**Combined measles, mumps and rubella vaccines: Response of the Medicines Control Agency and Department of Health to issues raised in papers published in "Adverse Drug Reactions and Toxicological Reviews, volume 19 no 4, 2000 "**


**Summary**

The MCA rejects any suggestion by Dr Andrew Wakefield and Dr Peter Fletcher that combined measles, mumps and rubella (MMR) vaccines were licensed prematurely. The MCA is confident that the licensing process was properly conducted on the basis of the safety, quality and efficacy of the vaccines in adequate numbers of children.

MCA has carried out a review of the licensing of MMR vaccines and can assure the public that the licensing followed normal procedure and was based on robust studies.

Dr Wakefield claims in the paper, due to be published in *Adverse Drug Reactions and Toxicological Reviews* on Monday, that there was insufficient research carried out before MMR vaccine was promoted in the UK. This is factually incorrect as many studies recorded safety data up to six weeks, which is standard for vaccines, and some studies recorded data for longer – up to a year in some cases.

Combined MMR vaccines had been extensively tried and tested in Scandinavia and the USA before they were introduced in the UK in 1988. Now MMR is successfully used in over 30 European countries as well as USA, Canada, Australia and New Zealand. In addition, a publication in 1988 lists 30 published studies where combined measles, mumps and rubella vaccines were studied and follow up extended up to ten years. The safety of the combined MMR was studied and shown to be the same as that for the component vaccines.

The safety of combined measles, mumps and rubella vaccines has been reviewed repeatedly by the Government's independent expert scientific advisory committees including , the Committee on Safety of Medicines (CSM) and the Joint Committee on Vaccination and Immunisation (JCVI). They have concluded that the evidence does not support any association between MMR vaccine and inflammation of the bowel or autism. The use of the MMR vaccine is also endorsed by the World Health Organisation and professional bodies such as the British Medical Association, the Royal College of General Practitioners, and the Royal College of Nursing.

By 2000, several hundred million doses will have been given worldwide. Extensive data demonstrates the safety of combined MMR vaccines. The safety of giving two doses has also been studied and no study has found unexpected adverse effects.

The paper by Dr Wakefield does not present any new data - it merely reviews a number of published articles. It is highly selective as opposed to the scientific standard of being systematic, and studies that do not support the author's views are not mentioned. No search for all relevant publications has been done. It is easy for scaremongering to sap public confidence by biased presentations that are contrary to the large amount of data that provide real reassurance

The comments by Dr Fletcher, a former principal medical officer at the Department of Health are on a flawed report and must be regarded in this light.

The Department of Health vaccination programme uses the combined MMR vaccine because it is the safest and most effective means of protecting children from these diseases. The child is put at greater risk of contracting these infectious diseases because of the gap between vaccinations.

MCA and DoH are not aware of any country in the world that recommends MMR be given as three separate vaccines. In Japan, where they do not have a suitable MMR vaccine, there have been 79 measles deaths between 1992 and 1997. In the same period in the UK there were no deaths from measles.

Parents and health professionals should have no doubts about the benefits of MMR vaccines. Adverse effects are not frequent and, even when they do occur, are generally minor and transient. Vaccination with MMR is the most effective means of preventing serious and occasionally fatal diseases and children should not be denied this protection.

**Purpose of this document**

The publication in volume 19 no 4, 2000, by Drs AJ Wakefield & SM Montgomery entitled *'Measles, mumps, rubella vaccine: Through a glass, darkly'* together with published reviewers' comments has been examined carefully by expert assessors of the Medicines Control Agency (MCA) and Department of Health (DoH). In addition, a pre-publication draft of the Wakefield and Montgomery publication, provided by the authors, has been reviewed by the Committee on Safety of Medicines (CSM), and the Joint Committee on Vaccination and Immunisation (JCVI). Both committees are independent expert scientific advisory committees to the Government.

This document sets out the response of the MCA and DoH to the issues raised by these publications, together with the advice of expert committees on the safety of combined measles, mumps and rubella (MMR) vaccines.

