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FOR DEBATE
Did a then unknown virus, HHV-6/7, give rise to the whooping cough vaccine controversy of the 1970s?

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SUMMARY

During the 1970s there was a gross loss of public confidence in infant diphtheria-tetanus-pertussis (DTP) vaccination in the UK. As well as febrile reactions and convulsions, permanent neurological damage was ascribed to the pertussis component of the vaccine, and those concerns resonated worldwide. The subsequent recognition of human herpes virus 6 (HHV-6) and 7 (HHV-7) as common sources of fever in infancy suggests that they were the main underlying cause of what was reported as DTP constitutional side-effects. With more precise data on the incidence of HHV-6/7 and other virus infections in early life it would be possible to model the concurrence of viral illnesses with routine immunizations. Adventitious viral infections may be the cause of side-effects ascribed to the numerous childhood immunizations now being given.

Key words: DTP vaccine, HHV-6/7, modelling, side-effects.

INTRODUCTION

Whooping cough was one of the leading causes of death in infancy until pertussis vaccine transformed it from an epidemic to a low-incidence disease [1]. In the UK that vaccine came into general use in the late 1950s, and since then it has been routinely given along with diphtheria and tetanus toxoids (DTP) in various three-dose schedules. In the 1970s the routine UK DTP schedule for immunizing infants was at 3, 5 and 10 months, although this has since been altered to an 'accelerated' 2, 3 and 4 months schedule. This provides young infants with a degree of protection, and a further dose of DTP in early childhood protects them more fully. The later dose means that older children are less likely to infect their infant siblings with pertussis.

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By the early 1970s the acceptance rates for the DTP vaccine in UK were high enough to prevent epidemic whooping cough entirely, and this virtually eliminated the disease in infancy. By then, however, recall of the severity of unmodified infant whooping cough had begun to wane, and when in 1974 Wilson and colleagues reported from Great Ormond Street Hospital, London, a series of cases with arrested neurological development following DTP immunization the safety and purpose of the pertussis component of the vaccine were called into question [2]. The publication of these retrospectively gathered cases from a prestigious centre attracted the notice of the Press, as it did of a Glasgow epidemiologist, Professor Gordon Stewart. Stewart was sceptical about the value of pertussis vaccine in an era when, he argued, rising levels of child health meant that infants were no longer so vulnerable to respiratory illness. He collected cases of alleged post-DTP reactions, and by 1981 he was able to describe 197 'well documented' cases selected from 1127 that had been reported to him [3]. The cases

dated from the 1950s onwards, and Stewart used them to support his contention that there was a 'pertussis reaction syndrome' involving permanent neurological damage.

Among other less serious but more frequent side-effects reported in association with DTP by Stewart and others were local reactions, fretfulness, fever, spasm, febrile convulsions and temporary collapse, and so parents began to question the safety of the vaccine. Many chose to have their children immunized with the DT toxoids alone, and some refused vaccine altogether. Some immunization nurses and doctors, being unsure about the pertussis component, became reluctant to endorse DTP. There was fear of litigation by parents of damaged children, and some parents of handicapped children who had routinely received DTP in the past did indeed seek compensation from Government and/or the manufacturers [4].

Consequently, DTP acceptance rates in UK almost halved during the later 1970s, and statutory notifications showed that whooping cough was epidemic in 1978, 1982 and 1986. Meanwhile the pertussis component of DTP had also come under suspicion in the United States, Europe, Soviet Union, Australia and Japan, and although public health authorities strove to make the case for DTP the incidence of whooping cough, and infant deaths from it, rose. In the United States, in the absence of any publicly funded compensation for vaccine damage, the debate about the safety of DTP became as contentious as it was in UK [5].

Pertussis vaccine: safe or not?

In the light of more recent knowledge did those misgivings about pertussis vaccine have any substance? Two inquiries were set up in the UK at the time. The first, 'The Childhood Encephalopathy Study', reported in 1981 on the first 1000 young children notified to it by clinicians on the basis of serious neurological illness arising within a week of DTP or DT immunization [6]. Thirty-five (3·5%) of the children reported to the study and 1·7% of control children had received DTP within that interval. The estimated attributable risk of serious illness in the week following a DTP injection was 1: 110 000, and of persisting serious illness 1 year later, was 1: 310 000. After a 10-year interval 80% of the study cases and comparable controls were followed up [7]. The 12 children with a persisting adverse outcome who had had DTP within a week of its onset was proportionately no more than found in the controls. The authors concluded that there was a small excess risk of a severe neurological outcome immediately after a DTP injection, but that the risk of permanent damage, if any, must be very slight.

