

The Global Advisory Committee on Vaccine Safety reassuring about the risk of childhood leukaemia following hepatitis B vaccination

An abstract presented at the April 2002 meeting of the American Association for Cancer Research reported a link between hepatitis B

vaccine and acute lymphocytic leukaemia in children in California. These results have not been published in a peer-review journal since and the authors themselves, pointed out that these preliminary results should be interpreted with caution. The Global Advisory Committee on Vaccine Safety (GACVS) identified 4 additional studies previously conducted that considered the effect of vaccination on childhood leukaemia. None of these supported the suggestion that there may be an increased risk of leukaemia following hepatitis B vaccination or any other routine infant vaccination. The recent study mentioned above involved relatively small numbers. Furthermore, preliminary results from another US study do not show any association; they also suggest studies of this nature generally encounter and must overcome a number of methodologic problems. The California authors also speculate that their findings may be due to thimerosal preservative in hepatitis B vaccines. This is somewhat curious as they would be at most, a very minor source of vaccine-associated mercury received by children.

On the basis of current evidence, the committee has concluded that the evidence does not support the initial finding of an alleged association between hepatitis B immunization and childhood leukaemia and does not recommend a change in current vaccination practices with hepatitis B vaccine.

Statement from the Global Advisory Committee on Vaccine Safety

The Global Advisory Committee on Vaccine Safety reassuring about suggested risk of childhood leukaemia following hepatitis B vaccination

An abstract (1) presented at the April 2002 meeting of the American Association for Cancer Research reported an association between hepatitis B vaccine and acute lymphocytic leukaemia in 334 children in northern California. The investigators suggested that thiomersal may play a role in the association as they found that the effect was more likely to occur with repeated dosing. The authors pointed out that the results should be interpreted with caution. The research suggested a link only between thiomersal in the hepatitis B vaccine and leukaemia. Other childhood vaccines containing thiomersal were not implicated.

Ethyl mercury, as thiomersal, is excreted rapidly from the body, mostly disappearing within 5-6 days. Such brief exposure to minute amounts of mercury is unlikely to be a sufficient carcinogenic stimulus to trigger childhood leukaemia. There is no other documented association between mercury and any human cancer, leukaemia, lymphoma or other malignant or pre-malignant disease. In animal studies cancer has only been associated with metal carcinogens involving continual or repeated exposure. Upon review of the evidence, the Global Advisory Committee on Vaccine Safety (GACVS) concluded that the suggestion of an association between

hepatitis B vaccination and acute lymphoblastic leukaemia, from one study and based on small numbers, was not convincing and should be regarded as tentative at best and weighed against the proven benefits of hepatitis B immunization. The committee had resolved at that time that the issue should be kept under review and further investigated.

Four studies (in France (two case-control studies), Germany, and New Zealand) were identified that have considered the effect of immunization (and specifically of hepatitis B vaccination) on childhood leukaemia. None has supported the suggestion that there may be an increased risk of leukaemia following hepatitis B vaccination or any other routine infant vaccination. Additional Preliminary results from additional research on this topic in the United States also do not show any association; they also suggest studies of this nature generally encounter and must overcome a number of methodologic problems relating to differences in completeness of hepatitis B vaccination history between cases and controls, The most important of these is to verify that apparently incomplete vaccine series especially among controls are indeed incomplete and not the result of incomplete record keeping or data collection. This problem is especially important to consider for studies which do not find differences in ever/never exposure to a particular vaccine but find differences either in completion of the vaccine series overall or by a certain age. Furthermore the California researcher's speculation that their findings might be due to thimerosal preservatives in hepatitis B vaccines is inconsistent with the fact that this vaccine represents only a very minor source of vaccine-associated mercury received by children in the U.S.

On the basis of current evidence, the committee has concluded that the evidence does not support the initial finding of an alleged association between hepatitis B immunization and childhood leukaemia and does not recommend a change in current vaccination practices with hepatitis B vaccine.