**Contents**



**1. UK policy on MMR vaccination:**

Immunisation with MMR has been routine policy in the UK, recommended by JCVI, since October 1988. The reasons for the change from measles immunisation at 13 – 15 months, rubella vaccination just for pre-pubertal girls, and no mumps vaccination were to raise measles vaccination coverage, to interrupt the transmission of rubella amongst young children, and to prevent mumps. The outcome has been to almost eliminate measles, the further reduction of congenital rubella, and the prevention of mumps and its complications such as mumps meningitis. The latter condition had been responsible for 1,200 – 1,500 hospital admissions annually.

A two-dose MMR policy was introduced in 1996; its purpose was to provide a second opportunity for MMR immunisation for those who had missed the first dose, and to protect those who had not seroconverted to all three vaccine virus components after the first MMR immunisation.

## 2. Advice of expert committees on MMR vaccine

The safety of MMR vaccines has been reviewed repeatedly by the Government's independent expert committees, the CSM (responsible for advising on the licensing and safety of human medicines) and JCVI (responsible for advising on vaccination policy). In addition, ad-hoc working groups of the MCA and Medical Research Council (MRC) have also been set up to review the data on the safety of these vaccines. All of these expert groups have concluded that the evidence does not support an association between MMR and inflammatory bowel disease (IBD) or autism.

### 2.1 Advice of the MRC ad-hoc working group

At the then CMO's request the Medical Research Council held an independent scientific seminar on 23 March 1998 to review the work of the Royal Free Hospital group on MMR. The meeting included leading experts in virology, epidemiology, immunology, paediatrics, child psychiatry and gastroenterology. At the seminar, researchers from the RFH were given time to present their work fully. The meeting concluded that: the available virological and epidemiological evidence does not support a causal role for persistent measles virus infection in Crohn's disease; there is no evidence to indicate any link between MMR vaccination and bowel disease or autism; and, there is therefore no reason for a change in the current MMR policy.

Following on from the March 1998 seminar, the MRC's independent group of experts has continued to meet periodically to review any new evidence. The group issued a further statement in April 2000 confirming the conclusions of its earlier seminar. The group, which heard evidence from Dr Wakefield, reported that there was "no new evidence of a link between autism and MMR". The group did agree that much remains unknown about IBD and autism and that more research in these areas was needed. The MRC has announced that it is to fund Professor Andrew Hall of the London School of Hygiene and Tropical Medicine to conduct a computerised database study on risk factors for autism, including immunisation.

### 2.2 Advice of MCA Working Party on MMR vaccines

The MCA set up a Working Party on MMR vaccine in 1998 in order to review the suggested link between MMR and MR (Measles/Rubella) vaccine, autism and Crohn's disease. This Working Party conducted a detailed review of reports from parents of suspected side effects in children vaccinated with MMR or MR, received by the MCA via a firm of solicitors. This Working Party reported in June 1999 and concluded that the available information did not support the suggested causal associations or give cause for concern about the safety of MMR or MR vaccines.

### 2.3 Advice of JCVI

JCVI reviewed a pre-publication copy (supplied by the authors) of the Wakefield and Montgomery paper in October 2000. JCVI concluded the paper gave no new insights

or evidence that changed its views on the safety of MMR vaccines.

2.4 Advice of the CSM

The CSM considered a pre-publication copy (supplied by the authors) of the Wakefield and Montgomery paper, together with the available evidence on MMR safety, in January 2001. The CSM concluded:

- The Wakefield and Montgomery paper provided no new scientific data.

- The main points made by Wakefield and Montgomery in their draft paper are not justified on the basis of the overall evidence. Their approach is selective and the analyses flawed.

- At the time of licensing the data did not show any indications of a problem with unexpected adverse reactions to MMR. There was a theoretical concern that immunogenicity of the antigens might be reduced when they were given together. Comparison of seroconversion rates with MMR to published data with mono-component vaccines, and simultaneous antibody determination in sera from previously seronegative children post-MMR with sera from children who had received mono-component vaccines in previous studies, both showed no significant interference in immune responses when the three antigens were co-administered. This concern that there could be reduced efficacy giving three vaccines together has not been borne out in practice and MMR vaccine has proved to be highly efficacious.

