RESEARCH PAPER

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Immunogenicity and safety of purified chick-embryo cell rabies vaccine under Zagreb 2-1-1 or 5-dose Essen regimen in Chinese children 6 to 17 years old and adults over 50 years: A randomized open-label study

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Keywords: Essen regimen, immunogenicity, intramuscular post-exposure prophylaxis; purified chick-embryo cell rabies vaccine, rabies, rabies virus neutralizing antibody, Zagreb regimen

Abbreviations: AE, adverse event; CI, confidence interval; GMC, geometric mean concentration; IM, intramuscular; NIFDC, National Institutes for Food and Drug Control; PCECV, purified chick-embryo cell rabies vaccine; PEP, post-exposure prophylaxis; PPS, per-protocol set; RFFIT, Rapid Fluorescent Focus Inhibition Test; RVNA, rabies virus neutralizing antibody

The aim of this Phase IIIb, open-label, randomized study was to demonstrate the non-inferiority of immune responses and to assess the safety of a purified chick-embryo cell rabies vaccine (PCECV) in healthy Chinese children (6 to 17 years) and older adults (≥51 years) following 2 alternative intramuscular (IM) simulated post-exposure prophylaxis (PEP) regimens: 4-dose Zagreb or 5-dose Essen regimen. Serum samples were collected prior to vaccination on Days 1 and 15 and on day 43 to assess immune response by rabies virus neutralizing antibody (RVNA) concentrations. Solicited adverse events (AEs) were recorded for up to 7 days following each vaccine dose, and unsolicited AEs throughout the entire study period. PCECV vaccination induced a strong immune response at Day 15, and the non-inferiority in immune response of the Zagreb vs. the Essen regimen was demonstrated in children and older adults. At Day 15,100% of children (N = 224), and 99% of subjects ≥51 years of age (N = 376) developed adequate RVNA concentrations (≥0.5 IU/mL); at Day 43 all subjects achieved RVNA concentrations ≥0.5 IU/mL, for both PEP regimens. The well-known tolerability and safety profile of the PCECV was again observed in this study following either Zagreb or Essen regimens. Rabies PEP vaccination with PCECV following a Zagreb regimen induced immune responses non-inferior to those of the Essen regimen, and had a similar safety and tolerability profile to the Essen regimen in Chinese children, adolescents, and adults over 51 years. ClinicalTrials.gov identifier: NCT01680016.

Introduction

Rabies is a zoonotic disease caused by a lyssavirus infection, which is endemic in more than 150 countries and territories worldwide, and is conservatively estimated to cause 60,000 deaths every year.[1] More human deaths due to rabies are reported annually (about 30,000, half of the global estimate) in Asia than in other continents, and one of the most important rabies enzootic areas is found in China, where in 2012 rabies was the second leading cause of death due to infectious diseases.[1-3] Three major epidemics were reported between 1950 and 2007, the last one in 2000 after a rapid increase in the pet dog population in urban areas.[4] Although declining in recent years, more than 1,400 human deaths were reported in China in the year 2012.[3-7]

Following an incubation period of approximately 1–3 months after virus inoculation, the virus travels to the central nervous system, and causes an acute progressive encephalomyelitis followed by coma and death within 1–2 weeks in almost 100% of cases.[8] Although after the onset of clinical symptoms there is no known cure for rabies, timely prophylaxis by vaccination can avert the development of the disease even after exposure to the virus. In the event of suspected or confirmed contact with a rabid animal, the WHO recommends immediate post-exposure prophylaxis (PEP) based on thorough local wound cleaning, timely active vaccination with cell culture or embryonated egg-based rabies

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vaccines, and simultaneous passive immunization with rabies immune globulin, depending on the category of exposure.[1]

The WHO recommendation for PEP vaccination via IM injection in healthy, fully immune competent subjects following exposure to rabies is 2 different regimens: 5 doses of the vaccine given at 5 separate visits (Essen regimen; 1-1-1-1-1), namely on Days 0, 3, 7,14, and 28; or a 4-dose regimen (Zagreb regimen; 2-1-1) consisting of 2 doses given on Day 0 (1 dose in the right arm, and 1 dose in the left arm), and 1 dose given on each of Days 7 and 21. The Zagreb regimen, relative to Essen regimen, has been shown to induce earlier protective titers, to reduce healthcare costs, and to have a potential favorable impact on vaccination compliance, as it involves a reduced number of visits and vaccine doses.[9-11]