The second UK inquiry avoided bias inherent in assessing risk by collecting data on children already suspected to be vaccine damaged. It compared cohorts of infants prospectively according to whether they had received alum-absorbed DTP ($n = 6004$), or DT whether alum-absorbed ($n = 3024$) or unabsorbed ($n \approx 1000$) [8]. That study found a small excess of transient reactions after each dose of absorbed DTP, and more local though not constitutional reactions after the third dose both of DTP and DT; but at 6–8 weeks follow-up no persisting damage was reported with either vaccine. A similar prospective study in the United States compared 0- to 6-year-old recipients of 15 752 doses of DTP with the recipients of 784 doses of DT. Immediate brief local and constitutional reactions were more frequent in the DTP recipients, but none of the recipients had sequelae [9]. These and other 1980s data supported a medical consensus that the benefit of preventing epidemic whooping cough far outweighed any harm due to the reactions associated with DTP.

Forensic scrutiny also failed to find any characteristic or lasting neurological deficit related to DTP immunization so that in time more rigorous criteria began to be applied in UK and US courts. In a landmark English trial in 1988 before Mr Justice Stuart-Smith no compensation was awarded [4]. The UK Health Departments and their counterparts abroad became more confident in recommending DTP, and by 1990 acceptance rates in UK had returned nearly to their early 1970s level. UK statutory whooping cough notifications also fell sharply. Later, acellular pertussis vaccines with less local reactivity were adopted by several countries including the UK [10].

The discovery of HHV-6/7

Shortly after the landmark 1988 trial Yamanishi and colleagues reported that a recently discovered human herpes virus, HHV-6, was the cause of the rash disease of infancy, exanthema subitum [11]. A closely related virus, HHV-7, was also shown to cause the rash. It was reported that in early infancy the prevalence of maternally derived antibody that might protect from HHV-6 infection fell from 52% to 5%, and that then the incidence of primary HHV-6 infection became

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very high in the succeeding months. To quote: 'almost all children will be exposed … in the latter half of the first year of life and will have the antibody against the virus' [12]. Infection with HHV-7 tends to occur slightly later [13], but by age 2 years about 90% of children are seropositive for HHV-6/7 [14]. HHV-6/7 infections are probably due to exposure to the saliva of a virus-excreting parent, sibling or nursery contact, and such primary infections often cause fever and irritability lasting 3–5 days. In so far as convulsions in young children, most common in the second half of the first year and the second year of life, are due to high fever they are in part likely to be caused by HHV-6/7 [15].

Could HHV-6/7 infection have accounted for the pertussis vaccine associated effects?

In 1988 Mr Justice Stuart-Smith had not been in a position to implicate HHV-6/7, but he did allude to coincident viral infection as a possible cause of illness after pertussis vaccination. He may have been aware of the historical example of 'provocation' poliomyelitis [16]. Whether the clinical features of coincident HHV-6/7 infection in recently immunized infants can masquerade as DTP effects, and whether, perhaps, HHV-6/7 can potentiate the effects of vaccination may still seem to deserve attention, but a prospective age-matched controlled study of the relationship between HHV-6/7 infection and DTP immunization would now scarcely be possible as the current DPT schedule precedes the peak period for HHV-6/7 infection. There is, however, a general case for reviewing the acquisition of these and other known and unknown virus infections in infancy by 'open-ended' approaches such as the inoculation of cell cultures and the use of broad spectrum polymerase chain primers, and then modelling the results against prevailing vaccine schedules. The principle that a vaccination should be delayed if an infant is unwell depends on clinical recognition and it cannot wholly prevent infants being immunized during an intercurrent infection which is then interpreted as a vaccine side-effect.

DISCUSSION

Experience has shown that claims of a significant rate of vaccine side-effects that are based on retrospective clinical series are not always reliable, yet they can have very disruptive consequences. As regards the apparent side-effects of the pertussis component of DTP vaccine in the 1970s, the discovery of HHV-6/7 offers an alternative explanation for most of the effects reported, as has previously been suggested by Ward and colleagues [17]. Further routine childhood immunizations have been introduced since the 1970s, and with them have come reports of side-effects of varying plausibility [18–20]. Other coincidental virus infections may account for some of these effects so that it may well be worthwhile to model the coincidence of viral infections in the first years of life with routine vaccine schedules.

Reports of vaccine side-effects are not easy to evaluate. Nonetheless it is important to do so and to be able to prove that any established undesirable effects are both very rare, not clinically predictable, and greatly exceeded by the benefits of a routine immunization. Obtaining that proof may involve costly prospective studies against which preliminary modelling of possible intercurrent viral infections would be both quicker and cheaper. Furthermore, the possibility that an outbreak of a 'new' virus, e.g. a parechovirus [21], may be involved should not escape clinicians' minds.

Retrospective case series will remain important in alerting to vaccine side-effects, but investigation of their validity, particularly recognition of any pre-existing disabilities, is essential, and *post-hoc* conclusions must be avoided. As Dr Johnson is reputed to have said, 'it is incident I am afraid, in physicians above all men, to mistake subsequences for consequences'.

DECLARATION OF INTEREST

None.

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