- There are extensive data demonstrating the safety of MMR. The evidence is that the policy of giving MMR vaccine is safer than the policy of giving the three component vaccines separately: with the monocomponent vaccines given sequentially, children would be at risk of infection for longer periods; they would be exposed to the risk of local adverse reactions on each occasion; it is likely that there would be a significant dropout rate for successive vaccinations. There was no evidence of additional benefit from separate vaccinations.

- Parents and health professionals may be reassured of the benefits of MMR vaccines. The adverse effects are not frequent and, even when they do occur, are generally minor and transient. Vaccination with MMR is very effective at preventing serious and occasionally fatal diseases. The balance of benefit to risk is therefore highly favourable.

**3. Summary of answers to the key questions raised in the new publications**

This section summarises the answers to some of the key questions and suggestions raised in the new publications.

Q Was MMR was licensed too early?

A. No. A review of the licensing of the MMR vaccines has been conducted. Licensing followed normal procedure and was based on the provision of satisfactory data regarding safety and efficacy in adequate numbers of children. The MCA totally refutes any suggestion that MMR vaccines were licensed prematurely.

Q. Were the pre-licensing trials limited to a maximum follow-up of 28 days?

A. No. The majority of trials followed children for 4-6 weeks post-injection. There was longer follow-up in the Stokes trial (reference 8 of Wakefield and Montgomery) of six to nine weeks for adverse events. A minority of children (< 200) in trials were followed for one year.

Q. Has there been high quality research on safety of polyvalent vaccines?

A. Yes. There has been a great deal of research on polyvalent vaccination. No major concerns have been raised by this research. About 30 studies on combined measles, mumps and rubella vaccines were carried out prior to the MMR introduction in 1988. The combined vaccine has been compared with the individual components and no consistent increase in the rate of any adverse effects has been seen.

Q. Do the component viruses of MMR interfere with one another?

A. There was early concern that 3 antigens together would have less effect than the components given on their own. The studies of MMR showed that this reduced effect was small or non-existent. There were a number of studies of MMR combined with other vaccines including DTP and polio. No concerns about safety were raised in these studies.

Q. Has re-vaccination with MMR had its safety assessed?

A. Yes. Finland and Sweden, both of who have two-dose MMR programmes, have reported on safety and efficacy. Post-marketing surveillance from the US, where there has been a two-dose programme since the late 1980's, has not identified safety concerns following the second dose. The American Academy of Pediatrics states that "The rate of adverse reactions associated with revaccination of immune persons is lower than the rate observed in persons who are not immune". The safety of MMR vaccines has been continuously monitored by the MCA and assessed repeatedly by independent expert scientific committees. This was done for the MR campaign and the safety review was very reassuring.

**4. Detailed assessment of the issues raised in the publication by Wakefield and Montgomery**

The paper reviews a number of published articles and presents comments on them, but does not present any new data itself. It does not carry out a systematic review to answer specific questions. There is no suggestion that a comprehensive search for all literature on the question of MMR safety has been carried out. Classical studies such as the double-blind cross over randomised twin study of Peltola and Heinonen[1] are overlooked by the authors and referees alike.

The paper raises certain safety concerns about MMR vaccine but does not provide the reader with readily available information that lays those safety concerns to rest. Studies that fail to support the authors' views are not mentioned.

This section examines the points made by Wakefield and Montgomery, and the evidence from the papers that they cite as giving credence to their view.

1 *Randomised trials are the best opportunity for identifying acute adverse events.*

This is generally agreed, but the problems of using such trials for rare events or those with a long delay to their appearance are well known (See for example Sackett et al[2]). Wakefield and Montgomery do not discuss these concerns.

