

Post-marketing surveillance of immediate allergic reactions: polygeline-based versus polygeline-free pediatric TBE vaccine

Olaf Zent^{a,*}, Renald Hennig^b

^a Chiron Vaccines, Clinical Research and Medical Affairs, P.O. Box 1630, D-35006 Marburg, Germany

^b Chiron Vaccines, Pharmacovigilance, P.O. Box 1630, D-35006 Marburg, Germany

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Abstract

Scattered cases of immediate allergic reactions occurred in the nineties after widespread use of the original (polygeline-based) pediatric tick-borne encephalitis (TBE) vaccine and were reported to Pharmacovigilance, Chiron Vaccines. Although, still indicating a very rare frequency of about two cases per 100,000 doses sold, the benefit/risk assessment resulted in its withdrawal from the market in early 1998. An intensive evaluation revealed that polygeline used as a vaccine stabilizer was the most probable cause of the reported allergic reactions. Consequently, an improved pediatric TBE vaccine, free of polygeline and other protein-derived vaccine stabilizers, was developed. A post-marketing surveillance analysis covering the first two vaccination seasons after the introduction of this new pediatric TBE vaccine in early 2002 reveals a very low reporting rate of immediate allergic reactions post immunization (within the range as noted for other widely used vaccines for childhood immunization), i.e., 0.08–0.24 cases per 100,000 doses sold depending on case definition and medical assessment. In conclusion, this analysis provides post-marketing surveillance evidence that the change in the vaccine formulation, with regards to the potential risk of immediate allergic reactions, has led to an intended improvement in the vaccine's safety profile.

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1. Introduction

Prophylactic vaccination against tick-borne encephalitis (TBE) has proven to provide effective prevention against TBE disease including its serious complications, such as meningitis, meningoencephalomyelitis and encephalopathy [1]. Although this neurotropic virus infection has been known for more than 70 years, no curative treatment is available as yet. A prophylactic vaccination strategy has therefore been implemented in different TBE endemic countries for both children and adults for many years [1]. The first TBE vaccine specifically designed for children was licensed in 1994 in Germany. The introduction of this pediatric TBE vaccine followed results of dose finding studies, showing a dose dependent

reactogenicity in children [2]. Compared to the adult version, the pediatric vaccine contained half of the antigen dose administered to adults. After widespread use of this TBE vaccine, scattered cases of immediate allergic reactions in children were reported to Pharmacovigilance, Chiron Vaccines, especially in 1997. This resulted in an intensive evaluation of reported cases and a voluntary withdrawal of marketed vaccine batches in 1997 [3]. As a further result of this evaluation, the registration of this pediatric TBE vaccine was voluntarily withdrawn in early 1998 (prior to the start of the TBE vaccination season). Between 1998 and 2001, a new pediatric TBE vaccine formulation was developed excluding any proteinaceous stabilizers such as gelatin-based compounds (e.g., polygeline) or human serum albumin commonly used in former or present TBE vaccines. At the same time an improved vaccine version for adolescents and adults (also free of proteinaceous stabilizers) was developed. A large clinical program

* Corresponding author. Tel.: +49 642 139 4759; fax: +49 642 139 4667.
E-mail address: olaf.zent@chiron.com (O. Zent).

showed that the removal of proteinaceous stabilizers did not show any negative impact on the safety or immunogenicity of the vaccine [4,5]. The first marketing authorization for the new pediatric TBE vaccine was granted in late 2001; subsequently, it has been marketed in more than 15 countries.

To support conclusions from pre-clinical investigations and clinical studies, and to support the rationale that polygeline removal would significantly decrease the risk of immediate allergic reactions, particular attention was paid to the post-marketing surveillance evidence following widespread use of the new vaccine formulation. Hence, this paper compares post-marketing surveillance experience with regards to immediate allergic reactions of both the former and the new pediatric TBE vaccine formulations, particularly as these reactions were the reason for reformulating the vaccine. In this context, the relevant results leading to the withdrawal of the former pediatric TBE vaccine will also be provided.

