Measles, mumps, rubella vaccine: Through a glass, darkly

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Introduction

In the face of mounting enthusiasm for new, multiple antigen (polyvalent) childhood vaccines[1] concerns have been raised over safety, particularly for the measles, mumps, rubella (MMR) vaccine. Delayed adverse events involving chronic inflammation of the gastrointestinal tract and regressive autistic spectrum disorder are subjects of both continuing debate and ongoing litigation, in this respect.[2-6] These concerns are unlikely to abate in the foreseeable future, and certainly not until both the medical profession and the public can be reassured about the integrity of the foundations that were laid in the original safety trials, and upon which current dogma rests. The official position is that MMR vaccine is safe;[7] this paper examines the evidence.

The principal focus of this paper is pre-licensing studies of MMR. It is the conduct of these trials, where inclusion of appropriate controls is possible, that provides the best opportunity for not only identifying acute adverse events, but also, for establishing appropriate mechanisms for long term surveillance to identify delayed sequelae. It becomes increasingly difficult to identify appropriate control groups beyond the point of widespread introduction of a vaccine. The first thing to note is that these were short-term safety studies, with periods of observation lasting at most 28 days, and often considerably less.[8-10] For live viral vaccines—particularly when combined—delayed, unpredictable, and insidious adverse events should also have been a concern. When considering how short-term safety studies of live viral vaccines might act as a sentinel for identifying unexpected long-term adverse events, we are provided with a model *par excellence* in measles virus. Measles virus, and to a lesser extent, measles containing vaccines, are causally associated with both acute and delayed encephalopathic events.[11-14] For measles virus, this association was evident at the time MMR vaccines were developed, particularly since the discovery of this agent as the cause of subacute sclerosing panencephalitis (SSPE) in the mid- to late 1960s.[15,16] Accordingly, in order to monitor the impact of monovalent

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measles vaccine upon this condition, SSPE case-registers were established in both the United Kingdom (UK) and United States of America (USA) circa 1968.

Beyond 1968, therefore, it was known that measles virus could produce both acute and persistent infection of the central nervous system, and that this infection could cause acute and delayed encephalitis, respectively. In pre-licensing trials of MMR, acute adverse events involving alternative anatomical sites might have alerted the authorities to the potential for delayed pathology. For example, since measles is an enteropathic virus, capable of causing acute gastroenteritis, mesenteric adenitis, acute appendicitis and ileo-colitis,[11,17-20] the gastrointestinal tract would be one such site. Had complications such as acute gastroenteritis been identified in these trials, the potential for delayed pathology might have been considered equally plausible. The potential for delayed intestinal pathology is borne out by Fournier *et al.*'s demonstration of persistent measles virus infection of the diseased appendix in 1968.[21] We are now aware that delayed excess mortality months or even years following vaccination has been observed with some measles vaccine formulations.[22]

Pre-licensing safety trials of MMR

Prior to its licensing in the USA in 1975, trials of combined MMR vaccine safety were the subject of two relatively small-scale controlled studies.[8,9] These studies were preceded by a smaller pilot study of MMR in 1969,[23] which will be referred to later in this paper.

In 1971, Stokes *et al.* reported a comparison of 228 children who received MMR vaccine (Moraten strain measles) with 106 unvaccinated controls.[8] Two geographically distinct populations were examined, one from a developed country (Philadelphia, USA), and one from developing countries (Costa Rica and San Salvador). Data on adverse events in both groups were gathered for 28 days post vaccination and combined for the purpose of statistical analysis.

Given the current concerns over possible gastrointestinal adverse events following MMR vaccine, these merit particular attention when reviewing the data. Gastroenteritis, although specifically recorded, did not emerge as a cause for concern in the analysis, as presented.[8] Clearly, when interpreting these data one must first address the question of the comparability of two culturally, economically, and geographically distinct groups and consider, therefore, whether a combined analysis may obscure some relationships? For example, it is evident from the data that, over the 28-day period of clinical reporting, the difference in the background rate of gastroenteritis in unvaccinated controls from Costa Rica–San Salvador (44%) compared with Philadelphia (5.6%) was highly statistically significant (odds ratio 13.1; confidence interval (CI) 5.19–35.06; $P < 0.001$).

The difference between these populations comes as no surprise, being entirely consistent with the marked difference in patterns of childhood enteric infection

Table 1.
Summary of cited, peer reviewed studies bearing on safety of polyvalent measles containing vaccines, prior to licensing of MMR in the UK (1988)

Study & Year	Location	Study & Vaccine	Cases	Controls	Length of follow up for detection of adverse events	Relevant outcome
Buynak et al.[18] 1969	US	Comparison of serological and clinical responses to MMR, MM, and monovalent measles vaccines	166 (7–38 children per group)		12 days	Viral "interference" identified
Stokes et al.[8] 1971	US/ Costa Rica/ San Salvador	Safety and efficacy MMR	228* (US=77 of total*)	106* unvaccinated	28 days	Gastroenteritis identified as a significant adverse event in US children
Minekawa et al.[57] 1974	Japan	Comparison of serological and clinical responses to MMR, MM, and monovalent rubella vaccines	174 (5–44 per group)		15 days	Viral "interference" confirmed
Schwarz et al.[9] 1975	US/Santo Domingo/ Panama	Safety and efficacy MMR	1232* (US=282 of total*)	249* placebo	21 Days	None—data merged in analysis and not provided for individual countries
Crawford & Gremillion[58] 1981	US	Safety and efficacy measles–rubella, monovalent measles and monovalent rubella vaccines	512	835 unvaccinated	19 Days	Viral "interference" confirmed
Miller C et al.[10] 1987	UK	Safety and efficacy MMR	10000	None	21 days	Gastroenteritis identified as a specific adverse event Diarrhoea "common"(26% of vaccinees)

between developed and developing countries.[24,25] This difference in the background rate of gastroenteritis—an analysis not presented in the original study—may be important to the interpretation of the possible adverse effects of MMR. When data for children from Philadelphia are analysed independently of those from Costa Rica–San Salvador, gastroenteritis is statistically significantly more common in vaccinees (22.4%) compared with unvaccinated controls (5.6%) (odds ratio 4.8; CI 1.89–12.92; $P < 0.001$; significance was unaltered by Fisher's exact test. Figure 1). In contrast, in the Costa Rica–San Salvador cohort there was no statistically significant difference in the rate of gastroenteritis between recipients of MMR vaccine (50%) and unvaccinated controls (44%) (odds ratio 1.27; CI 0.88–1.83; $P > 0.1$). Combination of the data sets, as presented, obscured these facts due to the high background rate of gastroenteritis in Costa Rica–San Salvador. Moreover, it is biologically plausible that measles, a virus that readily causes enteric infection[11,17-20,26] is responsible for the clinical pathology that was observed.

