

**Executive summary of  
Report: Hepatitis B vaccine and putative associations with**

- (a) Arthritis**
- (b) Chronic Fatigue Syndrome**

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Introduction

WHO commissioned this report to examine the published literature on the putative associations between HBV vaccine and arthritis and chronic fatigue syndrome (CFS). A full report is available of which this is a summary.

Methods

A bibliographic search using MESH terms “hepatitis B vaccine”, “adverse events”, “arthritis”, “chronic fatigue syndrome” and “myalgic encephalomyelitis” was performed in PUBMED and EMBASE up to 10<sup>th</sup> September 2005. Relevant literature – case reports, case series, conference proceedings and abstracts - regarding the association between HBV vaccine and specific chronic adverse reactions of rheumatoid arthritis and chronic fatigue syndrome were identified and obtained. The bibliographic references in these articles were hand-searched for further articles that reported examining the association between HBV vaccine and arthritis or chronic fatigue syndrome. Both English and non-English articles were obtained for this review.

Results

**1. Arthritis/Rheumatoid Arthritis**

**Table 1** summarises case reports (some as part of series of cases) found in the literature (references indicated refer to full report). It has not been possible to separate those that are reactive arthritis from true rheumatoid arthritis since sufficient information is not always available to apply the appropriate diagnostic criteria. However for some cases there is no doubt that these were true cases of rheumatoid arthritis with onset soon after a dose of hepatitis B vaccination. Nevertheless the nature of published case reports means that these could be entirely due to chance.

One publication in 1998, by Pope *et al.* described a series of 10 rheumatoid arthritis cases that were seen after Engerix B vaccination in previously symptom-free individuals [1]. A cluster of five male fire-fighters (age 41 to 58 years old) working at different fire stations in a local city fire department developed inflammatory polyarthritis after HBV vaccination. Two rheumatologists confirmed the existence of arthritis in the fire-fighters and checked if they satisfied the revised ARA criteria as well as verified relevant history from the fire-fighters. It is noted by the author that some of

the patients had their examination performed by another rheumatologist. 4 out of the 5 satisfied the criteria.

The authors noted at least 2 different lots of Engerix B were used to vaccinate the fire fighters. All except one (from a family physician) received HBV vaccine in the workplace. They developed symptoms within 2 to 3 weeks of the second dose, one developed arthralgias within 2 weeks of the first dose and then arthritis after the second dose. 2 of the 5 fire-fighters had persistent inflammatory arthritis 5 years after the vaccination (the most recent follow-up mentioned by the authors). All the fire-fighters shared the HLA DRB1 allele 0301 and the DQ $\beta$ 1 allele 0201 with which it is in linkage disequilibrium. The expected frequency of this in the population is 20-25%.

This last study raises the possibility of an adverse reaction in a genetically selected sub-group.

Analytical studies have been of two types. There have been three case control studies, each by different authors. The other analytical studies have all been of the VAERS (Vaccine Adverse Events Reporting System) database and by the same authors.

1. Fisher *et al.* [2] used the USA National Health Interview surveys of 1993 and 1994 as sources of data. They compared those children aged 0-5 with prevalent arthritis to the population without arthritis in terms of hepatitis B vaccination. They found an association with an odds ratio of 5.91 (1.05-33.14) based on 14 affected children of whom 12 had received hepatitis B vaccine and 2 had not. Clearly those with a chronic disease may be more likely to access health services for vaccination but this could not be controlled for in this analysis. In addition, as noted below, there were other potential problems with this analysis.

Fisher *et al.*'s paper was mentioned in a review in 2003 pointing out that GACVS criticised their results which alleged that HBV vaccination is positively associated with chronic arthritis, ear infection, pharyngitis and nasopharyngitis in the US children less than six years of age. The following points were mentioned: (1) The results of the study was in contradiction to the conclusions; (2) lack of representativeness of the different age cohorts and distribution of subjects; (3) the definitions of adverse events were not provided and there was no due consideration of confounding variables; (4) flaws in the analysis of the results and absence of biological plausibility; and (5) the exclusion of a large proportion of the initial study population due to missing immunization status information.

2. Harrison *et al.* [3] studied patients presenting with inflammatory polyarthritis with duration of more than 4 weeks in a defined population of Norfolk. They took a history of vaccination and compared clinical features in those who had received vaccination in the six week period preceding onset of symptoms to those who had not. They found no difference in clinical presentation or subsequent disease course. They also conducted a small case control study of preceding vaccination. This included all cases aged between 16 and 70 years of age who presented between May 1994

and May 1995 with disease duration of less than one year. Controls were age and sex matched from the Norfolk family health register (ie those registered with GPs in the same study population). They found that 9/165 subjects with inflammatory polyarthritis had received a vaccine in the preceding six weeks compared to 5/178 controls – giving an odds ratio of 1.7 (0.5-5.4). It is not stated what vaccinations were received but in a separate report of 21 cases [4], 19 had received tetanus, one influenza and one hepatitis B vaccination. Thus this carefully conducted study in a defined population provides no support for an association.