2 *These trials are also the best place for putting in place mechanisms for long term surveillance of safety.*

This is certainly questionable. The difficulties of long-term follow-up for non-fatal diseases (except cancer) are very high, and the likelihood that follow-up of small trials will fail to detect problems is not discussed. The numbers included in the trials, even if they were all followed up long term, would not be sufficient to detect rare problems. (Sackett et al[2] make it clear that good cohort and case-control studies are required). There are good systems already in place for monitoring the safety of medicines, including record linkage studies, with spontaneous reports (Yellow Cards) drawing attention to possible problems.

3 *The pre-licensing trials were short-term with a maximum follow-up of 28 days.*

This is not correct. There was longer follow-up in the Stokes trial (reference 8 of Wakefield and Montgomery) of six to nine weeks for adverse events. Several other trials had longer follow-up and follow-up for persistence of immunity was continued for up to 10 years[3, 4,5.]

4 *Measles virus was known as a cause of subacute sclerosing panencephalitis (SSPE) so, as SSPE case registers were set up in the UK and US to monitor the impact of vaccination on this disease, this should also have led to monitoring for GI events.*

Long-term gastro-intestinal events after measles or MMR vaccines have only recently been postulated by Wakefield, and have failed to be confirmed by independent observers. It is therefore illogical to suggest *post hoc* that long-term gastro-intestinal events should have been monitored.

Wild measles virus causes SSPE and since the introduction of measles immunisation in North America and in the UK it has become extremely rare[6,7]. The extreme rarity of SSPE has continued since MMR vaccine was introduced. The few cases that have occurred in vaccinated individuals appear to have been caused by wild measles[8] acquired before immunisation. The number of deaths per year certified as being caused by SSPE has fallen significantly in England & Wales since the introduction of MMR, particularly in those aged under 20 years of age[9]. Having raised safety concerns over the possible impact of concurrent infection with measles and other viruses, as risk factors for SSPE, the authors should have been able to reassure readers that US and UK evidence showed that MMR protected against SSPE.

The early trials did not raise a signal regarding GI events – see the discussion

on those trials below.

5 *MMR was licensed in the US in 1975 on the basis of two small-scale controlled trials and a pilot study, each of which was published. These gave indications of a problem with gastro-intestinal events when analysed correctly.*

This is not correct. MMR is a registered trademark for one manufacturer's vaccine. There are other vaccines containing measles, mumps and rubella viruses. The first such vaccine was licensed in the US in 1971 and in the UK in 1972. The UK assessment in 1972 was by medical scientific experts at the then Medicines Division of the Department of Health and the National Institute for Biological Standards and Control. Data from five studies, including some of those cited by Wakefield and Montgomery, were available. The first measles, mumps and rubella vaccine that was licensed in the UK was not used in the national immunisation programme. By 1987 when the second and third combined measles, mumps and rubella vaccines were licensed in the UK, there were several more published and unpublished studies available and considerable experience in using the vaccines had been obtained in the USA and Scandinavia.

A thorough review of the licensing of the MMR vaccines has now been carried out, prompted by the public concerns raised by the Wakefield and Montgomery article. The CSM has concluded that, based on the data available at the time of licensing, combined measles, mumps and rubella vaccines were licensed appropriately.

Wakefield and Montgomery quote the Stokes et al (reference 8) paper in support of their opinion that gastro-intestinal adverse events were overlooked. They wrongly state that the paper reports " a comparison of 228 children who received MMR vaccine (Moraten strain) with 106 unvaccinated controls". In fact, this paper reports symptoms in 685 vaccinated children (228 in the US and 457 in South America) and compares these with symptoms reported in 281 sibling controls (106 in the US and 175 in South America). The results for both geographical groups are given separately and they were not combined for the statistical analysis, of which there is little mention. Thus, there appears to be no basis for the statement by Wakefield and Montgomery that the data from both groups "were combined for the statistical analysis".

