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Letter to the Editor

Death following hexavalent vaccination

To the Editor,

Zinka et al. [1] have submitted a letter entitled "*unexplained cases of sudden infant death shortly after hexavalent vaccination*" the letter was accepted the day it was received, according to the policy of Vaccine not to review letters. However, unfortunately this letter could be viewed online as "article in press" suggesting that it is an article – but it was accepted as letter [12].

May I take the opportunity to comment on several serious flaws of this letter. Citations from the Zinka et al. paper are given in *italics.*

In the introduction, the authors state that *compared to their pentavalent predecessors, these hexavalent vaccines additionally contain hepatitis B serum.* A vaccine component must not contain a serum according to the European Pharmacopoeia vaccine definition. Although in Germany, the Yellow Press frequently uses the word "Impfserum" (vaccine serum) such a colloquial jargon should be avoided in a scientific journal. Obviously, the authors are not familiar with vaccines, since in the discussion they again use the misleading phrase "hexavalent sera". The hexavalent vaccines are described in the introduction to be *used for immunisation against diphtheria, pertussis, tetanus, influenza, poliomyelitis and hepatitis B*.

After more than 16 million doses distributed by the end of 2004 in Europe medical professionals should be aware that the hexavalent vaccines are not "influenza" component vaccines, but contain a conjugated polysaccharide antigen protecting against *Haemophilus influenzae* type b infections. Forensic doctors should be aware that there is a difference between a viral infection with influenza virus and a bacterial infection.

In addition the authors claim that *children are to be vaccinated with this vaccines at the age of 2, 4, 6 and 12–14 months*. The 2, 4 and 6 months schedule is only one of three possible ones, according to the summary of product characteristics (SPC) of these vaccines. But the last booster should not be given at 12–14 month according to the SPC of Infanrix-Hexa but at least 6 month after the 3rd shot but preferably before the 18th month, the SPC of Hexavac recommends a booster between months 12 and 18. So, not even the SPC of both vaccines are correctly cited.

In the section "case reports" no details are given about the fatalities. There is no table of age, weight, head circumference, organ weights etc. No information is given if and which vaccines have been given in addition to the hexavalent vaccine such as pneumococcal, MMR or varicella vaccines or others. There is even no information given how many doses of hexavalent vaccines the children received before they died. In such natural tragedies such as SIDS/SUDI, I strongly feel that it is the right of the children to have an autopsy according to a standardised protocol as for example published by a working group of the Royal College of Pathologist and Paediatrics and Child Health [2] and other bodies. However, there is no indication in the manuscript whether the children have been examined according to such a standard autopsy protocol.

Although according to a standardised protocol all organs should be systematically examined, the authors only describe an extraordinary brain edema and some abnormal neuropathological findings of the brain without giving details on whether this occurred in all children or whether this is just a summarised finding. Only some details of histological liver pathology are given. No information is given which (and if at all) virological tests (virus isolation, PCR etc.) have been performed. No information is given which (and if at all) microbiological tests have been performed.

It is claimed that *increased serum levels of mast cell tryptase and IgE* could be tested in three of the six cases, and that *mast-cell tryptase was slightly above normal in one*. It is highly questionable how the authors were able to find cell-tryptase "slightly above normal", when it is stated in the discussion that *there are no reference values available regarding mast cell-tryptase plasma concentrations* in this age group.

The paper states *three of this* (sic!) *six cases could be investigated concerning increased levels of mast cell tryptase and IgE* but in the next sentence it is claimed that *on the other hand IgE levels were normal*. So, it is completely unclear if IgE levels were increased or normal. Both statements are made in the laboratory testing section. However, in the discussion, it is again claimed once more that only cell-tryptase

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were increased (without having reference levels) and that IgE levels were normal. Although Zinka et al. refer to the publication of Buckley et al. [6], it is unclear whether the mast cell-tryptase activities the authors tested was α-tryptase or β-tryptase. Only β-tryptase (the form secreted on anaphylactic degranulation) seems to be increased in children with SIDS according to Buckley et al. [6].