2. Materials and methods

2.1. Evaluated vaccines

2.1.1. Encepur[®] K (1994–1998)

Aluminium adjuvanted TBE vaccine containing 0.75 µg formalin-inactivated TBE virus strain K23 in 0.5 ml (manufactured until 1997 by Chiron Behring GmbH & Co. KG; formerly Behringwerke AG, Marburg, Germany) [2]. Excipients in this formulation were 1.0 mg aluminium hydroxide, 4.08–4.96 mg polygeline, 0.35–0.42 mg potassium glutamate (Table 1).

2.1.2. Encepur[®] children (since 2001)

Aluminium adjuvanted TBE vaccine containing 0.75 µg of formalin-inactivated TBE virus strain K23 in 0.25 ml (manufactured since 2001 by Chiron Behring GmbH & Co. KG, Marburg, Germany) [4]. In addition, this formulation contains 0.5 mg aluminium hydroxide and 12.5 mg sucrose as excipients (Table 1).

2.2. Post-marketing surveillance analysis of suspected reports on immediate allergic reactions following TBE immunization in children

This report analyses suspected adverse drug reaction reports (ADRs) indicating immediate allergic reactions after administration of the former and the new pediatric TBE vaccine, received by Pharmacovigilance, Chiron Vaccines. To ensure a consistent reporting environment, this evaluation refers exclusively to cases spontaneously reported from the German market.

Analysis of suspected case reports of immediate allergic reactions was performed essentially similar to a previous analysis referring to a selected group of commonly used vaccines [6]: in short, spontaneously reported ADRs originated from the passive post-marketing surveillance system established in Germany. All reports on suspected ADRs were entered in the company's adverse event database using MedDRA (Medical Dictionary for Regulatory Activities) terminology for coding. All cases were documented regardless of causality—lay reports were only documented if they had been verified by a health care provider. In order to identify all case reports on suspected immediate allergic reactions, the database was queried for the following MedDRA codes: allergic reaction, anaphylactic reaction, anaphylactoid reaction, angioedema, bronchospasm, face edema, hypotension, larynx edema, maculopapular rash, pruritus, rash, shock, stridor, tongue edema and urticaria. The resulting case reports were then checked against the following case definition [6]:

An immediate allergic reaction was assumed if:

- the reported symptoms occurred within 24 h after vaccination;
- very probable alternatives had been excluded; and
- at least one of the following symptoms was reported: generalized urticaria, generalized exanthema, generalized itching, swelling of face or eyelid, glottis oedema, bronchospasm.

Every single report that fulfilled the criteria of the case definition of an immediate allergic reaction was checked with

Table 1
Composition of the former and new pediatric TBE vaccine

	Former pediatric TBE vaccine	New pediatric TBE vaccine
Antigen details		
TBE virus strain	K23	K23
Origin of production virus seed	PCEC	PCEC
Amount of antigen (µg)	0.75	0.75
Excipients		
Adjuvant	Aluminium hydroxide	Aluminium hydroxide
Preservative	None	None
Stabilizer	Polygeline (4.08–4.96 mg)	No additional
Sucrose	Not specified	12.5 ± 2.5 mg
Subjects		
Age limit	1–11 years	1–11 years

PCEC: primary chicken embryonic cells.

Table 2
Degrees of severity for classifying anaphylactic reactions, modified according to [21]

Severity grade	Skin reaction	Gastrointestinal system	Respiratory system	Cardiovascular system
I	Itching, urticaria, flush, centralization (cold, sweaty extremities)			
II	As above (not obligatory)	Nausea	Dyspnea	Tachycardia
III	As above (not obligatory)	Vomiting, defecation	Bronchospasm	Shock
IV	As above (not obligatory)	Vomiting, defecation	Cessation of breathing	Cessation of circulation

respect to gender, number of previous vaccinations, medical history of atopy/allergic disposition and divided into clinical degrees of severity (Table 2).

Based on clinical symptoms it is hardly possible to distinguish IgE-dependent immediate type allergic reactions from pseudo-allergic reactions. Therefore, the term immediate “allergic” reaction is used to describe both.