Clinical trials conducted with purified chick-embryo cell vaccines (PCECV) have consistently reported that protective virus-neutralizing antibodies (RVNA) are usually induced by Day 14 following first vaccine dose, and the immunogenicity/efficacy and safety profiles of the vaccine have been well established in children and adults in previously simulated PEP studies involving healthy subjects or post exposure studies in subjects exposed to suspected or confirmed rabid animals.[12-19] Moreover, a study assessing the anamnestic response following a single booster dose administered 2 years after a primary 3-dose immunization with PCECV indicated that it was potentially able to elicit long-lasting immune responses even after 14 years.[20]

In China, where 12–15 million doses of rabies vaccine are estimated to be administered annually,[7,21,22] the traditional 5-dose Essen regimen recommended by the WHO has been widely adopted since years,[23] while the Zagreb regimen has been only recently approved for PCECV preparations. A previous clinical trial conducted in healthy adult Chinese subjects aged 18–50 years indicated that immunization following the Zagreb regimen with PCECV was non-inferior to that following the Essen regimen, and had an acceptable and similar if not more favorable safety profile.[23]

Although all age groups are susceptible to rabies, there is a need to specifically study children and elderly populations. Children are at higher risk of rabies exposure than adults for several reasons, including the increased likelihood of receiving extensive bites to the face and head, which is associated with a higher possibility of contracting rabies, their curiosity and attraction toward animals, and their lack of awareness of the potential dangers.[1,24] Indeed, the highest incidence of rabies across all developing countries is observed in children aged <15 years, with 60% of cases occurring between 0 and 12 years of age.[24,25] It is also well documented that older subjects above 65–70 years of age have a decrease in the quality and quantity of immune responses because of immunosenescence that leads to decreased efficacy of vaccines.[26-28]

In the present study of simulated PEP, the primary objective was to determine the non-inferiority of immune response induced by PCECV (Rabipur®, Chiron Behring Vaccines Pvt. Ltd., Ankleshwar, India) following the Zagreb regimen compared to the 5-dose Essen regimen by measuring RVNA geometric mean concentrations (GMC) at 14 days after the first vaccine dose in 2 age cohorts: healthy children and adolescents (6 to 17 years) and older adults (≥51 years).

Materials and Methods

Study design and objectives

This was a Phase IIIb, open label, age-stratified, randomized study conducted between September 2012 and January 2013 at the Center for Disease Control and Prevention of Mengshan, Guangxi province, China (ClinicalTrials.gov identifier: NCT01680016). The protocol was approved by the appropriate Independent Ethics Review Committee, and was conducted in accordance with the principles of the Declaration of Helsinki, Good Clinical Practice guidelines and local regulations. All participant subjects or the subject's parents/legal guardian, as applicable, provided written informed consent before enrollment.

As per Novartis convention and the Clinical Data Interchange Standards Consortium (CDISC), the day of first vaccination in this study was study Day 1. WHO and ACIP consider the first day of vaccination (treatment) as Day 0.[1,29] Ensuring vaccination days are shifted accordingly, study Days 1, 4, 8, 15 and 29 in this clinical trial were equivalent to vaccination Days 0, 3, 7, 14 and 28 of WHO and ACIP recommendations.

The primary objectives of the study were to establish non-inferiority of immune response after simulated PEP with PCECV (Rabipur®, Chiron Behring Vaccines Pvt. Ltd., Ankleshwar India) following the 2-1-1 Zagreb regimen to 1-1-1-1-1 Essen regimen in healthy children 6–17 years of age and in older adults ≥51 years of age by means of the GMC of RVNA at Day 15. Moreover, the study evaluated the percentage of subjects with RVNA concentrations ≥0.5 IU/mL at Days 15 and 43 following the first vaccine dose (Day 1). The total study participation for the subjects was 43 days. Secondary objectives included the assessment of antibody response by means of GMC at Day 43, the percentage of subjects with RVNA levels ≥0.5 IU/mL (defined as adequate to confer protection from rabies virus infection)[30] at Day 15 and Day 43, and also the safety and tolerability of the vaccine according to each regimen, in both age cohorts.