3. A matched case-control study was conducted as part of the VAID (Vaccine Auto Immune Disease) study in France [5]. This used the 1989-1998 data from the GPRD (General Practitioners Research Database) and included 2814 patients with an RA code and 27040 controls [5, 6] (**Table 2**). Cases were defined by diagnosis of RA in two circumstances, once by a specialist and the second as a 'valid history prior to the first symptom'. The date of onset of symptoms was the index date. Each case was matched on age, gender, general practice and calendar time to up to 10 controls. The estimated incidence of RA was 11.8 per 10 000 person years and was twice as frequent in females with the highest incidence in those more than 60 years of age. The results of the study gave an adjusted odds ratio (OR) of 1.1 (95% CI 0.8-1.4) and was not statistically significant. Recent infections (OR=1.4, 95% CI 1.2-1.6) and other prior vaccinations in the one year preceding onset of symptoms (OR=1.2, 95% CI 1.1-1.3) were significant risk factors. [5, 6].

This study only appears as an abstract and has not been published as a full paper. A problem with the GPRD in addressing this question lies in two areas. First the validity of codes for RA in the GPRD has not been examined (although a study is ongoing by Hall, Cooper and Thomas). Secondly, in the UK, hepatitis B vaccine may be given outside General Practice – particularly at travel clinics and by occupational health services. Such vaccinations are unlikely to be recorded in the GPRD. This misclassification of exposure using GPRD is likely to lead to bias since it is the less well and those not in employment who are likely to have their vaccination recorded there. This makes interpretation of studies of hepatitis B vaccination in the GPRD problematic.

### VAERS analyses (**Table 3**)

Geier and Geier have produced a series of 8 publications [7-14] addressing arthritis and hepatitis B vaccine using this publicly available database. They have used it to estimate the frequency of various combinations of outcome code amongst those who have been reported following hepatitis B vaccine. They then convert this to a rate per 10,000,000 doses using US data on the numbers of doses distributed. They compare this "incidence rate" to similar estimates following tetanus-diphtheria (Td) vaccine or tetanus-toxoid (TT) alone. They have done this for various and overlapping periods of time. In all of their analyses they

have found an excess of arthritic like events in the those receiving hepatitis B vaccine.

However these analyses are inappropriate for VAERS data for the following reasons:

1. The system does not capture all adverse events – only certain events are required to be reported by law and this varies from vaccine to vaccine and from time to time. Thus there is a potential for both under-reporting and differential reporting by vaccine type. Newer vaccines have higher reporting frequencies than older ones. The number of events is highly influenced by publicity.
2. The coding system used (COSTART) includes both medical diagnoses and symptoms under the same code. Reports may receive multiple codes. The codes may be related to multiple vaccines and not just to one.
3. Incidence rates can not be calculated from VAERS data since the denominator – the number of doses distributed – does not necessarily represent doses given. Since vaccines such as hepatitis B are multi-dose schedules it is unknown how many people are represented by the number of doses. There is no breakdown by age group or sex and therefore confounding by these can not be controlled.
4. Finally the use of other vaccines as a control group is inappropriate given the points above about multiple dose schedules, age sex and reporting rates for vaccines of different maturity in the health care system.

In conclusion: The evidence for an association between rheumatoid arthritis and hepatitis B vaccination is limited and frequently difficult, if not impossible, to interpret. The one study that represents a population based case control study with careful case definition and appropriate control selection found no association but had limited power (Harrison *et al.* [3]). Whilst there is no evidence for an association, nor is there strong evidence against it. Research could be done to address this. The GPRD is not an appropriate for this question because of the incomplete and biased recording of hepatitis B vaccine. However linkable databases in Scandinavia or data held by HMOs in the USA might be used to address the question using appropriate epidemiological designs.

## **2. Chronic Fatigue Syndrome (CFS) (Table 3)**

The concern that CFS is linked to HBV vaccine started in October 1990 in Canada following a Francophone television programme where a nurse alleged that she developed CFS after receipt of the vaccine. After this program, sixty-nine people reported similar experience [15, 16]. Subsequent to this, the Nightingale Research Foundation issued a statement that CFS was a consequence of HBV vaccination.