A significant excess of "unrelated illness" (including otitis, allergy, viral infection, and abdominal pain) was also seen among the Philadelphia vaccinees: 39% compared with 12.2% of controls (odds ratio 4.58 CI 2.33–9.15; $P < 0.0001$. Fig. 2). Some of the excess of gastroenteritis and "unrelated illness" among vaccinees is likely to be due to reporting bias as the controls did not receive placebo. However, the strikingly different temporal trends in reporting gastrointestinal symptoms and "unrelated illness" (Figs 1 and 2) suggest that
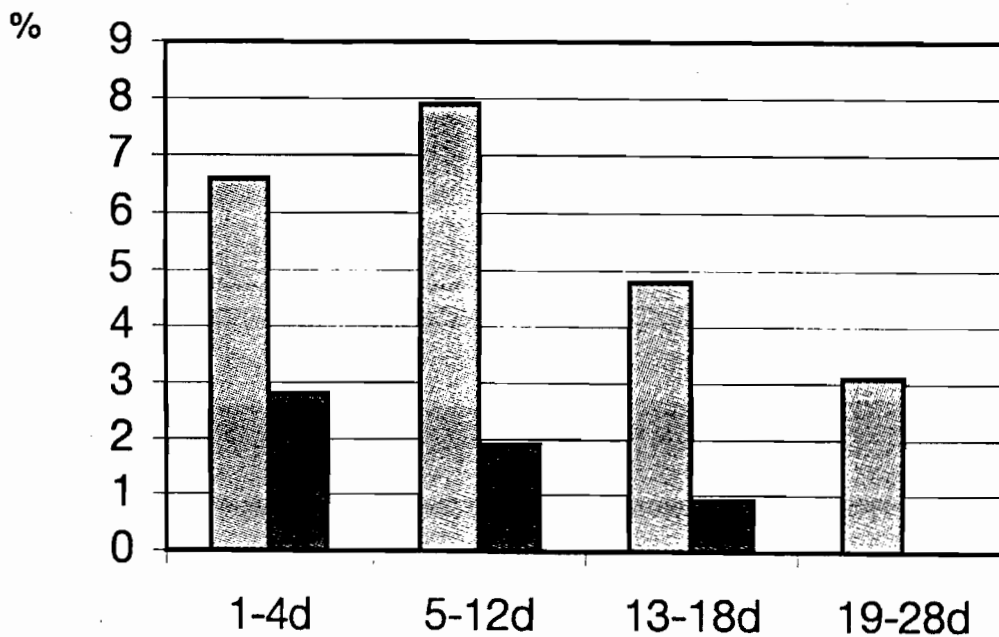

Fig. 1. Frequency of gastroenteritis in vaccine recipients (▨) compared with controls (■). Even at days 19–28 (x-axis) there is a > 3-fold difference between vaccinees and controls. Y-axis shows the % of children exhibiting clinical features. From Stokes et al.[8]
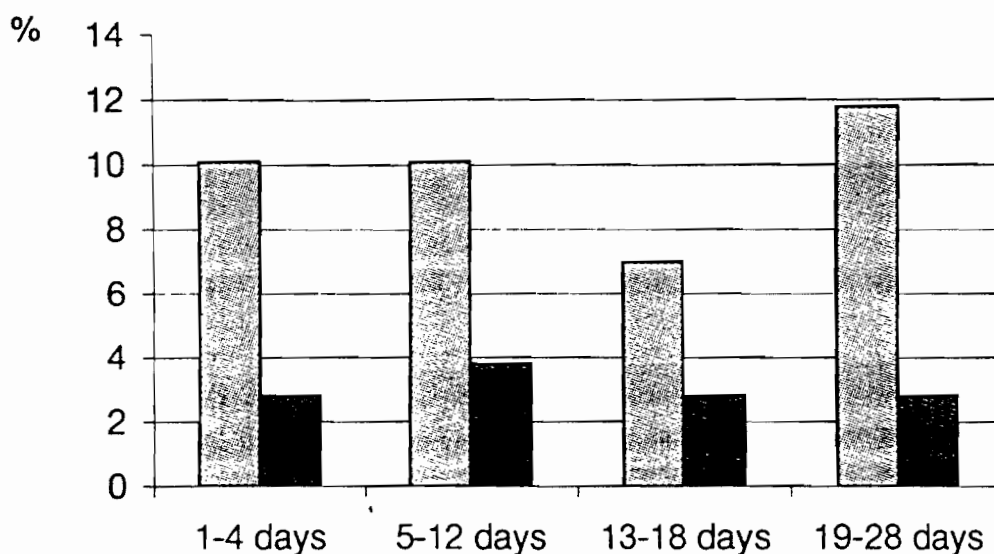
Fig. 2. Frequency of "unrelated complication" comparing MMR vaccine recipients (■) with controls (■). Even at days 19–28 (x axis) there is a > 5-fold difference between vaccinees and controls, with no signs of declining. Y-axis shows the % of children exhibiting clinical features. From Stokes et al.[8]

this bias may not fully account for both sets of symptoms. It is unfortunate that the unrelated illnesses are not presented separately as this may also mask relationships. Clearly, a more detailed sub-analysis should have been presented, and beyond this point these events should have been a focus of specific attention in studies of MMR in developed countries. Some of these events have since been associated with exposure to measles containing vaccines.[26,27]

Availed of this information, Schwarz et al.—representing commercial competitors—conducted a study of MMR vaccine (Schwarz strain measles) that was reported in 1975.[9] Like the Stokes study[8] it comprised two socio-economically distinct populations: first, 282 children from Ohio and, second, 926 children from Santo Domingo in the Dominican Republic and 373 children from Panama. The groups were randomized to receive MMR vaccine (1232—of whom only 36.2% were susceptible to all three infections) or placebo (249). As with the Stokes study,[8] data from all countries were combined for the purpose of statistical analysis. Unlike the Stokes study, however, no data were provided that allowed for independent analysis of the adverse events from Ohio and Santo Domingo–Panama. However, there is no reason to suspect that Schwarz's MMR vaccine should behave qualitatively differently from that used by Stokes et al. A comparative analysis of three monovalent measles vaccines showed no statistically significant difference in the rate of gastrointestinal symptoms, by 28 days, between recipients of either Schwarz strain (22/284; 8%), Stokes–Moraten strain (28/273; 10.2%), or Enders–Edmonston strain (28/256; 10.9%).[29]

In a small post-licensing study in the UK, reported in 1991, that compared reactions to MMR (Schwarz strain measles, Urabe AM/9 strain mumps) with

those of monovalent measles vaccine (Schwarz), Eddes identified a very high rate of "gastrointestinal disorders" occurring in 41.9% and 37.8% of children receiving the respective vaccines.[30] This reaction was as frequent as the established clinical features of rash and pyrexia. Without reference to the American pre-licensing studies,[8,9] the authors dismissed the gastrointestinal problems as representing normal "background" illness. Unfortunately, without an unvaccinated control group, it is very difficult to assess what proportion of these gastrointestinal symptoms represent the "background" rate. Differences in definitions and surveillance practice make it difficult to compare background rates, but without detailed investigation the rates reported by Eddes *et al.* appear comparable to those for children in developing countries in the early 1970s.[8]