Moreover, their attempts to reanalyse the results by comparing within each geographical cohort the incidence of gastro-intestinal symptoms in vaccinated and unvaccinated controls are invalid. The original authors presented the number of children with gastro-intestinal symptoms in days 1-4, 5-12, 13-18 and 19-28. Wakefield and Montgomery have added up all the occurrences of gastro-intestinal symptoms across the entire 28-day period, regardless of whether the same child or episode is being counted more than once. When analysing such trial data, it is essential to compare the numbers with symptoms in a specified period, each child only being counted once. It is misleading to add across all intervals as Wakefield and Montgomery have done since many children will be counted twice or more.

Wakefield and Montgomery have undertaken an invalid analysis since they

appear to confuse prevalence with incidence. There is no real evidence of a gastro-intestinal problem specific to MMR vaccines, when compared with measles vaccines alone.

6 *High titre measles vaccines, as used in trials in certain developing countries, were withdrawn from use by WHO. This withdrawal was because of delayed mortality, largely associated with gastro-intestinal effects.*

These findings apply only to monovalent high titre measles vaccines and do not apply to standard titre measles vaccine, either singly or in combination in MMR. No such observations have been found with MMR. Overall, the value of measles vaccines, including high titre vaccines in developing countries, has been to reduce morbidity and mortality wherever they are used.

7 *There was early evidence that the component viruses of MMR could interfere with one another. There have been studies that showed that sero-conversion is affected by other vaccines.*

Theoretically there is a potential for interaction between the individual attenuated viruses in a combined vaccine such that immune responses to one or more components of the combined vaccine might be less than those seen in following administration of mono-component products. This phenomenon is termed *immunological interference*. In addition, there is a theoretical potential for an increased incidence of adverse reactions when three live attenuated viruses are administered compared with three separate injections with mono-component vaccines. It is important therefore to examine those studies that have compared the effects of the individual components with the combined vaccine.

In Table 1 of Wakefield and Montgomery, there are three studies where viral "interference" is claimed, leading to adverse effects.

The first, Buynak et al, (reference 18 in the table and in the text at page 272, but numbered 23 in the list of references) is a misleading citation. The "interference" relates to rash, where 4/13 (30.8%) of those with one form of mumps and measles (MM) vaccine had a rash (The small numbers involved are not quoted by Wakefield and Montgomery). The numbers with a rash who had MMR vaccine was 1/28 (3.6%) and 1/38 (2.6%) with another MM vaccine. The overall pattern of results is compatible with chance and does not give evidence of an increase in adverse effects with MMR.

The second study is by Minekawa et al (1974), reference 57, and this paper shows clearly that combining the three vaccine viruses tended to lead to a **reduced** rate of clinical reactions; however, fever was the only outcome studied. This was mirrored in a tendency to a reduced immunogenicity of the measles vaccine under some circumstances. Minekawa state "the clinical reactions caused by measles vaccines were considerably alleviated [when combined with mumps and rubella]". This is the opposite of what is implied by Wakefield and Montgomery. The numbers in the studies were not large, varying from 5 to 44 given a particular combination, and no statistical analysis was carried out.

The third paper by Crawford & Gremillion (1981) reference 58, was an observational study carried out on US Air Force recruits. Again, this study focused on adverse events and not on immunological interference Most of the recruits were given no vaccination against measles or rubella, while some were given the single components and a small proportion were given MR. All had been given "routine immunizations", (DT, A & C meningococcal vaccine, adenovirus types 4 & 7, influenza and trivalent polio vaccines) four days previously. There were higher rates of diarrhoea, fever and sore throat among those given the MR vaccine, though the statistical analysis of the data is not entirely valid. It is also clear that those given MR were in different years to the comparator groups so that valid comparison may not have been made. The authors conclude, "measles and rubella among young adults can be safely and effectively controlled with attenuated viral vaccines". The implication for MMR in children is certainly not that it has a higher rate of adverse effects than the single component vaccines.

Edees et al (not Eddes as in their reference 30) is not given in the table, and it does not show any evidence of "interference". There are other studies comparing single and multiple vaccines that do not show "interference"[4].

The evidence presented by Wakefield and Montgomery is highly selective and the overall pattern of results does not show that MMR has any higher adverse event rates than the component vaccines.