The Laboratory Centre for Disease Control (Canada) proceeded to investigate these reports. Thirty-one people (53%), the majority female, satisfied the 1988 Holmes criteria for CFS [17]. Administration of HBV

vaccine to these patients took place between 1983 and 1990. An independent working group led by Dr. Gilles Delage was set up to evaluate the alleged link [18, 19]. The working group concluded that there was no evidence for any link for the following reasons: (1) The case series consisted of self-reporting individuals and it is known that health care workers have always made up the majority of cases seen at CFS clinics, before HBV vaccine was licensed for use in Canada. There is the problem of reporting bias after the televised program of a fellow health-care staff who alleged the link. Of the 69 people who called in to report a similar presentation, only 31 satisfied the Holmes criteria for CFS and most developed symptoms within three months of HBV vaccination, with 'no clear pattern of distribution of time intervals'. (2) The Pennie *et. al* [20] study among 700 health care students did not show any evidence of chronic fatigue after each dose of the vaccine. (3) No dose-response relationship was reported: The majority of CFS patients reported development of symptoms after the first dose of HBV vaccine and there was no report of increased severity of the symptoms after subsequent doses (i.e. after completion of 3-dose schedule). (4) An ongoing matched case-control study (later published in 1997) by Salit *et. al* [21] interviewed 134 CFS clinic attendees and 35 controls. The numbers compared were small but the proportion of those who had a history of vaccination within 3 months of onset of symptoms was small to begin with (10 out of 134). This was the first study that considered, *a priori*, vaccination as a possible risk factor and the participants were specifically asked about their vaccination status. The working group compared this rate to a recent health survey conducted among a representative population in Canada (stated in report). The HBV vaccination rates were similar in the CFS patients and the general population. (5) Lack of biological plausibility: Chronic fatigue or tiredness is not one of the common symptoms among chronic HBV carriers without underlying chronic inflammation of the liver. If there is an involvement of a common underlying biological inciting mechanism among individuals with HBV infection and individuals administered the HBV vaccine, one would then accept the possibility of a similar manifestation of symptoms. (6) Lack of consistency: CFS is disease that is investigated by many researchers, both locally and internationally. No studies or reports of similar alleged association with HBV vaccine have been otherwise identified. After this meeting, they recommended ongoing post-marketing surveillance of possible adverse events after HBV vaccination to continue.

A case-series in Canada consisting of 4 patients who fell ill with CFS and another 4 with MS immediately after recombinant HBV vaccination was reported by Dr. Byron Hyde of the Nightingale Research Foundation at a conference in Brussels in 1999 but there were no details nor follow-up of these group of patients [22].

De Becker *et. al* conducted a case-control study in Brussels, Belgium of 1546 CFS patients and 301 controls who did not satisfy the CFS criteria (because of the exclusion criteria under Holmes or Fukuda) [23]. All the patients were Caucasian and examined by one physician. They were interviewed on events prior to the onset of their symptoms. They

investigated twenty-six possible triggers of which HBV vaccination was one. 86.7% of the patients were female with a mean age of onset of 30 years. Only 5% of the CFS patients had previous HBV vaccination. There was no difference (no data provided) for HBV vaccination in the control group. They noted that patients considered under the Holmes criteria had different onset events associated if they satisfied the Fukuda criteria. They compared patients with sudden onset of symptoms and gradual onset of symptoms and 6.9% of the sudden onset CFS patients reported previous HBV vaccination compared to 1.0% of the gradual onset CFS patients. They reported an odds ratio of 7.0 (95% CI 2.8-17.6,  $p < 0.0001$ ). As CFS is possibly a multi-factorial disease, the authors also investigated the clustering of different onset events in various combinations in the study participants. They reported that the clustering of events among males and females were similar. They reported that two onset events of blood transfusion with HBV vaccination (OR=7.8, 95% CI 5.2-12.0,  $p < 0.0001$ ) and pneumonia with HBV vaccination (OR=4.9, 95% CI 2.9-9.0,  $p < 0.0001$ ) were associated with an increased odds of CFS. They went on to report that the onset factor combinations (eight noted in paper) occurred only in CFS patients or more frequently among CFS patients than non-CFS patients.

Although the analysis of this study looked at combinations of events it did not fit any regression models, not did it do this by examining interactions – therefore confounding was not controlled. From the description of the methods used it appears that all the reported odds ratios were from univariable analysis.

In conclusion the evidence linking CFS to HBV vaccination largely consists of data generated from publicity. The two studies that have addressed the question analytically – Salit and De Becker et al – used case control designs with limited power and inappropriate analysis. There is therefore no current evidence that there is, or is not, an association.