It is evident that the numbers of children included in these studies[8,9,10,30] were too small to detect uncommon adverse events in susceptible children receiving MMR. Combining two distinct groups with widely differing background morbidities, in both pre-licensing safety studies of MMR vaccine,[8,9] may have masked gastroenteritis as a significant adverse event in children from developed countries. Since the denominator population was skewed heavily in favour of children from the developing countries in both studies (77%[8] and 81%[9]), masking of gastroenteritis as a possible adverse event in American children, is highly plausible. There is also evidence to suggest that, due to differences in early environmental exposures, children in developing countries may be at less risk of chronic inflammatory bowel diseases, putative adverse events following MMR vaccination.[31,32]

In the year prior to its general introduction in the UK in 1988, when it replaced monovalent measles vaccine, a surveillance of adverse reactions to MMR was conducted on approximately 10000 children.[10] The trial was not controlled and follow up was 3 weeks. Although acute gastrointestinal adverse events are described as common, occurring in up to 26% of vaccinees, no comparison data are available. As such, there is little further information that can be gathered from the trial reports.

In the context of possible delayed gastrointestinal complications from measles vaccines, warning shots were received from a series of studies of monovalent measles vaccine undertaken in Senegal,[33] The Gambia,[34] Guinea Bissau,[22] Haiti[35] and Peru.[36] In an effort to identify a measles vaccine strategy for developing countries that could overcome the effects of passive, maternal antibody—a biological barrier to seroconversion in infants—high titre measles vaccines were administered to babies under 1 year of age. Unexpectedly, there was significant delayed excess mortality in female recipients of high titre— compared with standard titre vaccine. Diarrhoea deaths were prominent. In addition there was a delayed excess morbidity involving both wasting and growth that was observed in males and females with both medium and high titre measles vaccines when given at 9 months of age.[37] Insights into a possible mechanism for these delayed adverse events were provided by a study from Leon *et al.* in Peru.[36] The authors identified subtle but consistent aberrations in

cellular immunity in recipients of high titre compared with low titre measles vaccine. The effect was observed in both sexes, although it was more pronounced in females than males, consistent with the morbidity and mortality data. Garenne, who was among the first to report the findings of delayed excess mortality in west Africa, is revealing in his summary of the events that led up to the World Health Organization's withdrawal of high titre measles vaccines, when he wrote; "there was early enthusiasm [for this vaccine] and negative findings tended to be ignored".[38] Hilleman of Merck, when reviewing these studies, highlighted both the diarrhoea-associated deaths and persistent immunodeficiency,[39] stating that, "The process bears resemblance to AIDS". It is notable that in children with autistic regression where the parents suspect a link with MMR, immunodeficiency and enterocolitis have been identified.[3,4,40-42]

One important aspect of these acute safety studies was the period of what may be loosely termed "clinical observation". Griffin (1996) reminds us that replication and spread of the measles virus occurs during a latent period of infection of up to 21 days, that spans the time from exposure to appearance of clinical symptoms.[43] Therefore, periods of observation of less than 21 days would not comprehensively cover even the latent period. Despite this, rather than increasing the period of follow-up, 4 years later Schwarz et al. had reduced it to 21 days,[9] the time frame that was subsequently adopted in the UK study of Miller et al.[10]

The restricted view that was provided by such a narrow window of observation has been highlighted by studies on the association between MMR and idiopathic thrombocytopenic purpura (ITP), the onset of which may be up to 59 days post-vaccination.[45] A further example was provided by Farrington et al. of the Public Health Laboratory Service (PHLS), in their reporting of meningo-encephalitis caused by the Urabe strain of mumps virus, as a component of the MMR vaccine.[45] The "at risk" period for this event is considered to be 15–35 days, with the majority of cases in the original report occurring either at or beyond 3 weeks post vaccination.[46]

Viral interference and compound effects

A major consideration in the context of polyvalent vaccines such as MMR, is the potential for adverse interactions between the component live viruses, particularly in view of the immunosuppressive properties of measles virus.[1] In addition to the elements of unnatural age for exposure to the normal disease, route, dose, and strain of infectious exposure, the childhood immune system must cope with a combination of viruses that it would have been extremely unlikely to encounter under circumstances of natural exposure. In an executive summary, members of a committee to whom vaccine-related events were reported in the USA, reiterated this anxiety in the context of virus-induced immunosuppression and polyvalent vaccines.[47] They stated, "It may be asked, then, whether the use of combination viral vaccines might exacerbate the

potential problem of immune suppression. The committee found no report of a systematic comparison of the effects of monovalent and polyvalent live attenuated vaccines on immunity".

In 1995 concerns over the potential for interference between the components of vaccines were raised again at a meeting of USA vaccine officials.[48] Specifically, Belshe (St Louis) stated that: "To be confident that a particular vaccine had no effect on another vaccine given simultaneously, comparative studies should be performed".

Halsey (Johns Hopkins) considered that such studies would be both "too large" and "unnecessary". Halsey conceded, however, that: "If there is a biological reason to suspect that there may be interference or blunting or blocking, then comparative studies should be done"

Is there a "biological reason" to suspect that "interference" may occur between the component viruses of MMR? It is evident from a literature search prior to 1977, that the outcome from measles infection may be influenced by close temporal exposure to another virus. A close temporal exposure to measles virus and another infection, for example, chickenpox[49] or an encephalitogenic enterovirus,[50] is associated with an excess risk for SSPE. Virological data suggest that SSPE may actually be caused by concurrent cerebral infection with measles and another viral agent.[51,52] With respect to possible adverse events that are currently topical, atypical patterns of exposure to measles, mumps, rubella and chickenpox have been associated with both autism[53,54] and, for measles virus, developmental regression.[14,55] *In utero* and infant exposures have been identified as periods of apparent susceptibility, when both the brain and the immune system are undergoing rapid development. It is notable that a close temporal relationship in the exposure to more than one of these infections during periods of susceptibility, may compound both the risk and severity of autism.[53] Similarly, atypical patterns of measles infection, including a close temporal exposure to mumps infection, but not other common childhood infections, has been identified as a significant risk factor for classical inflammatory bowel disease, Crohn's disease and ulcerative colitis.[56]

Clues that the component viruses of MMR could interfere, one with another, were provided in the very first pilot studies of this vaccine. In 1969, Buynak *et al.* sought to examine the effects, in humans, of various combinations of measles, mumps and rubella strains.[18] Their stated purpose was to examine; "the least quantity of virus required to induce effective immunity; the durability of antibody response, and; the stability of the rubella vaccine". Safety is not mentioned, although in addition to seroconversion, end-points included the comparative frequency of measles rash and fever. Children (7–38 per group) aged 10 months to 13 years, were given trivalent MMR, bivalent measles and mumps, or monovalent measles (Enders or Moraten strains), mumps (Jeryl–Lynn strain) or rubella (HPV-77 strain) vaccines. Despite the fact that the study was further complicated by the use of different viral doses in different combinations, some interesting observations were made.