Subjects

The study planned to enroll a total of 640 healthy Chinese volunteers: 240 children aged 6 to 17 years, further divided into 2 age subsets of children: ≥6 to ≤11 years and ≥12 to ≤17 years of age, and 400 older adults aged ≥51, further divided into 2 age subsets of adults: ≥51 to ≤60 years and ≥61 years of age. Subjects within each age subset were randomized in a 1:1 ratio to receive 4 vaccine doses following the Zagreb regimen or 5 doses following the Essen regimen.

Both age cohorts had not been studied previously with PCECV in the Chinese population. The sample sizes estimation and the noninferiority margin used for this clinical trial were derived from the study design and the data obtained in a previous study with PCECV in adult Chinese subjects[23]. In the previous study, a standard deviation of 2 in log2 scale was observed in the Essen group. Same standard deviation (2 in log2 scale) was used

in estimating the sample size for the children cohort and a higher value (2.59 in log2 scale) was assumed for the older adult cohort. With these standard deviations and a 2-sided Type I error of 5%, 105 evaluable subjects in the children cohort, and 176 in the older adults cohort per regimen were needed to assess each of the primary non-inferiority objectives at a 95% power using a 0.5 fold non-inferiority criterion in ratio of GMCs between Zagreb and Essen regimens. The planned enrollment accounted for an approximately 10–15% drop-out rate.

Enrolled subjects were of both genders, and in good health at study entry as judged by the clinical investigator through medical history and physical examination. Main exclusion criteria were allergy to any of the vaccine components; having previously received any rabies vaccine or rabies immune globulin; and receiving or planning to receive antimalarial medications 14 days prior to first vaccination through to study termination; any progressive or severe neurologic disorder, seizure disorder or Guillian-Barré syndrome; known or suspected impairment of the immune system; known bleeding diathesis or any condition that might be associated with a prolonged bleeding time. An additional specific exclusion criterion for subjects 6 to 17 years was to ever have had a malignancy; for adults aged ≥51 years, to have had a malignancy (excluding nonmelanotic skin cancer) or lymphoproliferative disorder within the past 5 years.

PEP Vaccination regimens

After a dose reconstitution, 1 mL of the rabies PCECV (Rabipur®, Chiron Behring Vaccines Pvt. Ltd. manufactured in Ankleshwar, India; Lot number 1980) containing inactivated rabies virus (Flury Low-Egg Passage [LEP] strain), with a potency ≥2.5 IU/mL, was administered intramuscularly to the deltoid muscle based on the regimen assigned after randomization: 2 doses on Day 1, and one dose on each of Days 8 and 22 for subjects in the Zagreb regimen, and one dose on each of Days 1, 4, 8, 15, and 29 for subjects in the Essen regimen.

Immunogenicity assessment

Blood samples (approximately 5 mL) for immunogenicity testing were obtained from subjects prior to vaccination (Day 1 and Day 15), and at Day 43 (−2/+3 days). Blood draw at day 7 for immunogenicity testing was not included in the study design because it was considered not adding additional information; results from a previous clinical registration trial in Chinese adults[23] showed in fact no more than 10% of subject with RVNA concentrations ≥0.5 IU/mL after only 2 vaccine doses (day 7). RVNA concentration levels were determined by means of a Rapid Fluorescent Focus Inhibition Test (RFFIT),[31] with rabies virus strain CVS-11 as the challenge virus for the assay, carried out at the National Institutes for Food and Drug Control (NIFDC) laboratory in China.

Safety assessment

The occurrence of immediate adverse reactions was monitored for 30 minutes after each vaccination at the site; the frequency and severity of all solicited adverse events (AEs) were recorded for up to 7 days following each vaccination; unsolicited AEs were recorded throughout the study up to Day 43. Solicited local AEs were erythema, induration, and pain at the site of injection; solicited systemic AEs included loss of appetite, nausea, headache, myalgia, fatigue, arthralgia; other indicators of vaccine reactogenicity were fever (defined as an axillary temperature ≥38°C) and use of analgesics/antipyretics. The relationship of the study treatment to an AE was to be determined by the investigator, who also determined the severity and the seriousness of unsolicited AEs.

Statistical analysis

Descriptive demographic statistics at enrollment were summarized by PEP regimen. For the immunogenicity objectives, the per-protocol set (PPS) was used as the primary analysis set, and defined to include subjects who correctly received the vaccine according to the regimen that they were randomized to, who provided an evaluable serum sample at Day 15 or Day 43 and who had no major protocol deviations.