8 *Re-vaccination with MR and MMR has not had safety assessed. Professor Sir Michael Rawlins as "Head of the UK Committee on Safety of Medicines" relies upon "available evidence" rather than a vigilance with "no limit".*

Revaccination with MMR has been addressed. The adverse events reported after the UK 1994 MR campaign have been described[10]. US studies have shown that adverse event rates are lower at the second dose than for those administered a first dose[11]. The overall vigilance applied to vaccines does need to be maintained, and pharmacovigilance combined with epidemiology in the UK for vaccines is recognised to be of the highest quality. Spontaneous reporting of suspected adverse reactions to vaccines is the best known way of generating "signals" of rare problems, and epidemiological studies are the best way of testing them. It is surely sensible to rely on evidence.

9. *The authors conclude that since, in their view, safety data on MMR is insufficient, that separate vaccines should be given a year apart. They suggest delaying mumps vaccine and instead giving it to every child aged two.*

It is unproven that the population immunity acquired after two years of age would be adequate to protect those less than that age. Furthermore, the suggestion that a one-year delay would not significantly increase the pool of susceptible children is misleading: If mumps immunisation were given at two years of age, then for rubella immunisation there would then be a two-year delay. Wakefield and Montgomery's advice could lead to resurgence of congenital rubella syndrome as pregnant women caught rubella from their children, or could lead to viral meningitis and encephalitis from mumps. If

measles immunisation were delayed, then children would be left susceptible at the age of high mortality and especially high risk of SSPE.

## 5. Detailed assessment of the issues raised by the published reviewers' comments

The journal Adverse Reactions and Toxicological Reviews has published the comments of the reviewers adjacent to the paper itself. This section assesses the reviewers' comments and responds to the issues raised.

5.1 Referees comments: overview

The editor of the journal suggests that these were the original referee's comments on the paper by Wakefield and Montgomery. If that is so, it is clear that none of them is the usual type of referee's report with critical views to help the authors improve their paper. They are simply rather general comments stimulated by Wakefield and Montgomery's review. It seems that the referees do not have current expertise in vaccines. It is unfortunate that the journal Editor did not seek the views of at least one current expert in vaccinology. Had such input been available, then errors and omissions in the Wakefield and Montgomery paper might have been identified.

None of the referees points out that Wakefield and Montgomery's views are at variance with most of the worldwide scientific community (only "officialdom").

These reports taken as a whole do not show the peer review process or journal in a good light. It is commendable that the reports themselves are published, but they have limitations as to assessing the weakness of the review under consideration.

5.2 Assessment of the comments of individual referees

Given below is a summary of the key points made by each referee together with a response from expert assessors at MCA and DoH.

**<u>Comments by Hurley</u>**

Summary:
The comments are generally positive about the review by Wakefield and Montgomery: "Well-referenced … thoughtful and provocative, a welcome contribution to the ongoing scientific debate".

- Makes it clear that causal associations of MMR with autism/IBD are considered unproven. She notes CSM conclusions on this.

Response: This point is agreed.

- States that decreased coverage because of lack of parental confidence "must not be allowed to happen"

Response: This is exactly what publication of this flawed paper risks.

- Points out that long-term safety studies are difficult, and does not agree with "Wakefield and Scott [sic]" that their hypothesis of "late vaccine damage" is certainly testable.

Response: This is agreed.

- Cites a recent publication by Plesner on Gait disturbance.

Response :

- She does not note that the recent publication by Plesner is a follow-up to an earlier Lancet paper. Both refer to a series of spontaneous reports without a control group. So far, the results have not been confirmed elsewhere. The MCA view is that this is a potential "signal" of a problem that merits further investigation using epidemiological methods. Such a study is being carried out by the UK Communicable Disease Surveillance Centre of the Public Health Laboratory Service and early indications are that the effect is not caused by MMR vaccination.

- The comments do not note that JCVI and the MRC, two further independent sets of experts, as well as international bodies such as the Centers for Disease Control in the USA have also concluded that there was not a causal association between MMR and autism or inflammatory bowel disease.