In terms of a measles rash, a feature that reflects the cellular immune response to this virus,[11] Enders measles vaccine combined with mumps produced rash in 30.8% of children compared with 3.4% using the Enders vaccine alone (odds ratio 12.44; CI 1.00–633.91; $P = 0.026$). What is surprising about this result is that the titre of monovalent Enders vaccine was 6-fold greater than that used in the bivalent vaccine, and yet the frequency of measles rash was 10 times less.

A temperature of greater than 99 °F was induced in 100% of those receiving the bivalent vaccine but only 76% of those receiving monovalent Enders vaccine, although this difference was not statistically significant.

In those receiving Moraten measles vaccine alone compared with those receiving bivalent mumps and Moraten measles vaccine (at an equivalent dose to those receiving the monovalent vaccine alone), pyrexia was detected in 28.6% and 47% respectively. This did not achieve statistical significance although the numbers studied were small. Taken together, these clinical data suggest an influence of mumps vaccine upon the clinical response to measles vaccine that, for the latter, is strain dependent.

Mumps seroconversion rates also differed, although the data are difficult to interpret since the dose of mumps vaccine that was used, varied markedly between the 3 combinations that were compared.

Despite evidence of the potential for dose- and strain-dependent interactions between the component viruses in the MMR vaccine, in the context of antiviral immune responses and, therefore, possible adverse events, the matter was left in abeyance.

Six years after Buynak's study, in 1974, the potential for interference in MMR was subject to a more detailed follow up of the original observations, by Minekawa et al.[57] Once again, the most striking observation was of a dose-dependent influence of the mumps vaccine (Urabe AM-7 strain) upon not only clinical reactions to the measles component (Fig. 3), but also seroconversion to rubella vaccine. This same pattern of interference was also indicated by the study of Eddes et al. that compared clinical reactions to monovalent measles and MMR vaccines.[30] Despite using a 10-fold higher titre of measles virus in the MMR compared with the monovalent vaccine, the frequency of measles rash was lower, with rates of 43.9% and 51%, respectively.

The ability of mumps virus to interfere with the cellular immune response to certain strains of measles virus and, thereby, in particular combinations potentially to reduce viral clearance and increase the risk of persistent infection and/or initiate immune dysregulation, is an intriguing hypothesis to some of those involved in the current debate. Whatever the ultimate merits of this hypothesis, the contemporaneous interpretation of the authors was that further studies were necessary.[57] However, it does not appear, from the published literature, that these further studies were undertaken.

Further compelling evidence of viral interference—in this instance, between the measles and rubella vaccines—comes from Crawford and Gremillion's study
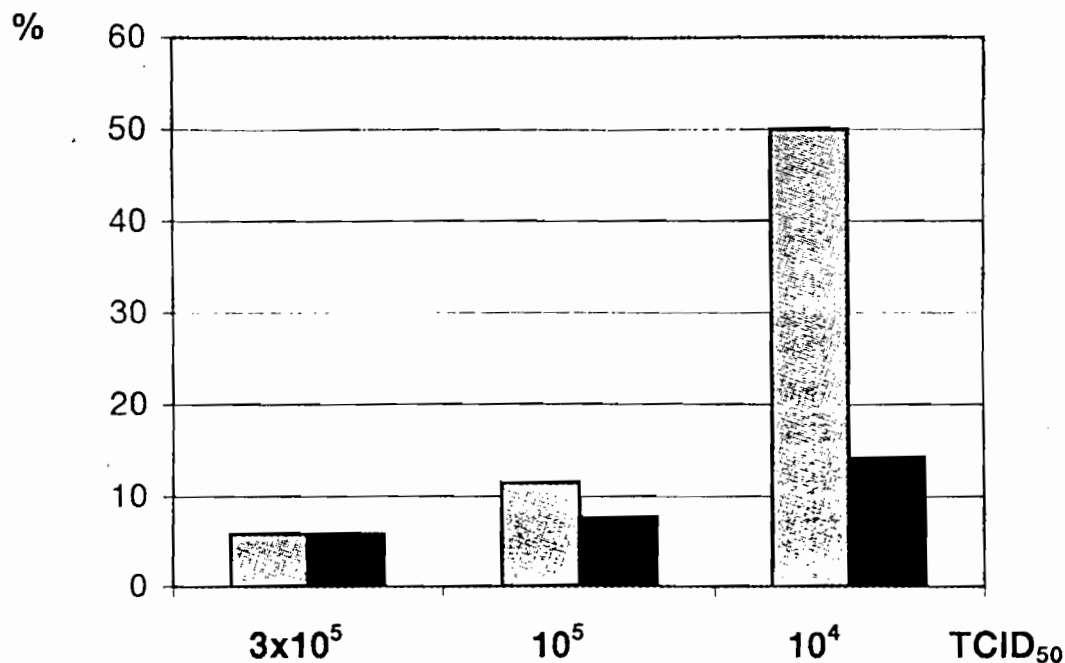
Fig. 3. Dose-dependent interference of mumps virus in the clinical response (fever ■, rash ■) to measles virus in the bivalent measles mumps vaccine. Mumps dose (x-axis) is expressed in tissue culture infective dose-50 (TCID50). Y-axis shows the % of children exhibiting clinical features. From Minekawa et al.[57]

