AGENDA ITEM NUMBER 13 *PAPER NUMBER JCVI(04)37*

NOT FOR PUBLICATION

JOINT COMMITTEE ON VACCINATION AND IMMUNISATION

TITLE OF PAPER
(annual yellow card update)
Vaccine-Associated suspected adverse reactions

REASON FOR INCLUSION (*please say whether this is a discussion paper or for information).*

For information

ACTION REQUIRED BY THE COMMITTEE

None

LIST OF PAPERS/ARTICLES ATTACHED (*if applicable)*

ANY OTHER COMMENTS

VACCINE-ASSOCIATED SUSPECTED ADVERSE REACTIONS

The data on suspected adverse reactions (ADRs) for each year included in this report are taken from the adverse drug reaction on-line information tracking (ADROIT) database using the extract dates 1 January to 31 December. It should be noted that the reporting of a suspected ADR to the MHRA does not necessarily mean that the vaccine caused the condition. Other factors such an underlying or concurrent illness and other medications being taken may be alternative explanations.

Exposure data are based on estimated distribution data for each fiscal year. Data is not provided on the exact number of vaccinees immunised within each year. Please note that exposure data for hepatitis A and B vaccines are based on sales data provided by Aventis Pasteur MSD and GlaxoSmithKline and are commercially confidential.

1. Wholecell DTP/DTwP+Hib

The total number of suspected ADRs reported in association with wholecell DTP and DTwP+Hib for the last 3 years is shown below (table 1). It is of note that the number of ADRs reported and the estimated reporting rate of serious reports (ERR)/1000 doses has more than doubled compared to 2002. The serious ERR is lower than 2001. Also, the reporting rate for serious ADRs in 2000 was 0.07/1000 doses based on 85 serious reports (figures not shown).

Table 1: Total number of reports and doses distributed (serious reports in brackets)

	2001	*2002*	*2003*
Total no of reports	150 (34)	122 (21)	247 (64)
Total no of reactions	261 (40)	222 (22)	487 (81)
Total fatal	1	0	2
Total no of doses distributed	922,366	1,608,754	2,136,178
ERR for serious reports per 1000 doses	0.037	0.013	0.029

ERR = Estimated Reporting Rate

A graph of the total number of serious ADRs in each System Organ Class (SOC) reported for the last 3 years is attached (Figure 1). On the whole, the types of serious reactions reported in 2003 were broadly similar to those reported in the previous two years. However, there was an increase in the neurological disorders SOC which included 15 reports of hypotonia, 6 depressed level of consciousness and 9 convulsive disorders. There was also an increase in cases relating to consequences of Hib disease resulting from vaccine failure when DTwP+Hib was given as part of a course including DTaP+Hib; such cases have been assessed separately.

Suspected ADRs with a fatal outcome: One case of cardiac arrest and one case of pneumonia (co-suspect with oral polio and MenC vaccine).

Given that the ERR for serious ADRs for 2003 is lower than in 2000 and 2001, it may be that the overall reporting rate in 2002 for DTwP was unusually low. Also, as nurses

were introduced as reporters to the Yellow Card Scheme in Q4 2002, it is perhaps not surprising that the reporting rate has increased relative to 2002 as a whole.

No significant safety issues have been identified.

2. Men C

The total number of suspected ADRs reported in association with Meningococcal GP C conjugate vaccine for the last 3 years is shown below (table 2). The total number of reports received in 2003 was similar to 2002.

Table 2: Total number of reports and doses distributed (serious reports in brackets)

	2001	*2002*	*2003*
Total no of reports	293 (82)	161 (50)	117 (49)
Total no of reactions	529 (97)	297 (60)	259 (67)
Total fatal	3	1	2
Total no of doses distributed	1,757,586	1,901,179	2,206,858
ERR for serious reports per 1000 doses	0.047	0.026	0.022

ERR = Estimated Reporting Rate

A graph of the total number of serious ADRs in each System Organ Class (SOC) reported for the last 3 years is attached (Figure 2).

Suspected ADRs with a fatal outcome: One case of cardiac arrest and one case of pneumonia (co-suspect with oral polio and DTP vaccine).

A possible risk of relapse of nephrotic syndrome following MenC vaccine was considered by CSM in November 2003. This assessment was provided for information at the last JCVI meeting.

No other significant safety issues have been identified.