GMCs of RVNA and associated 2-sided 95% CIs were calculated by exponentiating the least square means and the lower and upper limits of the 95% CIs of the log transformed titers for each PEP regimen. The ratio of GMCs for each age cohort at day 15 between the Zagreb and Essen PEP regimens was computed by a 2-way Analysis of Variance (ANOVA) adjusting for factors of regimen and age subset.

Non-inferiority of the Zagreb regimen to the Essen regimen was demonstrated if the lower limit of the 2-sided 95% CI for the ratio of GMCs between regimens was >0.5. Moreover, for each age cohort the percentage of subjects with RVNA concentrations ≥0.5 IU/mL and the associated 2-sided 95% Clopper-Pearson CIs was computed by PEP regimen at all applicable visits. Safety was analyzed for all subjects exposed to PCECV who provided post-vaccination safety data, and was summarized by regimen, providing the frequency and proportion of subjects reporting an event. All statistical analyses were conducted at the Biostatistics and Clinical Data Management (BCDM) group of Novartis Vaccines using SAS software version 9.2.

Results

A total of 243 children aged 6 to 17 years were enrolled; 121 of them were assigned to the Zagreb regimen, and 122 to the Essen regimen; 115 (95%) and 114 (93%) of subjects completed the study on Day 43, respectively (**Fig. 1**). A total of 401 subjects ≥51 years were enrolled; 201 were assigned to the Zagreb regimen, and 200 to the Essen regimen; 196 (98%) and 195 (98%) subjects completed the study on Day 43, respectively (**Fig. 1**).

Except for sex, the demographics and other baseline characteristics of subjects in both age cohorts were balanced across the 2 vaccine regimens (**Table 1**). The overall mean age in the 6 to 17 cohort was 10.9 ± 3 years; in the ≥51 age cohort, the overall mean age was 62.0 ± 6.6 years. In both age cohorts, overall the majority of subjects was female (51% in the 6 to 17 years, and 60% in the ≥51 cohort), and in the Zagreb regimen the proportion of enrolled females was lower than in the Essen regimen for both age cohorts (40%