of US Air Force recruits in 1981, 7 years prior to the introduction of MMR in the UK.[58] In a relatively large prospective study, safety and efficacy of measles and rubella vaccines (given either alone or in combination) were compared with unvaccinated controls. Five hundred and twelve vaccinees were compared with 835 unvaccinated controls and data were stratified by sex. The authors noted an increase in reports of fever and diarrhoea in those immunized with both vaccines simultaneously. In women there was an increase in complaints of myalgia after simultaneous immunization. The data merit more detailed consideration; in recruits receiving either monovalent measles or rubella vaccines there was no significant increase in diarrhoea compared with unvaccinated controls (measles vaccinees versus controls [men] odds ratio 2.51; CI 0.06–9.99) and [women] odds ratio 3.61; CI 0.26–50.42; $P > 0.5$; odds ratios for rubella vaccinees versus controls cannot be calculated since no men or women reported diarrhoea after rubella vaccine alone (Fig. 4). In contrast, compared with unvaccinated controls there was a significantly increased risk of diarrhoea following simultaneous measles and rubella vaccination in both men (odds ratio 7.31; CI 1.11–34.64) $P < 0.001$) and women (odds ratio 17.29; CI 1.14–247.09; $P < 0.001$). It can be seen from Fig. 3 that, in the context of gastrointestinal adverse events (diarrhoea), the effect of simultaneous measles and rubella vaccination is not additive but apparently synergistic (compound). Despite being remarked upon
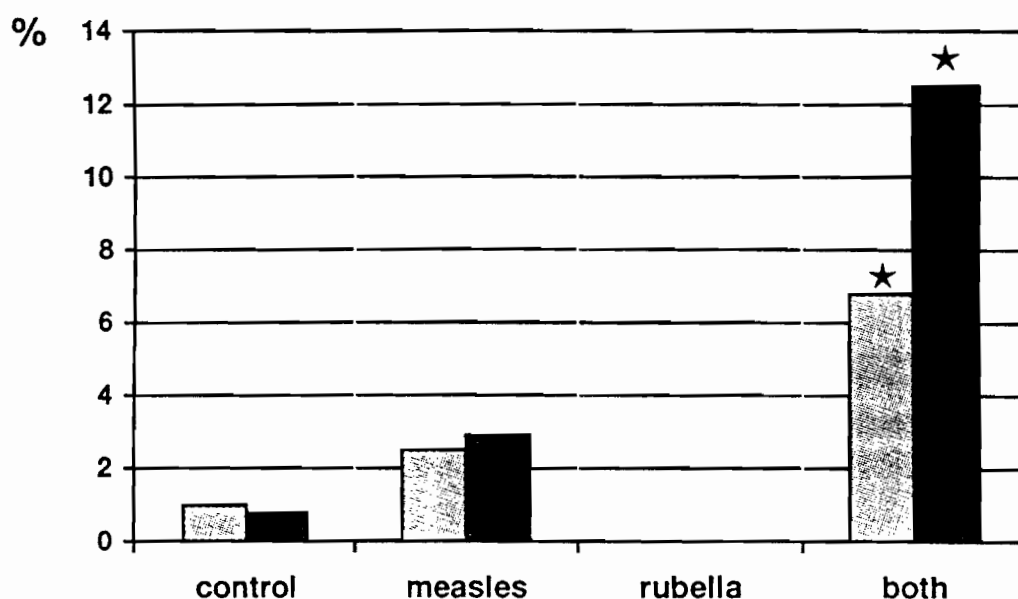
Fig. 4. Frequency of diarrhoea in US Air Force recruits (men ▩, women ■) comparing unvaccinated controls and recipients of monovalent measles vaccine, monovalent rubella vaccine or simultaneous measles and rubella vaccines. ★ = $P < 0.001$ versus controls. From Crawford and Gremillion.[58]

in the results, these observations received no further consideration in Crawford and Gremillion's report.[58]

Indications that novel adverse events might be associated with the combined MMR vaccine, rather than the monovalent component vaccines, have come from Plesner *et al.*'s study of gait disturbance following MMR in Denmark.[13] Several prior studies had indicated that gait disturbance might occur in up to 1 in 1000–4000 recipients of MMR.[59,60] In Denmark this association had not been detected with any other vaccine administered to children of the same age, prior to the introduction of MMR in 1987. In a recent follow up of the mandatory passive reporting system operated in Denmark, Plesner not only confirmed this association but also indicated that the more severe cerebellar ataxias following MMR may be associated with residual cognitive deficits in some children.[13] This association is specifically relevant to the debate on MMR and autism, as parents of autistic children who suspect a link with MMR, not infrequently report gait disturbances.

None of this is to say that vaccine manufacturers do not recognize that the problem of interference exists. Douglas of Merck stated recently. "The complexity of vaccine delivery today in clinical practice with 15–17 injections in the first two years of life emphasizes the need for development of combination pediatric vaccines, for example, putting DTaP, HBV, HIB and IPV together. This has proved to be far more difficult than previously believed due to unpredicted immune interference and incompatibilities on mixing of different

components, demonstrating again the inadequacy of our understanding of how vaccines work and the empiric nature of the science."[1]

Candidly, Douglas admits that we see through this particular glass, darkly. Why, however, in spite of evidence provided by studies undertaken two decades earlier, should such interference be considered "unpredictable" and, indeed, remain unstudied?

Revaccination with MR and MMR

Systematic revaccination with MMR, with the stated aim of measles elimination, started in Sweden in 1982.[61] Christenson, as one of the architects of this programme, was contacted by one of the authors (AJW) to inquire about safety studies of 2-dose MMR schedules. She replied, "I must avow that I don't quite understand what you mean with if there has been any safety studies of the 2-dose measles vaccine schedule. We have followed the 12-year old children with blood specimens drawn before vaccination and 2 months after vaccination. This is a form of safety study."

Clearly, measurement of serum antibodies following revaccination of 12 year olds was not a safety study. Christenson later confirmed that there had been no safety studies of 2 dose schedules from Sweden, nor was she aware of any having been performed elsewhere. Nonetheless, the "Swedish experience" has served as a template for re-vaccination strategies elsewhere in the world.

In 1994 in the UK, a re-vaccination campaign using bivalent measles and rubella (MR) vaccine was undertaken; this targeted all school-age children from 4–18 years of age. Since that time a second dose of MMR has become routine as a pre-school booster at 4 years of age.

"Assumptions"[62] about the safety of re-vaccination are compounded, as extrapolation from assumptions about safety that were based upon the early studies of MMR vaccine. Anxieties about these assumptions were emphasized in the proceedings of a meeting of measles experts that was convened under the auspices of the European Union in 1993, prior to the UK re-vaccination campaign.[63] In addition, the experts identified the "main areas which require epidemiological input include the evaluation of the safety and efficacy of two dose schedules of standard titre vaccine".

This—a two dose schedule—was precisely the strategy that was adopted in the UK, one year later, without comprehensive monitoring of safety—a priority that was clearly endorsed by European measles experts. Cutts, one of the two epidemiologists present at the EU meeting of measles virus experts, in commenting on the November 1994 re-vaccination programme in a *BMJ* editorial, in which she strongly endorsed this programme, wrote, "The need to appraise risks as well as benefits is an obligation for vaccination programmes".[64] Such piety is to be commended. Nonetheless, other than passive surveillance, a system that is acknowledged by the regulatory authorities to have serious

limitations,[45,47,66] this "obligation" was not met. Consequently, possible adverse events have become by definition anecdotal and "coincidence". Parents of children who may be vaccine damaged have been left to cope with the consequences. In the absence of either medium- or long-term safety studies of MMR vaccine Cutts, in her *BMJ* editorial, went on to state that, "If the measles–rubella campaign had not been conducted large numbers of children would have had measles, with a much higher risk of long-term serious effects than that potentially associated with vaccination".[63]

At the immunological level, what are the possible implications of re-vaccination with a measles-containing vaccine, particularly in individuals persistently infected with measles virus? Recent data confirm that failure to induce an adequate cytotoxic T cell response to measles virus, despite the generation of specific antibody—the conventional measure of immunity—is associated with immunopathology upon re-exposure.[66] Failure to clear cells expressing viral antigen may lead to immunopathology that is directed against these viral epitopes upon re-exposure, a situation that could make revaccination for measles particularly hazardous in the presence of persistent infection.