From this contradictions, it can be concluded that the autopsy was of poor quality without quality assessment. According to [2] every child who dies deserves the right to have their sudden and unexplained death fully investigated in order to determine a cause of death and to exclude homicide. With the missing information about the autopsy protocol (if any protocol was observed) and the contradictory results the authors clearly violated the children rights stated in [2].

In the discussion, the authors write that *the neuropathological findings are unlikely to explain the death, since early postvaccinal encephalopathy is mostly associated with a congestive and edematous brain without relevant inflammatory infiltration. Post-vaccinal encephalopathies are mentioned especially in relation with pertussis* . . .. In this context, two references are provided. The first one is an article by Steinman et al. PNAS 1985;82:8733–6 (with a spelling error of the first author). However, this paper describes a mouse model for encephalopathy induced by pertussis immunisation. This encephalopathy was induced by purified pertussis toxin plus bovine serum albumin. A SIDS/SUDI case after immunisation with a purified pertussis toxoid can hardly be compared with a mouse model where immunisation was performed with heat-killed *B pertussis* containing pertussis toxin and coimmunisation with bovine serum albumin, a xenogenous protein. The second reference cited for pertussis-induced encephalopathy is an article by G. Buchwald, Med Welt 1971;43:1697–701. While this paper has the words "post-vaccinal encephalitis" and "encephalopathy" in the title, it describes brain damage after smallpox vaccination, i.e. a well known complication of this live vaccine (vaccinia). It is highly ill advised when discussing potential brain alterations after inactivated hexavalent acellular pertussis vaccination to refer to a paper on brain damage with live vaccinia vaccines.

In addition the author of this 1971 paper is the well known German anti-vaccine-movement protagonist Gerhard Buchwald who is infamous for statements like the following in 1991 [3]: *Otherwise the pertussis vaccination may be the most dangerous method of vaccination nowadays. It is performed predominantly with infants and the destruction process of the brain can already start some hours after vaccination, since it is a vaccination by injection with germs, which immediately spread in the body* (translated by WM).[1] It is clear that pertussis vaccine always was an inactivated vaccine which cannot spread in the body. In a typical anti-vaccine-book – published in 2004 – [7] in which the outrageous claim is made that rabies can be cured with homeopathic remedies, footbaths and enemas (!), Buchwald claimed that loss of intelligence leads to criminality and the reason for this is vaccination.

Why did the Zinka et al. neglect to discuss the literature that refutes a causative role for whole cell pertussis vaccine in encephalopathy? [4]. Why did they not mention the Canadian Impact study where no pertussis-vaccine attributable case was found following administration of >6.5 million doses of whole cell or acellular pertussis vaccine [5]?

In conclusion, I believe the letter of Zinka et al. is a very poor letter, the authors not being even familiar with their own data. The preprint of Zinka (uncorrected proof) has been presented on internet boards of the anti-vaccine movement. A German translation – translated by a well known activist in the anti-vaccine scene – is available since 1st June 2005 on http://www.impfo.ch/frame.html (go to news). There it is stated, that the letter is in press in Vaccine May 2005 (accepted 9th of March). And that the publication on the website of this vaccine critical group was kindly permitted by B. Zinka, the first author. All this happened before the paper was available on the Elsevier homepage. I had access to the Zinka paper on 30 May 2005 through a colleague who was alerted to the manuscript on an American vaccine discussion board.

Deaths do occur after vaccination and deserve thoroughly and appropriately investigated. The European Medicines Agency is aware of this very rare fatalities after hexavalent vaccination and on 21 April 2005, the CHMP concluded its review of one of two hexavalent vaccines that no regulatory action is necessary [9].