The GACVS will continue to review the evidence and any epidemiological data that might emerge from on-going studies. On the basis of current evidence, GACVS does not recommend a change in current vaccination practices with hepatitis B vaccine.

The GACVS is a scientific advisory body established by WHO to provide a reliable and independent scientific assessment of vaccine safety issues in order to respond promptly, efficiently and with scientific rigour to such issues. Membership includes experts from around the world in the fields of epidemiology, statistics, paediatrics, internal medicine, pharmacology and toxicology, infectious diseases, public health, immunology and autoimmunity, drug regulation, and safety.

1. Ma X, Does M, Buffler PA, Wiencke JK. Hepatitis B vaccination and the risk of childhood leukaemia. Poster session abstract 3801, American Association for Cancer Research annual meeting, San Francisco, April, 2002.

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> **Questions and answers**

Q: Is hepatitis B vaccination associated with a risk for leukaemia?

A: No.

Five studies have reviewed the risk of leukaemia following hepatitis B vaccination. The only suggestion of a potential association comes from the preliminary results from the Northern California Childhood Leukemia Study by Xiaomei Ma, Monique Does, Patricia A. Buffler, John K. Wiencke. The authors presented a poster at American Association for Cancer Research Annual Meeting, San Francisco, April 9, 2002. This study reports an epidemiological association between receipt of hepatitis B vaccine and childhood leukaemia in a group of 334 children in northern California. This is the first study to ever report such an association. In their presentation, the authors hypothesize that thimerosal, a mercury-containing preservative may be the cause of the association.

However, there is some evidence suggesting that hepatitis B vaccination does not cause childhood leukaemia. During the period 1991 to 1998, when the rate of hepatitis B vaccination in American 2-year-olds was climbing from zero to over 80%, there was no corresponding increase in childhood leukaemia. According to the National Cancer Institute, "Childhood leukemias appeared to increase in incidence in the early 1980s, with rate in the preceding years at fewer than 4 cases per 100,000. Rates in the succeeding years have shown no consistent upward or downward trend and have ranged from 3.8 to 4.8 cases per 100,000." National Cancer Institute Cancer Facts, February 12, 2002 http://cis.nci.nih.gov/fact/6_40.htm.

Four additional studies conducted in Germany, France (two studies) and New Zealand do not indicate any link between hepatitis B vaccination or vaccination with thimerosal-containing vaccines and leukaemia.

Preliminary results from another US study do not show an association; it also suggests such studies must overcome a number of methodologic problems relating to differences in completeness of immunization history for cases and controls

Q: Is hepatitis B disease or infection associated with leukaemia?

No such association has ever been reported.

Q: Is there evidence that mercury is associated with leukaemia?

A: No. Outbreaks of leukaemia have not followed accidental exposure to large amounts of mercury, such as in Minamata, Japan and in Iraq. These exposures included pregnant women. Occupational exposure to mercury also has not been associated with leukaemia. The association of thimerosal containing hepatitis B vaccine and leukaemia is not biologically plausible as cancers associated with metal carcinogens involve continual or repeated doses before cancer reveals itself and thimerosal contains ethyl mercury, a form of mercury that is excreted rapidly from the body. Furthermore, hepatitis B vaccine is a very minor source of vaccine-associated mercury received by children in the U.S.

Q: Is there further research being done on the risk of leukaemia

following hepatitis B vaccination?

The authors of the most recent study have planned to reanalyze their

data. Other US researchers with access to a large database are also studying this research question. In addition this issue is still being investigated in France in the context of a wider study of risks factors for childhood cancers including leukaemia. The study results will be expected by mid-2004.

Q: Should parents continue to get their children vaccinated against hepatitis B?

A: Yes. The risks of hepatitis B remain. The study from California does not change the current WHO recommendations as clearly stated by the Global Advisory Committee on Vaccine Safety.

In their presentation, the authors of the California study have said, "Given the importance of hepatitis B vaccine in preventing hepatoma [liver cancer], especially in high risk populations such as infants born to hepatitis B surface antigen positive mothers, the known risks of serious disease outweigh the suspected risks suggested by this study..."