Reflecting further upon the perception of the regulatory authorities, Rawlins, as head of the UK Committee on Safety of Medicines, maintained recently that, "MMR and its component parts have undergone rigorous testing before being licensed for use in this country. Efficacy and safety have been convincingly demonstrated in hundreds of millions of children world wide who have been immunised with these vaccines during the last 20 years. Published evidence for safety is available in: [Stratton KR *et al*. Adverse Events Associated With Childhood Vaccines. *Natl Acad Press* 1994[47]]." (Personal communication: Barr R, Alexander Harris Solicitors).

In contradiction to the reassurances given by Rawlins, the authors of his suggested reference state that, "In the course of its review the committee encountered many gaps and limitations in knowledge bearing directly and indirectly on the safety of vaccines. These include: inadequate understanding of the biologic mechanisms underlying adverse events, insufficient or inconsistent information from case reports and case series, inadequate size or length of follow-up of many population-based epidemiologic studies." They concluded that, "Clearly, if research capacity and accomplishment in these areas are not improved, future reviews of vaccine safety will be similarly handicapped."

Rawlins' response is not reassuring. "The comments [Stratton *et al.*] have been taken out of context because they apply to research needed to provide further reassurance about vaccine safety. We would not agree with the authors when they criticise the low number of available experimental studies since they underestimate the difficulties of performing such studies. In conclusion we consider that the body of available evidence supports the view that the benefits of MMR and MR vaccines outweigh their risks." Surely, when a medical intervention is intended for universal use, particularly in healthy infants, there is almost no limit to the vigilance that should be exercised. Finally, Rawlins falls

back upon generic argument that seeks reassurance in "available evidence". On reflection, this might be considered ill advised.

In summary, analysis of pre-licensing trials of MMR reveals that gastrointestinal, and other possible adverse events were evident in children from developed countries. Although evidence of gastrointestinal adverse events was a recurring feature of post-licensing studies, they were not considered to be of clinical significance. Follow up for detection of adverse events was reduced from 4 weeks in the initial controlled trial, to 3 weeks in subsequent studies. It is worthy of note that the bowel symptoms associated with recent concerns about MMR and regressive autism would not have been detected by any of the reported safety studies. The onset of these symptoms was, typically, insidious and usually first observed outside the time frame of these safety studies. While the excess of specific gastroenterological symptoms observed among vaccinees in the cited studies is unlikely to represent a risk for autism, they serve to illustrate that insufficient attention may have been paid to adverse gastrointestinal reactions among MMR recipients.

There was evidence beyond 1968, that the component viruses of MMR could exert both dose- and strain-dependent interference upon the clinical and immunological response of the host to the individual constituent viruses. This effect, for which the influence of mumps virus upon the measles virus component was particularly evident, merits thorough investigation. Clearly, one plus one, plus one never did equal three. There is more than a theoretical risk, supported by more recent studies,[56] that interference with clearance of measles virus might increase the risk of persistent infection and/or delayed disease. The official argument that the mumps vaccine is less effective alone, but potentiated by combination in MMR, is tacit admission of "interference". Finally, two-dose MMR vaccine schedules appear to be unsatisfactorily tested for safety.

The foundations to claims of MMR safety have failed this structural survey. Since the temple was constructed, we have become aware of the contamination of MMR vaccines with avian retrovirus,[67] bovine viral diarrhoea virus[68] and the potential for their contamination with bovine prions.[69] The success of vaccination programmes, the goals and benefits of which are laudable, depends upon trust—specifically of the public in those charged with the broad remit of "vaccine safety". Loss of this trust has the very real potential to compromise vaccination strategies across the board, rather than just reducing the uptake of a particular vaccine that may be under scrutiny. The UK Department of Health's decision to withdraw the licence for importation of monovalent measles vaccine, whether implemented directly or indirectly, was wrong. If protection against measles is a principal concern, surely it is important to continue to allow parents to use the monovalent vaccines where they are concerned—rightly or wrongly—about the safety of MMR. Those on both sides of the debate will continue to publish hypothesis testing, peer reviewed studies that seek to clarify this matter. However, until such time as this matter is

resolved to everyone's satisfaction, the public must, at the very least, be offered a choice. As the last Minister for Health, the Hon. Frank Dobson said recently, in the context of another medical intervention, "If there is even a hypothetical risk [of harm] and a safer alternative exists, we should use it." For MMR, autism, and inflammatory bowel disease, a significant index of suspicion exists without adequate evidence of safety.[2-4,70]

With time, what is now opaque—the complexities of host-vaccine/vaccine–vaccine interactions—may become clear. In the meantime, the foregoing might be perceived as an argument for, rather than against vaccination, although with strategic modifications. If the risk of chronic immune-mediated disease is increased by concurrent exposure to the component viruses of MMR, either in their natural or vaccine form, then by the use of, for example, spaced monovalent measles, mumps and rubella vaccination we have the ability to artificially dissociate these exposures, and the possible associated risks. Some may argue that delaying mumps vaccination by one year increases the risk of exposure and associated morbidity. This would be most unlikely if herd immunity were maintained by monovalent vaccination of 2 year olds. When calculating these risks, the PHLS may recall that its own senior members were equivocal about the merits of a mumps vaccine as recently as 1991.[71]

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IN VIEW OF THE SERIOUS IMPLICATIONS OF THE ABOVE PAPER BY WAKEFIELD AND MONTGOMERY THE PAPER WAS SENT TO A NUMBER OF REFEREES WHO HAVE AGREED TO THE COMMENTS THEY MADE ON THIS PAPER BEING PUBLISHED. THESE REFEREES INCLUDE THE FORMER CHAIR OF THE MEDICINES COMMISSION; A FORMER MEMBER OF THE COMMITTEE ON SAFETY OF MEDICINES; AND A FORMER PRINCIPAL MEDICAL OFFICER IN MEDICINES DIVISION NOW MCA, OF THE DEPARTMENT OF HEALTH WHO SERVED AS MEDICAL ASSESSOR TO THE COMMITTEE ON SAFETY OF MEDICINES, AND A CONSULTANT NEUROLOGIST.

Referee 1

Measles, mumps, rubella vaccine: through a glass darkly by A. J. Wakefield and Scott M. Montgomery

This well referenced review will bolster the debate on the long term safety and possible late adverse sequelae in some recipients of the living attenuated strains of viruses that are incorporated into a single polyvalent vaccine (MMR), licensed and introduced into United Kingdom (UK) practice in 1988 as one subcutaneous injection to be given to children at about 15 months of age. The short term safety of the vaccine, up to 28 days post vaccination, and its efficacy are not in doubt, buttressed as they are by pre-licensure studies and trials in 10 000 UK children before its general introduction; nor is its great value in preventing morbidity and mortality from these formerly commonplace diseases in question. The case for population vaccination[1] has been argued persuasively in a Report from the Association of the British Pharmaceutical Industry (ABPI), reminding us that lack of parental confidence in the whooping cough component of diphtheria, tetanus and pertussis vaccine (DPT) resulted in a calamitous fall of vaccination coverage and a resurgence of major epidemics with deaths in the 1970s and 1980s, although confidence has now returned to the benefit of the public health. This must not be allowed to happen in the case of MMR vaccine.