The Zinka letter will definitely not be a useful contribution to determine the causes of death which occurred in a short time frame after hexavalent vaccination of infants. Instead, this ill written paper is already being spread by the anti-vaccine movement and induces unfounded anxiety in young parents. Ultimately, this may lead to decreased vaccination rates and resurgence of vaccine preventable diseases, similar to what is currently happening in the United Kingdom as a consequence of the dissemination of the paper of Wakefield et al. claiming a – refuted – connection between MMR vaccination and autism [10] in the lay public.

Is there any evidence from the epidemiology of SIDS/SUDI that points to a problem with hexavalent vaccines? I have compiled the SIDS cases in Austria starting with the year of introduction of general vaccination with monovalent HIB vaccines in 1992/3, and covering the inclusion of HBV-vaccines in the childhood vaccination schedule in 1997 and the introduction of general vaccination with hexavalent vaccines in January 2001 (Fig. 1). One million doses of hexavalent vaccines (97% Hexavac, 3% Infanrix Hexa, [11]) have been distributed from 2001 until the end of 2004 in Austria corresponding to a vaccination coverage of 98% in 2004 (the Austrian annual birth cohort is 75,000–78,000). In 2000, the year before the introduction of hexavalent vaccines

[1] Original in German G. Buchwald [3]: Andererseits dürfte die Keuchhustenimpfung das gefährlichste der heute gebräuchlichsten Impfverfahren sein. Sie wird vorwiegend bei Kleinkindern durchgeführt, und hier kann der Zerstörungsprozess des Gehirnes bereits wenige Stunden nach der Impfung einsetzen, weil es sich um eine Spritzimpfung mit Erregern handelt, die sich sofort im Körper ausbreiten.

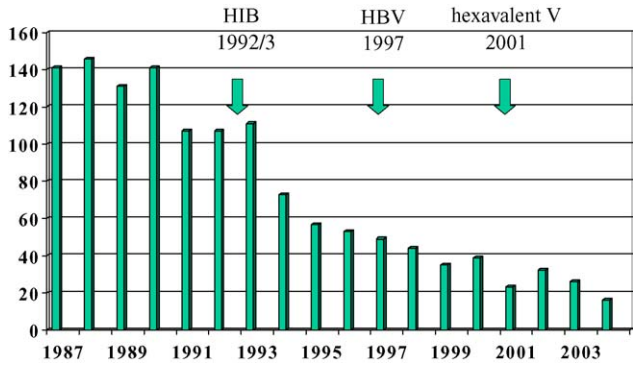

Fig. 1. SIDS cases in Austria and general vaccination with HIB, HBV and hexavalent vaccines in the vaccination schedule of the first 2 years of life.

39 SIDS cases were diagnosed. However, in 2001 when hexavalent vaccines were nearly exclusively used, only 23 SIDS cases were diagnosed. In 2004, only 16 cases were found—an all times low of SIDS cases [8]. In 2003 one child died of aspiration shortly after vaccination. Unfortunately also this case was autopsied below international standards. It is hard to conceive how hexavalent vaccines could play a causative role in SIDS/SUDI when cases have dropped by more than 50% since the universal usage of hexavalent vaccines at an all times high vaccine coverage.

Vaccines are of imminent importance in preventive medicine. Allegations regarding vaccine safety need to be well founded and based on carefully and thoroughly conducted investigations. Considering the substantial public impact and assumed credibility of letters published in peer reviewed journals, extraordinary care should be taken in writing a letter, knowing that a letter is not peer reviewed. The Zinka et al. manuscript was extremely poor regarding their own data and extremely poor in the discussion merging known adverse events of live vaccines with a mouse model of pertussis encephalopathy comparing this with the refuted hypothesis of pertussis vaccine encephalopathies. One can only hope that this poor letter will not contribute to a decrease of the highest vaccine coverage we ever had. However, the Zinka letter meanwhile was seeded among the anti-vaccine movement at least in US, Germany, Italy and Switzerland – in that case with kind permission of the author B. Zinka.

Finally I propose that also in the online version of Vaccine a letter should be visible as letter to avoid confusion. In addition I propose a retraction of the Zinka et al. letter by the authors.

Acknowledgement

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