On the basis of the number of cases identified and the vaccine doses sold, an overall reporting rate of immediate allergic reactions can be calculated.

This analysis summarizes all case reports on suspected immediate allergic reactions following the administration of the former pediatric TBE vaccine from 1 January 1994 to 31 December 1997. In this context, detailed data is presented on those vaccinees that were subject to further investigations leading to the voluntary withdrawal of the vaccine in 1998. The analysis of the new pediatric TBE vaccine covers all notified case reports of immediate allergic reactions between 1 January 2002 and 31 December 2003.

2.3. Specific IgE testing for polygeline

In 1997, vaccinators were contacted and allergy tests suggested in those vaccinees with immediate allergic reactions after administration of the former pediatric TBE vaccine where serology still appeared to be reasonable (based on the time of the reported allergic reactions and conduct of allergy tests). As one of these tests, sera of the respective vaccinees were tested for presence of gelatin-specific IgE with an EAST at Allergopharma Joachim Ganzer KG, Reinbek, Germany. The test method was based on preparation of polygeline containing allergen discs according to a technique described elsewhere [7].

Furthermore, the suggested allergy tests included a screening for common allergens (e.g., acarian-mix, food-mix, inhalation-allergens etc.) in order to identify subjects with atopy/allergic disposition.

3. Results

3.1. Immediate allergic reactions leading to the withdrawal of Encepur® K

After having received scattered reports on suspected allergic reactions after administration of the former pediatric TBE vaccine, especially during the TBE vaccination campaign (mainly lasting from early spring to summer)

in 1997, Pharmacovigilance, Chiron Vaccines, initiated a thorough investigation. All case reports were documented and reported to the respective regulatory agencies. Based on the total number of vaccine doses sold, a reporting rate was calculated and checked against experience gained from other commonly used vaccines: Between 1994 and 1997 a total of 38 case reports on immediate allergic reactions that met the criteria of the case definition (see chapter Section 2) were registered in the post-marketing surveillance system. During this evaluation period, more than 1.8 million doses of the former pediatric TBE vaccine were sold in Germany. This corresponds to a reporting rate of approximately 2 case reports per 100,000 doses sold (95% confidence interval: 1.5–2.9 cases per 100,000 doses sold). This reporting rate still indicates a very rare frequency (according to the definition of the European Commission, Notice to Applicants; A Guideline on Summary of Product Characteristics, Dec 1999, page 10). Nonetheless, it was higher compared to experience with other commonly used vaccines indicating a background incidence of approximately 0.22 case reports of immediate allergic reactions per 100,000 vaccine doses (when referring to the same country and same methodology of analysis) [6]. Consequently, marketed vaccine batches were voluntarily withdrawn from national and international markets [3]. Contemporaneously, a more detailed analysis of individual case reports was performed: 20 of the 38 physicians/vaccinators who reported immediate allergic reactions following the administration of the former pediatric TBE vaccine were contacted for further diagnostics in the concerned vaccinees. Fourteen of these 20 vaccinators and the respective vaccinees volunteered to participate in this investigation (70%): blood samples from 14 subjects who experienced immediate allergic reactions were taken for allergy tests. An overview of these 14 subjects with respect to vaccination history, allergic disposition/atopy, and results of specific IgE testing for polygeline is given in Table 3.

Notably, four of these vaccinees (>30%) had experienced allergic symptoms after the first TBE immunization. A total of five of these vaccinees (36%) were tested positive in the other allergy tests performed (data not shown) and had an underlying allergic disposition/atopy. Twelve of these 14 vaccinees were found to be positive for polygeline specific IgE (EAST class > 1). One vaccinator also initiated allergic tests in an additional subject who experienced a febrile reaction following TBE immunization and who is not included in the analysis above (as no indication for allergic symptoms was given): polygeline-specific IgE testing was negative.