Wakefield and Montgomery argue that the possibility of late vaccine damage—pervasive development disorder (autism) and inflammatory bowel disease—is biologically feasible given the propensity of the enteropathic measles virus to lodge in the gut; its known association with subacute sclerosing pan-encephalitis and its proclivity for both acute and chronic encephalopathies; and the phenomena of virus interference and immune suppression, arguing also that some of the pre-licensure studies might have been interpreted as sentinel for possible adverse events detected later than 28 days. Their contention is not entirely based on suppositional pathology, as the work of Plesner et al., 2000[2] on disturbance of gait following MMR vaccination suggests.

On the evidence then available the Committee on Safety of Medicines[3] was unable to credit a causal association between MMR vaccine and autism and inflammatory bowel disease. Griffin[4] believes that the issue should be remitted to wider scientific review. Wakefield and Scott incline to view the hypothesis as testable although experienced Regulators, such as Michael Rawlins, comment on a general underestimation of the difficulties posed by further studies, a view with which I concur. Such studies are not simply a matter of money and goodwill.

All in all Wakefield and Montgomery's review is thoughtful and provocative, a welcome contribution to the ongoing scientific debate.

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Referee 2

Measles, mumps, rubella vaccine: through a glass darkly by A. J. Wakefield and Scott M. Montgomery

This paper addresses the difficult area of benefit and risk in relation to a vaccine now in use, discussing only the published evidence and some official pronouncements about the vaccine.

Five questions, at least, need to be addressed in each such case; these seem to be:

1. What is the preventive benefit to risk ratio?
2. What are the benefits/risks of non-vaccination in a comparable group?
3. What are the risks; are they attributable; how reliably are they reported?
4. If risks are attributable, are they acceptable, and by whom?
5. Is the benefit within the protected individual alone, or is it partly related to protection of the 'herd'?

The difficulty is that these depend differently upon prevailing social conditions and perceptions; also the quality of the scientific evidence for each of them may differ markedly for any of several reasons.

The current paper reviews the evidence about all of questions 1 to 5. It is clearly set out and covers an extensive and relevant literature. For MMR vaccine, question 1 is clearly evidenced favourably, but the evidence on the others, even if of considerable amount, is patchy and incoherent except for question 2, where it is quite clear that non-vaccination carries immense risks of illness or death. There are substantial problems about the adverse reaction data; these are shown to be:

1. confusion between types of vaccine within pooled data, especially between single virus and multiple virus vaccines,
2. there were in some studies changes in therapy during data collection,
3. several studies omitted placebo groups or were otherwise uncontrolled,
4. in almost every case, observation periods were too short to include the time of onset of delayed neurological or other adverse events,
5. elided groups were not coherent, so obscuring adverse events potentially,
6. immunity may be depressed before it is enhanced after this vaccine, an effect which is worse with the (now abandoned) high dose vaccines. This might allow natural illness to be enhanced in frequency or in severity. The syndrome resembles AIDS; it is unknown whether some of the vaccinated children had AIDS before vaccination,

7. interaction between vaccines had not been considered adequately in children with multiple vaccinations and potentially ill-developed immune system; close paradigms are known in natural disease.

8. There is circumstantial evidence for a link between measles virus, gastroenteritis and cerebral adverse effects, with persistence of measles virus evoked by multiple immune responses. The evidence from existing studies throws no light on this possible connection, partly because some of the trial groups were drawn from populations with high natural incidences of gastroenteritis and related illness.

9. Much of the adverse event data came from passive, not active surveillance.

It is possible that a group of children exists who are developing a disorder with gastroenteritis, abnormal reactions to measles virus and neurological disease. In the present condition they are highly likely to be vaccinated. The existing data throws no light on the question and new comparative studies are needed to seek an answer to it. The paper argues the case for such a study.

The final issue is the official statements which have been made about the benefits and risks of measles vaccines. The paper criticizes these, but perhaps without the same clarity as that for the literature data. There seem to be two main problems about the official statements; they combine question 1 and 2 above with a trivializing of question 3, whilst ignoring questions 4 and 5. The benefits outweigh the risks when the former are clear and the latter obscure, both by extent and quality of evidence. Also, the answers to question 4 and question 5 depend not only on social conditions and perceptions, but also upon whether viewed by the giver or the recipient of the vaccine. One not insignificant detail is whether compensation for vaccine damage is available to an injured child and family, or is denied by the authorities who advocate the vaccine whilst denying the risks on the inadequate (if extensive) evidence available. All of these issues are brought out in the paper. A bit more clarity and less colour would help the case set out by the authors regarding the official statements; their case about the data could scarcely be more clear.

PROFESSOR D W VERE MD, FRCP

Referee 3

Measles, mumps, rubella vaccine: through a glass darkly by A. J. Wakefield and Scott M. Montgomery

In the United Kingdom (UK) the Medicines Act (1968) set down the legal requirements for the granting of licences for medicinal products and in so doing established the so-called 'Section 4 committees', one of which was the Committee on Safety of Medicines (CSM). It is the task of the CSM to evaluate the quality, safety and efficacy of these products which include vaccines and similar biological agents.

Over the years since the Act was implemented, matters of quality and efficacy have been assessed promptly and reliably. Safety has always proved to be a greatly more difficult problem. It must be stressed that this is not a problem peculiar to the UK but one which has been encountered by all major national regulatory authorities. The reason for this is simple to understand. Quality is largely a laboratory-based assessment and efficacy can usually be established by relatively short duration randomized, controlled clinical trials (RCTs). Safety is altogether more difficult particularly as we appear to be concerned by serious adverse drug reactions (ADRs) which occur more frequently than once in ten thousand or so exposures. The problem is made even more difficult since ADRs can arise many months or even years after exposure to the drug which implies long term monitoring.

The accompanying paper by Wakefield and Montgomery focuses upon this problem and is of considerable importance because of its implications for the millions of people who have received and will receive the combined mumps/measles/rubella (MMR) vaccine. As an old regulator I have asked the question—'With respect to the licensing of MMR has the system served us well on this occasion?'