**Comments by Vere**

- Vere raises issues of principle, which are not contentious. His detailed comment on Wakefield and Montgomery is limited but he says "their case about the data could scarcely be more clear".

Response: He does not seem to have examined all the available data in detail, particularly on multiple antigen vaccines, to see if Wakefield and Montgomery's claims are true.

- He raises substantial problems with the ADR data (9 listed points), the most important of which seem to be (3) short duration and (9) reliance on passive surveillance. He supports the need for further comparative study.

- Response: Modern epidemiology uses databases and record linkage rather than just passive surveillance to examine vaccine safety. These are on-going and have examined risks of autism and IBD without linking them to MMR. He does not point to the extensive experience of the MCA in pharmacovigilance or the epidemiological work done by CDSC.

- He states that "non-vaccination carries immense risks of illness or death".

Response: Agreed.

- Vere states categorically that giving MMR is to be recommended.

Response: Totally agreed.

**Comments by Fletcher**

- He has asked whether "with respect to the licensing of MMR the system has served us well". He repeats suggestions of problems with chronic GI problems, autism, SSPE and other acute and delayed encephalopathies.

Response: Licensing of MMR has been investigated and it was based on appropriate data. SSPE and viral encephalitis are reduced dramatically following the policy of giving MMR, these being caused by the diseases against which MMR is protective. There is convincing evidence that chronic GI problems are not caused by MMR or measles-containing vaccines. There are a number of studies that show that autism is neither an acute nor a long-term effect of MMR.

- He suggests that the impact of giving 3 antigens together was not fully investigated.

Response: The concern was that 3 antigens would have less effect than the components given singly. The studies of MMR showed that any differential effect compared with monovalent vaccine was small or non-existent, both in efficacy and adverse effects. There were a number of studies of MMR combined with other vaccines including DTP and polio. No concerns about safety were raised in these studies either. There were about 30 studies of MMR vaccines carried out prior to its introduction in the UK in 1988.

- Main theme relates to lack of large long-term studies

Response: There were long-term studies carried out, but the number of these done for any medicines at that time were limited. Fletcher suggests that there should have been post-marketing studies, and these require that MMR should have been licensed. This seems contradictory. We agree with Fletcher that observational studies can be valuable, but they need to be focused. Case-control studies and cohort studies have been and will continue to be carried out to examine specific hypotheses. At the time of licensing there were no hypotheses to test.

- He raises Wakefield and Montgomery's points about deaths in West Africa.

Response: It is not made clear that this was following use of high-titre monovalent measles and not MMR vaccine.

- Fletcher raises the spectre of Transmissible Spongiform Encephalopathies ("Mad Cow" types of disease) as "not a great stretch of imagination"; and says that the "prion-only hypothesis is far from satisfactory".

Response: This seems to be another hypothesis for which there is no evidence whatsoever. This is not a scientific judgement, and, so far, has not been suggested by Wakefield and Montgomery. It is not clear whether this is a serious suggestion that Variant Creutzfeldt-Jakob Disease is caused by MMR. The UK Spongiform Encephalopathy Advisory Committee (SEAC) has stated "The most likely

explanation of the cases of nvCJD to date remains exposure to BSE before the introduction of the SBO [Specified Bovine Offal] ban in 1989".

- He states that there has been little high quality research on safety of polyvalent vaccines and plugs observational studies rather than spontaneous reporting. He hopes that Wakefield and Montgomery will provide necessary stimulus to research.

Response: This is incorrect. There has been a great deal of research on polyvalent vaccination. No major concerns have been raised following this research.

- His conclusions raise the issue of licensing – evidence on safety "thin" and "caution should have ruled the day". Strong encouragement should have been given to a 12-month observational study. Licensing was "premature".