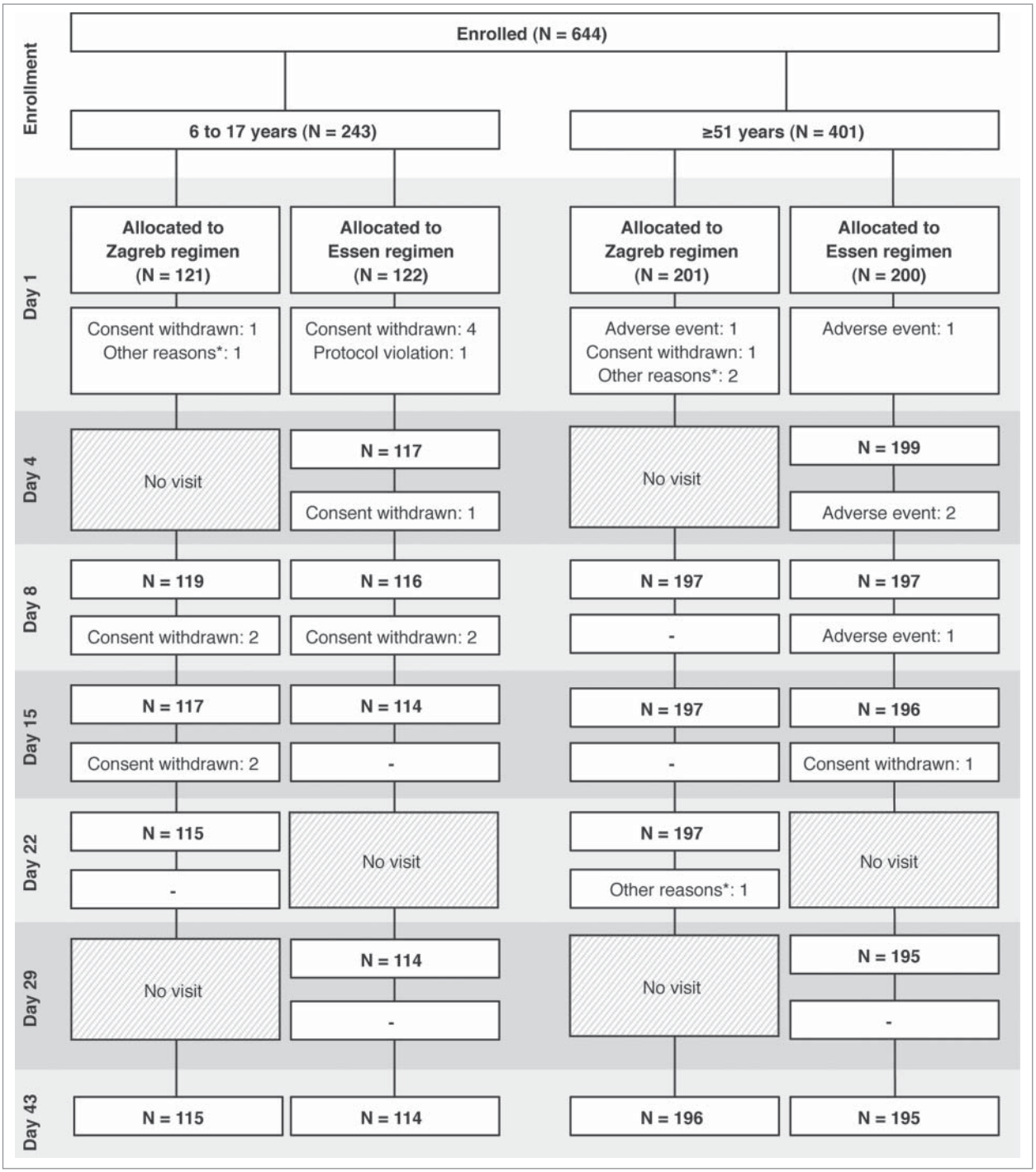

Figure 1. Flow diagram of the trial. *Other reasons included that the subject went out (2 subjects at Day 1, both in the Zagreb regimen, 1 in the 6 to 17 years cohort, the other in the ≥51 years cohort); screening failure (1 subject at Day 1, in the Zagreb regimen, and in the ≥51 years cohort); and withdrawal of consent for continuing study participation (1 subject at Day 22 in the Zagreb regimen, and in the ≥51 years cohort).

vs. 62% in the 6 to 17 years cohort, and 59% vs. 62% in the ≥51 cohort).

Immunogenicity

At Day 15 there was an increase in GMCs from baseline following both PEP regimens in children aged 6 to 17 years (12 and 14 IU/mL in Zagreb and Essen regimen, respectively) (**Fig. 2**). The ratio of GMCs between the Zagreb and Essen regimens (GMR) was 0.84 (95% CI: 0.69 −1.02), therefore meeting the non-inferiority criterion of the Zagreb to the Essen regimen (lower limit of the 95% CI GMR >0.5). At Day 43, GMCs were similar to those observed at Day 15 in the 4-dose Zagreb regimen

Table 1. Summary of demographic characteristics of subjects enrolled in the study, by age cohort

	Children 6 to 17 years (N = 243)		Adults ≥51 years (N = 401)	
Characteristic	**Zagreb regimen (N = 121)**	**Essen regimen (N = 122)**	**Zagreb regimen (N = 201)**	**Essen regimen (N = 200)**
Age, mean (SD), years	11.0 (3.0)	10.8 (2.9)	62.1 (6.5)	61.9 (6.8)
Gender, n (%)				
Male	72 (60)	46 (38)	83 (41)	77 (39)
Female	49 (40)	76 (62)	118 (59)	123 (62)
Weight, mean (SD), kg	33.59 (11.57)	32.85 (10.95)	52.93 (9.36)	52.57 (8.53)
Height, mean (SD), cm	139.1 (16.1)	137.9 (16)	153.5 (7.3)	153.2 (8.1)

(13.0 IU/mL), while, as expected, there was a further increase following a 5-dose Essen regimen (24 IU/mL).