3. Polio vaccine

The total number of suspected ADRs reported in association with oral polio vaccine for the last 3 years is shown below (table 3). It is of note that the number of ADRs reported has more than doubled compared to 2002 and the serious ERR/1000 doses has increased 3-fold. However, the reporting rate for serious ADRs in 2000 was also 0.012 based on 72 serious reports (figures not shown).

Table 3: Total number of reports and doses distributed (serious reports in brackets)

	2001	*2002*	*2003*
Total no of reports	81 (35)	56 (23)	101 (56)
Total no of reactions	187 (35)	123 (28)	257 (76)
Total fatal	0	0	2
Total no of doses distributed	5,268,740	5,352,520	4,701,710
ERR for serious reports per 1000 doses	0.007	0.004	0.012

ERR = Estimated Reporting Rate

A graph of the total number of serious ADRs in each System Organ Class (SOC) reported for the last 3 years is attached (Figure 3). The types of reactions reported are broadly similar to the previous 2 years. There was an increase in the neurological disorders SOC which included 10 reports of hypotonia, 5 depressed level of consciousness and 6 convulsive disorders. Many cases were co-suspect with DTwP and MenC vaccine. No cases of paralysis or poliomyelitis have been received since 1999.

Suspected ADRs with a fatal outcome: One case of cardiac arrest and one case of pneumonia (co-suspect with DTP and MenC vaccine).

As described above for DTwP, given that the ERR for serious ADRs for 2003 is lower than in 2000, it may that the overall reporting rate in 2002 for DTwP was unusually low and given that nurses were introduced as reporters to the Yellow Card Scheme in Q4 2002, it is perhaps not surprising that the reporting rate has increased relative to 2002 as whole.

No significant safety issues have been identified.

4. Single Hib vaccine

A specific review of the safety of the single Hib vaccine (Hiberix) given during the 2003 catch-up campaign was considered by the CSM Vaccine Working Group in April 2004 and is provided separately for information. No new safety issues were identified.

5. MMR vaccine

The total number of suspected ADRs reported in association with MMR vaccination for the last 3 years is shown below (table 4). Based on the doses distributed, the estimated reporting rate (ERR) for serious reports per 1000 doses is similar to the preceding two years.

Table 4: Total number of reports and doses distributed (serious reports in brackets)

	2001	*2002*	*2003*
Total no of reports	92 (55)	82 (36)	97 (40)
Total no of reactions	163 (70)	158 (41)	176 (49)
Total fatal	2	0	1
Number of doses distributed	1,546,548	1,354,794	1,391,040
ERR for serious reports per 1000 doses	0.035	0.026	0.029

ERR = Estimated Reporting Rate

A graph of the total number of serious ADRs in each System Organ Class (SOC) reported for the last 3 years is attached (Figure 4). The types of serious reactions reported in 2003 were broadly similar to those reported in 2002, and consisted largely of recognised reactions.

Suspected ADRs with a fatal outcome: One case of sudden infant death syndrome was reported in 2003.

Overall, the pattern and type of reactions reported does not appear to have changed and no significant safety issues have been identified.

6. DTaP+Hib

The total number of suspected ADRs reported in association with DTaP+Hib for the last 3 years is shown below (table 5). The number of serious ADRs reported has remained similar over the past 3 years, however, based on doses distributed the serious ERR/1000 doses has markedly increased in 2003.

Table 5: Total number of reports and doses distributed (serious reports in brackets)

	2001	*2002*	*2003*
Total no of reports	32 (19)	45 (21)	50 (24)
Total no of reactions	58 (19)	81 (21)	101 (24)
Total fatal	1	3	1
Total no of doses distributed	1,286,530	694,668	4,200
ERR for serious reports per 1000 doses	0.015	0.03	5.7

ERR = Estimated Reporting Rate

A graph of the total number of serious ADRs in each System Organ Class (SOC) reported for the last 3 years is attached (figure 5). The increased reporting rate can be explained almost exclusively by the increase in reports of Hib vaccine failure and associated complications for vaccinees immunised in 2000-2002. This safety issue has already been addressed separately.

Suspected ADR with a fatal outcome: One case of Haemophilus meningitis.

No other significant safety issues have been identified.

7. BCG vaccine

The total number of suspected ADRs reported in association with BCG vaccine for the last 3 years is shown below (table 6). The number of reports received in 2003 increased markedly compared to the previous 2 years. This coincided with introduction of the SSI BCG vaccine.