Table 3

Analysis of immediate allergic reactions after administration of the former and new pediatric TBE vaccine (see text for details)

	Former pediatric TBE vaccine (N = 14)	New pediatric TBE vaccine (N = 3) ^a
Sex		
Male	3/14	2/3
Female	11/14	1
Previous vaccination		
Unknown	1	–
>1	9/13	–
None (1. vaccination)	4/13	3/3
Allergic disposition/atopy	5/14	–
Severity grade		
I	3/14	3/3
II	8/14	–
III	3/14	–
IV	–	–

^a According to clinical assessment, only one of these three cases indicates a vaccine-related immediate allergic reaction (see text for details).

To summarize: the results from this post-marketing evaluation were used as the basis for the voluntary withdrawal of the marketing authorization for this vaccine in early 1998.

3.2. Immediate allergic reactions after vaccination with Encepur[®] children

During the evaluation period of the new pediatric TBE vaccine, three cases were reported that formally met the case definition of an immediate allergic reaction post immunization. One reported case refers to an almost 6-year-old boy, who experienced transient generalized rash (reported as “small spotted exanthema extending from legs to trunk”) 30–40 min after his first TBE vaccination. No other systemic symptoms or complications were noted. In two other cases, (11-year-old male patient presenting with fever and a “small follicular” exanthema one day post immunization, recovered; 18-month-old female presenting with fever, headache, irritability and subsequent “maculo-papular” rash one day post immunization, recovered) the clinical course possibly indicates different etiologies of the rash reported.

Based on more than 1.2 million vaccine doses sold in Germany during the vaccination seasons of 2002 and 2003, and taking all three cases into account, this corresponds to a respective reporting rate of about 0.24 per 100,000 vaccine doses sold (95% confidence interval: 0.1–0.7 per 100,000). However, if the two more questionable cases are excluded, the corresponding reporting rate is 0.08 per 100,000 doses sold (95% confidence interval: < 0.01 to 0.5 per 100,000).

4. Discussion

Prophylactic interventions like TBE vaccination must balance benefits (protection against TBE and its serious complications) against the risk of the intervention (such as adverse drug reactions). In order to improve tolerability of TBE vaccination in children, a specific pediatric TBE vaccine was developed in the early nineties. Clinical studies in children showed

a good tolerability using a pediatric dose [2]. However, the experience gained from widespread use of this vaccine indicated a potential risk for immediate allergic reactions: based on data from the German post-marketing surveillance system between 1994 and 1997, a respective reporting rate of around two cases per 100,000 vaccine doses sold was calculated. This reporting rate still indicates a very rare frequency, lower than assumed for therapeutic drugs [8] and other known prevention strategies, e.g., with commonly used antibiotics like penicillin [9]. However, it was noticeably higher than experience with other commonly used vaccines had shown: using a similar approach, an average reporting rate of 0.22 cases per 100,000 vaccine doses sold might be indicative for the overall risk of immediate allergic reactions post immunization [6].

Serological tests indicated that the gelatin-based vaccine stabilizer was the major cause of immediate allergic reactions after administration of the former pediatric TBE vaccine. A speculative explanation might particularly see the combination of polygeline and adjuvant (i.e., aluminium hydroxide) increasing the allergic potential of the gelatin-based stabilizer: polygeline is a polymer prepared by cross-linking polypeptides derived by denatured gelatin with a di-isocyanate to form urea bridges [10]. The original decision to use polygeline as a stabilizer was the consequence of the general discussion concerning theoretical risks of plasma derived products (i.e., human serum albumin). Other gelatin-based compounds have been used in various vaccines (e.g., MMR, Yellow fever, Varicella, DTaP) [11–15]. An increased risk for immediate allergic reactions leading to vaccine reformulation was, to our knowledge, only noted after the widespread use of the gelatin-based DTaP and live virus vaccines in Japan [15]: following a change in the childhood immunization schedule in Japan, an increased number of children experienced allergic/anaphylactic reactions to the live measles vaccines in the nineties. Laboratory tests for gelatin-specific IgG antibodies, led to the hypotheses that these reactions occurred as a consequence of a sensitization against gelatin following the common use of the DTaP vaccines [15]. Comparing vaccine compositions of the former pediatric TBE vaccine and

