 h, assuming that the compresses remained saturated. Some parents reported that they used compresses for up to 12 h. These calculations do not take into account methanol that is eliminated, but high-dose exposure quickly saturates the capacity of detoxifying enzymes and results in half-lives of greater than 24 h and non-linear elimination kinetics [13,14].

The symptoms and signs of methanol poisoning, which may not appear until after an asymptomatic period of about 12–24 h, include visual disturbances, nausea, abdominal and muscle pain, dizziness, weakness and Kussmaul breathing. Declining levels of consciousness, clonic seizures, and coma may develop. Death is usually due to respiratory arrest. Visual disturbances generally develop between 12 and 48 h after methanol ingestion and range from mild photophobia and misty or blurred vision to markedly reduced visual acuity and complete blindness [9]. The principal clinical feature is severe metabolic acidosis of the anion and osmolal-gap type [12]. The acidosis is largely attributable to the formic acid produced when methanol is metabolized. In addition to correction of the acidosis, the mainstay of treatment is administration of ethanol, which has a much higher affinity for alcohol dehydrogenase (the first step in the elimination pathway) than does methanol and is preferentially metabolized, preventing the accumulation of formaldehyde, which is metabolized to formate. Hemodialysis may be employed to remove both methanol and formate from the blood [6,9,11].

The clinical and laboratory findings in the six cases are consistent with methanol intoxication. The diagnosis of pneumonia in case 1, not supported by any recorded clinical or laboratory findings, may have been based on the observation of Kussmaul breathing. None of the children received specific therapy for methanol intoxication and all died. The finding that four other children who received methanol compresses became drowsy or unresponsive is also consistent with methanol intoxication. These children may have sustained sequelae to this exposure, such as

permanent visual deficit, and will be followed-up carefully for early detection and remedial measures.

Anecdotal evidence suggests that "red alcohol", on its own or mixed with vinegar, is widely used in this area as a topical rub and in compresses intended for anti-inflammatory and anti-pyretic purposes. Local medical staff expressed the view that this may have developed from an earlier practice of using vinegar for these purposes. The investigation team received some reports that the practice is found elsewhere in Egypt, and in other countries within and beyond the Middle East. These anecdotal reports require further investigation, to determine the extent of the practice and how it evolved. The clusters of deaths in Villages A and B only came to light because they were multiple, synchronous, events in close temporal relation to immunization. It is likely that there is preventable morbidity and mortality attributable to the misuse of methanol in application to injection sites which goes unrecognized and undiagnosed. The identification of 16 additional children treated in local hospitals who met the case definition clustering between 1 and 3 and at 7 months of age is compatible with the hypothesis of exposure to methanol through compresses applied at injection sites. Children below 2 months of age are less likely to receive injections of any kind which would result in application of alcohol compresses. As there was no available history of previously received injections and/or potential exposure to alcohol compresses, it is impossible to determine at this point which of these cases, if any, might actually be related to "red alcohol" applications. Such a potential relationship would need to be further investigated. Mapping shows that detected suspect cases originated from several districts; this indicates that the problem may extend beyond the two neighboring villages.

Comments from other medical practitioners indicated that because of its low price and easy availability, methanol finds occasional use even in the medical setting; ethanol and isopropanol are expensive and their availability is carefully regulated.

These practices suggest that old, previously well-known lessons have been forgotten and need to be re-learned. The red coloring and scent added to methanol were designed to alert people to the distinction between it and the less toxic ethanol and isopropanol, but in the absence of a warning of the dangers of misuse on the label, both the lay and medical communities were unaware of its dangers. Because the risks have been forgotten, the characteristic presentation of methanol poisoning was unfamiliar to physicians, who did not consider it in the differential diagnosis and hence, initiate life-saving therapy. Medical technologies are absorbed into the communities into which they are introduced and do not remain unaltered by their milieu; therapeutic and prophylactic programs must be aware of potential interactions with local practices.

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