In older adults ≥51 years there was also a robust increase in GMCs from baseline, which at Day 15 reached a mean of 8.57 IU/mL for the Zagreb regimen, and 7.89 IU/mL in the Essen regimen (**Fig. 2**). The GMR Zagreb/Essen was 1.1 (95% CI: 0.87 −1.35), also demonstrating non-inferiority of the Zagreb to the Essen regimen in this age cohort. At Day 43, GMCs had increased from Day 15, with a similar trend between groups: 12 IU/mL and 13 IU/mL for the Zagreb and Essen regimen, respectively.

All children achieved RVNA concentrations ≥0.5 IU/mL at Day 15 and at Day 43 (**Fig. 3**) following both PEP regimens. In older adults, the percentage of subjects with adequate antibody concentrations was 99% at Day 15, and 100% at Day 43, irrespectively of the PEP regimen (**Fig. 3**).

The analysis by age subset (children [6 to 11 years], adolescents [12 to 17 years], adults aged 51 to 60 years and ≥61 years) showed comparable results for all immunogenicity outcome variables as the overall cohorts of children or older adults.

Safety

Overall, 52% and 51% of the children aged 6 to 17 years reported solicited AEs after any vaccine dose following the Zagreb and Essen regimens, respectively. In older adults aged ≥51 years, the overall percentage of subjects reporting solicited AEs after any vaccination was 19% in the Zagreb regimen and 24% in the Essen regimen. After any vaccination, pain at the injection site was the most frequently reported solicited local AE, in both age cohorts (**Table 2**). Injection site pain was in fact observed in 38% and 40% of subjects 6 to 17 years in the Zagreb and Essen regimen, respectively, and in 9% and 11% of older adults, respectively. The most commonly observed systemic AE was fatigue in both age cohorts, reported in 15% and 13% of subjects of 6 to 17 years in the Zagreb and Essen regimens, respectively, and in 5% of the Zagreb and 4% of the Essen regimen in the older adults. Most of the solicited local and systemic AEs were mild to moderate in intensity.

The incidence of unsolicited AEs in children was 21% in the Zagreb regimen and 24% in the Essen regimen, and only 7% and 5% of the cases, respectively, were reported as at least possibly related to the vaccination. In older adults, 18% in the Zagreb regimen and 20% in the Essen regimen reported unsolicited AEs; 3% and 8% of them, respectively, were considered at least possibly related to the study vaccine. In both age cohorts, and regardless of the PEP regimen followed, the most commonly reported unsolicited AE (≥2% subjects) was upper respiratory tract infection. No SAEs were reported in the children's cohort, and none of the subjects withdrew prematurely due to an AE. In adults ≥51 years, 1 subject experienced a SAE, which was judged as not vaccine-related (a case of moderate acute pancreatitis in a 72 years old female with onset 40 day after first vaccine dose; the subject had significant medical history of gall stones; the subject

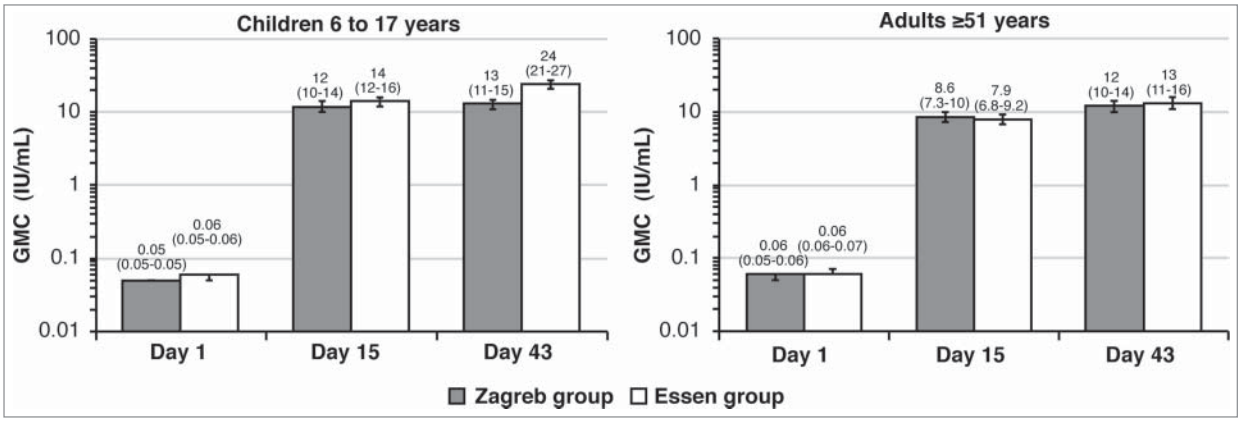

Figure 2. Rabies virus neutralizing antibody concentrations (GMC) in the Zagreb and Essen regimens (PP set) on Days 1, 15, and 43, by age cohort. Error bars and values in parenthesis represent 95% CI.