Ref	Year	Country	Vaccine	Diagnosis	Age	Gender	Time Frame	F/U
[24]	1984	Germany	PDV?	Rheumatoid arthritis?	33	Male	2 weeks after 3rd dose	persistence 9months 10months
				Rheumatoid arthritis?	55	?	rapidly after 3rd dose	
[25]	1987	Denmark	Hep-B-Vax	Reactive arthritis	36	Female	2 weeks after 2nd dose	Up to 1 year
[26]	1990	France	Hevac Br	Reactive arthritis	19	Male	May 1989, 2 weeks after 1st dose Recurrent attack 2 weeks after 2nd dose	
[28]	1990	UK	Engerix B	Erythema Nodosum Polyarthritis	31	Male	May 1989, next day after 1st dose	9/12 symptom free
[29]	1993	Italy	Engerix B	Reactive arthritis	41	Male	1991, 2 weeks after 2nd dose	4/12 symptom free
[30]	1994	UK	Engerix B	Reiter's Syndrome	29	Male	4weeks after 2nd dose	
				Reactive arthritis (migratory, polyarthritis)	41	Female	2weeks after 1st dose	
[32]	1994	Italy	Engerix B	? polyarthralgia	18	Female	1month after booster dose	Resolution of symptoms after two months Short period, resolution
				Arthritis of large joints (migratory)	35	Female	1990, 15 days after 2nd dose	
[33]	1994	UK	Engerix B	<b>Rheumatoid Arthritis</b>	49	Female	within 24hours of 1st dose	
[34]	1995	Germany	ND	<b>Rheumatoid Arthritis</b>	20	Female	4 days after a first dose	1985-1994 recurrent attacks Persisting knee arthritis 6months symptom slowly subsided
			Gen-HB-vax	Reactive Arthritis	15	Female	1 week after 1st dose	
			Gen-HB-vax	Reactive Arthritis	27	Female	2 weeks after 1st dose	
[35]	1995		Engerix	Psoriatic Arthropathy	29	Male	2months after 3rd dose	Progressed in 5 years
				Psoriatic Arthropathy	39	Female	6weeks after 3rd dose	
[36]	1996	Italy	Engerix B	Juvenile chronic arthritis	9	Male	3 weeks after 2nd dose	Resolution over 3 months
[37]	1996	France	Engerix B	Polyarthritis	44	Male	3 injections in 2 weeks 2 weeks after 3rd dose	symptom free x 1year with treatment
[38]	1997	France	Engerix B	Erosive polyarthritis	37	Male	September 1995, few days after 3rd dose	
[39]	1997	France	Genhevac B	<b>Rheumatoid Arthritis</b>	43	Female	1991, 3 days after 2nd dose and 4 days after 3rd dose	1991
[40]	1998	Canada	Engerix	<b>Rheumatoid Arthritis</b>	<b>54</b>	<b>Male</b>	2 weeks after	5 years
				5 firefighters	<b>41</b>	<b>Male</b>	2 weeks after	1 year
				4 met criteria for RA	<b>58</b>	<b>Male</b>	3 weeks after	5 years
					<b>58</b>	<b>Male</b>	2 weeks after	5 years
					<b>47</b>	<b>Male</b>	2 weeks after	5 years
				6 health-care workers	<b>25</b>	<b>Female</b>	2 weeks after	1.5 years
					<b>49</b>	<b>Female</b>	2 weeks after	3 years
					<b>57</b>	<b>Female</b>	After 1st injection arthralgia then arthritis	1.5 years
				3 doses	<b>46</b>	<b>Female</b>	2 weeks after	0.5 years
				3 doses	<b>44</b>	<b>Female</b>	less than 10 days	3 years
	<b>27</b>	<b>Female</b>	Initial arthralgias then arthritis	5 years				
[41]	1998	France	Engerix and Havrix	Still's disease (adult-onset)	38	Female	10 days after first dose (both Engerix and Havrix)	? Follow-up
[42]	1999	France	Recombinant	<b>Rheumatoid Arthritis</b> 6 cases 22 patients (3M, 19F)	25-45		after 1st injection <b>HLADR4+ 3/3</b> RF +ve 4/6 ANA +ve 4/5	1992-1997 vaccine receipt 1-18days

Table 1. Summary of case reports and case series reporting arthritic events and HBV vaccination