Response: All medicines, including vaccines, are licensed on the basis of their safety, quality and efficacy. The MCA has an entire division that concentrates on Post-Licensing issues, and actively examines on-going safety of medicines. At the time of licensing, safety cannot be other than "provisional"; in the case of MMR it was very much less provisional than for almost any other medicine. Its introduction to the UK immunisation programme in 1988 followed very extensive experience in other countries. Its safety continues to be monitored and the possibility of new safety problems will always be considered. New studies, including those by Dr Wakefield and those who collaborate with him, are always examined carefully. Where necessary, they are also considered by the Committee on Safety of Medicines.

**Comments by Earl**

- He states that Wakefield and Montgomery criticise the decision by the Department of Health to "withdraw the licence" for monovalent measles vaccine and suggests that using the monovalent vaccine would carry a lower risk of serious complications.

Response: This is incorrect. MCA has not withdrawn the license of any monovalent measles vaccine. There is no evidence at all that monovalent vaccines carry a lower risk of serious complications.

- States that frequency of SSPE greatly reduced by measles vaccination.

Response: Agreed. But Earl should have known that the reduction in SSPE was even greater after introduction of MMR in the US and the UK.

- Seems supportive of Wakefield and Montgomery and raises almost no critical comment.

Response: There are a number of deficiencies in Wakefield and Montgomery, but they may not be those that would be noticed by a neurologist.

**6. Conclusions**

- **Careful assessment of all the available data does not support a link between MMR vaccination, inflammatory bowel disease or autism. This conclusion has been reached in the UK by the CSM, JCVI, an MCA Working Group on MMR vaccine, and an MRC ad-hoc group on MMR vaccine. This conclusion has also been reached by various expert groups outside the UK including the World Health Organisation and Centers for Disease Control in the United States.**
- **After viewing all the available evidence in January 2001, the CSM concluded that the policy of giving MMR vaccine in two doses is safer than giving the three component vaccines sequentially with six injections. With the mono-component vaccines children would be at risk of infection for longer periods. They would be exposed to several times the risk of local adverse reactions. There would be a significant dropout rate for the sequential vaccinations. There was no evidence of additional benefit from separate vaccinations. The balance of benefit to risk for MMR is therefore highly favourable.**
- **The paper by Wakefield and Montgomery reviews a number of published articles and presents comments on them, but does not present any new data itself. It does not carry out a systematic review to answer specific questions. The paper contains important omissions, misinterprets data and is misleading. The paper does not change the conclusion that MMR vaccine is the safest way to protect children from these serious and sometimes fatal diseases.**
- **The reviewers whose comments have been published are not experts in vaccines. They seem to have based their comments largely on the Wakefield and Montgomery publication with all its shortcomings. The reviewers' comments are therefore likely to be based on mis-information.**
- **A review of the licensing of the MMR vaccines has been conducted. Licensing followed normal procedure and was based on the provision of satisfactory data regarding safety and efficacy in adequate numbers of children. The suggestion that MMR vaccines were licensed prematurely is completely incorrect.**
- **The safety of all medicines including vaccines is monitored continuously by the Medicines Control Agency and Committee on Safety of Medicines (the Government's independent scientific advisory committee on human medicines). Various data sources are used including reports of suspected adverse reactions received from the UK and world-wide, regular safety updates from companies, the world-wide medical literature, epidemiological studies and information from independent researchers as well as regulatory authorities around the world.**
- **The safety of combined measles, mumps and rubella vaccines has been reviewed repeatedly by the Government's independent expert committees, the Committee on Safety of Medicines (CSM) and the Joint Committee on Vaccination and Immunisation (JCVI). In addition, ad-hoc working groups of the MCA and Medical Research Council have also been set up to review all the available data on the safety of these vaccines. All of these expert groups have concluded that the evidence does not support an association between combined measles, mumps and rubella vaccines and inflammation of the bowel or autism. It is not that there is no evidence, but that there is evidence and is does not show an association.**

- **The CSM concluded in January 2001 that vaccination with MMR is very effective at preventing serious and occasionally fatal diseases. The balance of benefit to risk is therefore highly favourable:**

**Medicines Control Agency and Department of Health**

**21/01/2001**

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