Virtually all effective medicinal products are associated with ADRs and vaccines are not exceptions. Wakefield and Montgomery accept that MMR is of adequate quality and is efficacious but question its safety. The paper identifies a number of specific ADRs that have been reported since the combined vaccine was first used including chronic inflammation of the gastrointestinal tract, regressive autistic spectrum disorder, subacute sclerosing panencephalitis (SSPE) and other acute and delayed encephalopathies. The review deals mainly with safety orientated clinical trials that were conducted on the combined vaccine although the individual viral strains used were not always the same. The authors recognized that the impact of a vaccine including viral antigens for three different diseases is known to be different from those antigens administered separately although this aspect was not fully investigated. It is not the purpose of this short paper to re-review the ground covered by Wakefield and Montgomery but it would have been interesting to have a comprehensive comparison of the

immunological, as distinct from clinical, effects associated with mumps, measles and rubella vaccines given separately with administration of the combination. Would immunological differences be reflected in a different spectrum of ADRs? Extending this line of thought, could a knowledge of the immunological differences at the time of the regulatory submission have warned the authorities of potential problems ahead?

Two comparative clinical trials on relatively small numbers of patients are reviewed, both of which were conducted prior to licensing of the vaccine in the USA, and both, unfortunately, on patient populations which were partly from North America (Philadelphia and Ohio) and partly from Latin America (Costa Rica–San Salvador and Dominican Republic). In each study the populations were combined which invalidated any interpretation of ADRs. Nevertheless 39% of the vaccinees from Philadelphia (compared to 12.2% of controls) apparently complained of 'unrelated illnesses' (otitis, allergy, viral infection and abdominal pain) associated with the vaccination.

A postmarketing surveillance (PMS) study on approximately 10,000 children in the UK showed 26% of acute intestinal ADRs but unfortunately little other information. As the follow-up period was only 3 weeks it seems that the opportunities offered by a large observational cohort study were missed. PMS studies on 10,000 + patients followed for 12–18 months were available at this time and had been recommended in the Grahame-Smith Working Party report from Medicines Division. These studies may be criticized on the grounds that they are observational but they do yield large amounts of information. An apparently negative finding of no serious ADRs has the positive benefit of setting quantitative limits on their incidence.

Wakefield and Montgomery also draw attention to several other curious vaccine related events such as 'delayed excess mortality' in west Africa, diarrhoea-associated deaths and persistent immunodeficiency. They also note that in cases where autistic regression is a suspected vaccine association there is an increase in enterocolitis, immunodeficiency and persistent measles virus infection of ileal lymph nodes. The short observation period (28 days or less) of most studies has limited the extent to which these other suspected ADRs could be evaluated.

The possible clinical (as distinct from immunological) consequences of administering three viruses concomitantly are discussed and the known immunosuppressive properties of measles virus are noted. In particular exposure to measles virus in the same time frame as another virus such as chickenpox or an encephalitic enterovirus is associated with excess risk for SSPE. This rather broad spectrum of potential ADRs is of significance for several diseases that are still poorly understood. Ulcerative colitis, Crohn's disease and autism are just three that are referred to and it is not a great stretch of the imagination to include the spongiform encephalopathies which are currently of great concern. The 'prion only' hypothesis is far from satisfactory and the need for a second factor has been proposed by many experienced

researchers. It is regrettable that so little definitive high quality research has been done on the impact of polyvalent vaccines on safety. The authors refer to the perceived faults of 'passive surveillance' systems which have been criticized by many people including the regulatory authorities. This is an opinion that is not without some relevant support but, in the absence of better practicable methods, observational studies should not be neglected. The creation of several computerized systems of primary care over the past decade have not been adequately exploited even though they cover the records of many million patients continuously for 10 or more years. Rawlins refers to the difficulties of conducting safety studies on vaccines as some mitigation for the deficiencies in the available data but has not conceded that access to large patient numbers over extended time periods is now possible. There are serious questions that demand answers and it is to be hoped that Wakefield and Montgomery will provide the necessary stimulus.

Conclusions

With all the benefits of hindsight, what may now be said about the decision to grant a Product Licence (as they were then called) to MMR 10 or so years ago? Evidence on quality and efficacy was probably adequate so a decision had to be made on grounds of safety. Being extremely generous, evidence on safety was very thin, being realistic there were too few patients followed-up for insufficient time. Three weeks is not enough, even for RCTs, neither is 4 weeks. By 1988–89 we knew from experience with pertussis vaccination that longer duration was essential—how much longer it is difficult to say but as long as humanly possible. We also knew that numbers, big numbers, were equally necessary. Additionally we knew that observational cohort studies could be conducted on 10,000 or more patients for up to 18 months. Primary care computerized databases (GPRD for example) were already up and running which would permit prospective record surveillance on several million patients. There was insufficient information on the immunological effects of a trivalent vaccine compared to monovalent vaccines. Was there detectable immunosuppression with trivalent vaccine versus monovalent? From known clinical experience with measles, mumps and rubella infections we could make an estimate of the incidence of serious disease outcomes which would be prevented by effective vaccination. From these figures we could make an informed guess of ADR levels that could be tolerated. Did the available evidence on the trivalent vaccine support the belief that benefit would outweigh risk? On the basis that effective monovalent vaccines were available the CSM could be confident that delay in granting a licence would not result in a catastrophic epidemic of measles, mumps and rubella. Caution should have ruled the day, answers to some important questions should have been demanded and strong encouragement should have been given to conduct a 12-month observational study on 10–15,000 patients and a prospective monitoring programme set up

with a computerized primary care database. The granting of a Product Licence was premature.

A PETER FLETCHER MB BS PhD MFPM

Referee 4

Measles, mumps, rubella vaccine: through a glass darkly by A. J. Wakefield and Scott M. Montgomery

The authors of this critical review discuss at length the possible adverse effects of the administration of combined measles, mumps and rubella vaccine. They criticize the decision of the Department of Health to withdraw the licence for the importation of monovalent measles vaccine. They produce arguments that adequate consideration of those possible serious. though, admittedly rare complications of combined vaccine were not appropriately considered when decisions were made by the Department of Health to withdraw the licence for the importation of monovalent measles vaccine. They believe that the use of monovalent vaccine would carry less risk of serious and lasting complications, due to the persistence of measles virus in the intestinal tract and in the brain. They are not denying the importance of effective protection against measles (the most serious of the 3 infections), but believe that little would be lost by using monovalent rather than mixed vaccines.

Complications of immunization procedures against viral diseases are well known and date back to those encountered after smallpox vaccination and Pasteur's rabies vaccination. The mechanism in these is not related to direct invasion of the central nervous system (CNS) by live virus but appears to be an abnormal immune response. In addition to these 'reactive' encaphalopathies, invasion of the CNS by virus may also cause acute encephalitis. e.g. herpes viruses (zoster and simplex). A chronic encephalopathy, subacute sclerosing panencephalitis (SSPE) is related to the presence of persistent measles virus, which has certain abnormal characteristics, in the brain. It appears that the frequency of this condition in the population has been greatly reduced by the use of measles vaccine. The authors do not disagree with this observation but point out that the possibility that those cases of SSPE which still occur in small numbers in vaccinated populations may be causally related to the vaccination with multiple vaccine preparation and even those few but disastrous cases which still occur might be avoided by giving measles, mumps and rubella vaccine separately. They argue that such an immunization policy would not deny children the protection against infection which of course is very important.

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