Ref	Year	Country	Vaccine	Database	Cases and Controls	Age	Gender	Time Frame	F/U	Cases	Controls	Results
[61]	2005	US	Recombinant HBV	VAERS	Cases: SAAE from one type of vaccine Controls: other adverse events	24-39 (Median 36)	Male Female	7/71990 to 28/5/2004	3-19 days	53 HBV 1 TCV	963 HBV 334 TCV	Fisher's exact test for significance OR=18.0, p<0.0001, 95% CI=3.1-740
[21]	2004	US	Recombinant HBV	VAERS PubMed (1966-2003) VAERS	<b>153 Rheumatoid Arthritis, 407 Arthritis</b> <b>13 Rheumatoid Arthritis, 8 arthritis</b> Arthritis in identical twins (case report) 8 Arthritis, 11 Chronic Fatigue	36 (RA), 38 (arthritis) 44 (RA), 36 (arthritis) 27 (arthritis) 34 (chr. Fatigue)	Male Female	28 days (RA), 6 days (arthritis) 14 days 8 days (CFS)	1 year	153 RA 13 RA 11 Chr. Fatigue 8 arthritis	N.D	
[59]	2003	US	Recombinant HBV	Own case-reports VAERS	<b>1 case of Chronic Fatigue Syndrome</b> Report results of 2002, Ref [23]	51	Female	9 days after 3rd dose	2 years			
[58]	2002	US	Recombinant	VAERS 1997-2000 1991-2000	Cases: HBV reactions Controls: Td vaccine chronic reactions		Male Female		1 year			Incidence 0.88/million vs. 0.06/million. RR=15.0 (95% CI=7.0-36.0)
[22]	2002	US	Recombinant	VAERS 1997-2000 1991-2000	Cases: HBV reactions Controls: Td and TT vaccine groups	Mean age 34 years	Male Female	8.4 days		23 (16F,7M)	N.D	Incidence 14 arthritis cases per10million vaccinations vs. 3.5per10million TT and 2.4per10million Td. RR=4.0 (vs. TT), RR=5.8 (vs. Td)
[57]	2002	US	Recombinant HBV	VAERS 1997-1999 1991-1999	Cases: Chronic Arthritis cases Controls: Td and tetanus toxoid adult vaccine control	Mean 33	Male Female	16.1 days (1 year f/u)	1 year	9(7F,2M)	N.D	Incidence 0.56/million, RR=10 (vs. Td vaccine), p<0.0001. RR=6.1 (vs. TT), p<0.05 Incidence 0.054/million (Td), 0.088/million (TT)
[56]	2002	US	HBV	VAERS July1990-August1999 1991-1999	Cases: arthritis reactions Controls: Td vaccine-associated arthritic adverse reactions	Mean age 40 years	Male Female	4.5 days	N.D	193 arthritis (151F,42M) 93 joint disease (77F,16M)	N.D	Incidence 50/ten million vs. 2.4/ten million (p<0.0001) Total no. disabled = 30
[55]	2000	US	Recombinant	VAERS 1990-1997	319 arthritis reports	38.1+/-14.7	65M 200F	2days	N.D			
[53]	2000	France	Recombinant	GPRD (UK)	2814 Cases Up to 10 controls for each case, 27040 controls (Matched)		Male Female	1989-1998		52 HBV	449 HBV	RR=1.1 (95%CI 0.8-1.4) RR 2 fold higher in female vs. male RR=1.4 (95%CI 1.2-1.6) (recent infections one year prior to index date) RR=1.2 (95%CI 1.1-1.3) (vaccinations with any other vaccine one year prior to index date)
[45]	1994	US	Recombinant	VAERS Nov1990-Jul1992	17 polyarthritis 40 oligoarthritis	Mean 43 years Mean 46 years	1M,16F 11M,29F	Within 3 weeks Within 2 months				15 resolution with 3days-2months. 2 persistence up to 1year 6 already documented RA history. Documented 'flare-up'

**Table 2. Summary of analytical studies investigating arthritic events and HBV vaccination**

Ref	Year	Country	Type	Cases and Controls	Age	Gender	Time Frame	Results
[72]	1997	France	Recombinant	134 CFS cases 35 controls	39.2 36.1	73% F 77% F	3months prior to onset of symptoms 3 months prior for controls	3/134 (2%) 2/35 (6%)
[74]	2002	Belgium (Brussels)	?Recombinant	1546 CFS cases 309 prolonged fatigue patients (excluded using Holmes/Fukuda's criteria)	37.5+/-10.5	86.7% F		78/1546 (5.0%) No differences reported
[43]	1999	France	Recombinant	4 patients with Arthralgia, myalgia, fatigue (22 patients)	33-48	3Female 1Male	1992-1997 1-3/52 to 2/12	

**Table 3. Summary of reports of chronic fatigue syndrome cases and HBV vaccination**

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