Table 6: Total number of reports and doses distributed (serious reports in brackets)

	2001	*2002*	*2003*
Total no of reports	81 (33)	80 (27)	496 (151)
Total no of reactions	172 (38)	132 (36)	990 (212)
Total fatal	0	0	0
Total no of doses distributed	3,244,200	2,416,130	3,903,900
ERR for serious reports per 1000 doses	0.010	0.011	0.038

ERR = Estimated Reporting Rate

A graph of the total number of serious ADRs in each System Organ Class (SOC) reported for the last 3 years is attached (Figure 6). The safety of SSI BCG vaccine has been considered separately by CSM and its Paediatric and Vaccine Working Groups. In summary:

SSI BCG vaccine contains a different strain of mycobacterium bovis (Danish 1331) compared to the Evans vaccines (Copenhagen 1077). Data from the World Health Organisation suggest that the strain of bacterium in the SSI vaccine is a 'stronger' and more reactogenic strain than that contained in the Evans vaccines. Also, as SSI BCG is available only as an intradermal formulation, intradermal vaccination has replaced use of the percutaneous technique in younger children. As SSI BCG vaccine is a newly licensed product in the UK, it carries a Black Triangle symbol which means that the MHRA and CSM encourage reporting of ALL suspected ADRs via the Yellow Card Scheme.

As with all Black Triangle products, the safety of SSI BCG vaccine has been intensively monitored since its introduction. The overall reporting rate of *suspected* ADRs associated with the vaccine to date has been greater than that observed in association with Evans vaccines in the preceding few years. However, such an observation was anticipated as nurses were included as reporters to the Yellow Card Scheme at around the same time as SSI BCG vaccine was introduced. Also, it is known that suspected ADRs are more likely to be reported for new products compared to those which have been on the market for many years (such as the previously-used Evans BCG vaccines). For these reasons, comparison of overall ADR reporting rates associated with SSI and Evans BCG vaccine must be treated with caution.

Almost half of the suspected ADRs received in association with the SSI BCG vaccine to date have been immediate reactions most likely resulting from reactions to the injection *per se*, i.e. vaso-vagal episodes including syncope and related symptoms, rather than true adverse reactions to the vaccine contents. It is notable, however, that injection site reactions contribute almost a quarter of all reported ADRs, the vast majority of which were non-serious. Although a similar proportion of ADRs previously reported in association with Evans vaccine were also injection site reactions, a greater proportion of those reported following the SSI vaccine have occurred in young children. As no data are currently available to the MHRA on vaccination coverage for the neonatal and infant age group, it cannot be determined whether this increase in reporting of injection site reactions in this age group compared to Evans vaccine is merely a consequence of an increase in immunisation of neonates and infants over time.

On the basis of Yellow Card data and available exposure data, a robust assessment of the incidence rates of injection site reactions associated with SSI BCG vaccine compared to Evans vaccine is not possible. Nonetheless, the CSM and its Paediatric Working Group have reviewed these data and advised that no new safety signals have been identified. It was acknowledged that the product information for SSI BCG vaccine includes sufficient information on the possibility of injection site reactions and abscess. The product information gives detailed guidance on the administration technique and this should be adhered to. However, it was also acknowledged that the apparent increased reporting of such reactions in children possibly represents a

combination of increased/stimulated reporting coinciding with inclusion of nurses in the Yellow Card Scheme and use of a more reactogenic vaccine and a more difficult injection technique (compared to the previously used percutaneous technique) in this younger age group. The MHRA will continue to keep the safety of SSI BCG vaccine under review.

8. Hepatitis B vaccine

The total number of suspected ADRs reported in association with single hepatitis B vaccine for the last 3 years is shown below (table 7). The number of reports received in 2003 increased compared to the previous years. However, based on the number of doses distributed the reporting rate of serious reports is similar to the previous year.

Table 7: Total number of reports and doses distributed (serious reports in brackets)

	2001	*2002*	*2003*
Total no of reports	136 (62)	79 (49)	107 (60)
Total no of reactions	388 (85)	205 (74)	311 (88)
Total fatal	0	0	0
ERR for serious reports per 1000 doses	0.054	0.046	0.046

ERR = Estimated Reporting Rate

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A graph of the total number of serious ADRs in each System Organ Class (SOC) reported for the last 3 years is attached (Figure 7). The types of serious reactions reported have remained broadly similar over the last 3 years.