gelatin-based DTaP vaccines in Japan, the major consistency is a combination of aluminium hydroxide and gelatin compounds, the adjuvant aluminium hydroxide not being present in the other vaccines mentioned above. Similar to the experience from the gelatin-based DTaP vaccines in Japan [16], we found gelatin-specific antibodies in a high number of vaccinees with immediate allergic reactions (i.e., 12 of the 14 subjects who received the former pediatric TBE vaccine). This rate appears to be considerably higher compared to test results from respective vaccinees from both Finland and the United States who were administered measles, mumps and rubella vaccines and where the similar statistic was 28 and 27% [17,18].

Notably, varying amounts of gelatin were contained in the widely used DTaP and live virus vaccines; however, most of the reported cases of anaphylaxis were related to vaccines containing a large quantity of gelatin as was the case with the former (polygeline-based) pediatric TBE vaccine.

It is of particular interest that an increased reporting rate of immediate allergic reactions was only noted after administration of the former pediatric TBE vaccine in children, but not in adults receiving the adult vaccine formulation. Not only was the antigen dose different, but also the two vaccine formulations differed in their antigen-polygeline-aluminium hydroxide ratio.

Finally, it should be mentioned that a high percentage of vaccinees presenting with immediate allergic reactions (>30%) reacted after the very first administration of the former pediatric TBE vaccine, indicating a pre-sensitization against gelatin, possibly alimentary.

Based on a benefit/risk assessment, it was decided to recall this vaccine from the market voluntarily. The data presented led Chiron Vaccines in 1998 to change the vaccine stabilizer: one possible alternative, human serum albumin, was excluded from the further development as WHO recommended to establish human serum albumin free TBE vaccines [19]. Intensive research efforts led to sucrose as an alternative.

Clinical studies in more than 3500 children demonstrated a good tolerability of the new pediatric TBE vaccine [4]. However, even in view of this large number of study participants, the (remaining) risk of vaccine-related allergic reactions was not evaluable in a clinical program when taken into account their low background incidence in general. Therefore, particular attention was paid to experience gained from post-marketing surveillance.

Following the introduction of the new pediatric TBE vaccine in 2001, only one clinically suspected case of vaccine-related immediate allergic reactions (characterized by a mild clinical course) and two cases with “allergic” symptoms indicating however a different origin, have been noted so far, resulting in a reporting rate of 0.08–0.24 per 100,000 doses sold. Therefore, the remaining risk of immediate allergic reactions after introduction of the new pediatric TBE vaccine can be regarded as very low and within the range as noted for other widely used vaccines [6], particularly for those used for childhood immunization [20]. Whilst considering the lim-

itations of a passive surveillance system for assessment of safety risks, this analysis uses similar methods of evaluation as a previous analysis [6], thus leading to comparable data. Furthermore, there might even be a higher validity of data presented, as following the withdrawal of Encepur® K an increased awareness for the potential risk of immediate allergic reactions after TBE vaccination might be assumed: Immediately prior to the introduction of the new pediatric TBE vaccine in 2001, only the adult vaccine version was marketed in Germany (until replacement by the improved adult vaccine formulation). Due to the perceived risk of polygeline-related allergic reactions in general, the use of the adult vaccine version was only permitted under safety restrictions including a prolonged observation period of approximately 1 h post immunization and exclusion of subjects with a history of allergies or atopy.

The removal of polygeline can be regarded as the most relevant change compared to the previous vaccine formulation. Other vaccine compounds (e.g., traces of antibiotics originating from the manufacturing process) theoretically still remain as possible causative agents for (very rare) immediate allergic reactions post immunization. Alternatively, a pseudo-allergic origin of the otherwise not distinguishable clinical course has to be considered. This assumption is supported by the fact that the three case reports for the new formulation all refer to first immunizations, which otherwise require a pre-sensitization against vaccine compounds.

To conclude: this analysis provides post-marketing surveillance evidence that the change in the vaccine formulation has led to a substantial improvement in the vaccine's safety profile regarding the potential risk of immediate allergic reactions.

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