The CSM Vaccine Working Group considered an assessment of the postulated association between hepatitis B vaccine and rheumatoid arthritis (RA) in November 2003. To date, MHRA has received 7 reports of RA and 3 reports of RA aggravated associated with hepatitis B vaccine through the Yellow Card Scheme. The assessment included studies by Pope *et al* (*J. Rheumatol.* 1998; 25: 1687-1693), Maillefert *et al.* (*Rheumatology* 1999; 38: 978-983) and Gross *et al.* (*Scand. J Rheumatol.* 1995; 24(1):50-2). It was also noted that the US Centers for Disease Control and Prevention (CDC) is currently evaluating if there is a risk of RA in adults receiving hepatitis B vaccine through a case-control study and that published results from this study may be available in 2 years time.

The Working Group advised that no regulatory action is necessary until further evidence is available.

No other significant safety issues have been identified.

9. Hepatitis A vaccine

The total number of suspected ADRs reported in association with single hepatitis A vaccine for the last 3 years is shown below (table 8).

Table 8: Total number of reports and doses distributed (serious reports in brackets)

	2001	*2002*	*2003*
Total no of reports	50 (27)	45 (29)	30 (21)
Total no of reactions	117 (31)	104 (41)	67 (31)
Total fatal	0	0	0
ERR for serious reports per 1000 doses	0.016	0.025	0.017

ERR = Estimated Reporting Rate

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A graph of the total number of serious ADRs in each System Organ Class (SOC) reported for the last 3 years is attached (Figure 8). The types of serious reactions being reported are on the whole fairly similar with a slight increase in cardiovascular and immune system reactions.

No significant safety issues have been identified.

10. Influenza vaccine

The total number of suspected ADRs reported in association with influenza vaccine for the last 3 years is shown below (table 9). The distribution data for the vaccine was not available at the time of writing this report and as such, ERRs have not been calculated.

Suspected ADRs with a fatal outcome: One case each of pulmonary embolism, septicaemia, sudden death and Guillain-Barre syndrome.

Table 9: Total number of reports and doses distributed (serious reports in brackets)

	2001	*2002*	*2003*
Total no of reports	173 (84)	106 (73)	137 (96)
Total no of reactions	339 (105)	227 (83)	301 (124)
Total fatal	1	8	4
Total no of doses distributed	*N/A*	*N/A*	*N/A*
ERR for serious reports per 1000 doses	*N/A*	*N/A*	*N/A*

ERR = Estimated Reporting Rate
N/A: Not available at the time of writing this report.

A graph of the total number of serious ADRs in each System Organ Class (SOC) reported for the last 3 years is attached (Figure 9). The serious ADRs reported in 2003 were broadly similar to the previous two years. There was a slight increase in serious ADRs in the general and haemopoietic SOCs accounted for by a clustering of case reports of interaction with warfarin leading to raised international normalised ratio (INR). A systematic review of this signal was considered by the CSM Vaccine Working Group in April 2004. In summary:

It was noted that neither the Summaries of Product Characteristics (SPC) for influenza vaccines nor those for warfarin products refers to a possible interaction between the two. The 1996 'Green Book' also makes no reference to a possible interaction, however, the BNF has stated since 1992 that the effect of warfarin is occasionally enhanced by influenza vaccine. Twenty six cases of a possible interaction between flu vaccine and warfarin have been reported to MHRA. These reports were received over a period of 35 years and were of variable quality and for the vast majority of cases reported, insufficient information was available to allow a robust assessment of the association. In the majority of cases no clinical manifestation of the reported increase in INR was observed, however, it is of note that in 3 cases the outcome of the reaction was fatal The Working Group agreed that on the basis of these spontaneously reported data, no firm conclusions can be drawn.

The Working Group considered 13 relevant studies identified from the literature. These consisted of 3 studies supporting an interaction (Kramer *et al*, Paliani *et al* and Weibert *et al*), 8 studies not supporting an interaction (Raj *et al*, Arnold *et al*, Patriarca *et al*, Scott *et al*, Lipsky *et al*, Farrow *et al* and 2 studies by Gomolin *et al*) and 2 studies reporting the opposite effect (i.e. a decrease in INR; Poli D *et al* and Bussey & Saklad). It was agreed that on the basis of the overall results of these studies, if an interaction did exist, it may not be possible to define those at risk and it would likely be a rare effect, of varying onset and of small magnitude in the vast majority of cases. The Working Group advised that the available evidence does not allow any firm conclusions to be drawn on causality and no regulatory action was recommended.

No other significant safety issues have been identified.

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