Table 2. Percentage of subjects with any and severe solicited local and systemic AEs, and other indicators of reactogenicity, from 6 hours to 7 days following any vaccination

	Children 6 to 17 years		Adults ≥51 years	
	Zagreb regimen (N = 119)	**Essen regimen (N = 118)**	**Zagreb regimen (N = 197)**	**Essen regimen (N = 200)**
Local AEs, n (%)				
Erythema				
Any	2 (2)	1 (1)	1 (1)	3 (2)
Severe (>100 mm)	0 (0)	0 (0)	0 (0)	0 (0)
Induration				
Any	2 (2)	0 (0)	1 (1)	1 (1)
Severe (>100 mm)	0 (0)	0 (0)	0 (0)	0 (0)
Injection site pain				
Any	45 (38)	47 (40)	18 (9)	22 (11)
Severe	0 (0)	0 (0)	0 (0)	0 (0)
Systemic AEs, n (%)				
Loss of appetite				
Any	14 (12)	10 (8)	0 (0)	2 (1)
Severe	0 (0)	0 (0)	0 (0)	0 (0)
Nausea				
Any	7 (6)	10 (8)	2 (1)	2 (1)
Severe	1 (1)	0 (0)	0 (0)	0 (0)
Headache				
Any	11 (9)	10 (8)	7 (4)	8 (4)
Severe	0 (0)	0 (0)	0 (0)	0 (0)
Myalgia				
Any	11 (9)	13 (11)	0 (0)	2 (1)
Severe	0 (0)	0 (0)	0 (0)	0 (0)
Fatigue				
Any	18 (15)	15 (13)	9 (5)	7 (4)
Severe	1 (1)	0 (0)	0 (0)	0 (0)
Arthralgia				
Any	3 (3)	1 (1)	3 (2)	3 (2)
Severe	0 (0)	0 (0)	0 (0)	0 (0)
Fever (≥38°C)				
Yes	8 (7)	3 (3)	5 (3)	5 (3)
No	111 (93)	115 (97)	192 (97)	195 (98)
Other				
Use of analgesics/antipyretics	N = 119	N = 118	N = 197	N = 200
Yes	11 (9)	8 (7)	13 (7)	15 (8)
No	108 (91)	110 (93)	184 (93)	185 (93)
Body temperature ≥ 37.1°C	N = 30	N = 25	N = 13	N = 19
Low (37.1°C–37.5°C)	17 (57)	18 (72)	6 (46)	11 (58)
Medium (37.6°C–39°C)	13 (43)	7 (28)	6 (46)	8 (42)
(High >39°C)	0 (0)	0 (0)	1 (8)	0 (0)

was discharged from the hospital after 15 days, with complete resolution of the AE), and 5 subjects were prematurely withdrawn due to AEs: 1 in the Zagreb regimen (due to myocardial ischemia), and 4 in the Essen regimen (1 subject had mild tachycardia, 1 subject had mild headache, pain and pyrexia; 1 subject experienced moderate back pain, and 1 subject had moderate fatigue and headache persisting more than 7 days after vaccination). No deaths were reported during the study.

Discussion

IM rabies vaccination, after exposure to the virus (PEP) and when administered in a timely manner, is the only effective treatment and life-saving intervention to prevent the disease. The 5-dose PEP Essen regimen gives reliable post-exposure immunization, and has been widely used in developed and developing countries for several decades. In 1992, the WHO started to recommend the abbreviated 2-1-1 Zagreb vaccine regimen in order to reduce costs and offer a more simple and economical vaccination course with acceptable safety, immunogenicity and efficacy profiles.[32] Since 2010, the Zagreb regimen is recommended over the 5-dose Essen regimen by the Advisory Committee of Immunization Practices, as well as a reduced 4-dose Essen regimen (each dose on days 0, 3, 7, and 14) for healthy immunocompetent adults.[10]

In this study, PEP with PCECV via IM route elicited a strong immune response at Day 15 when administered under either the

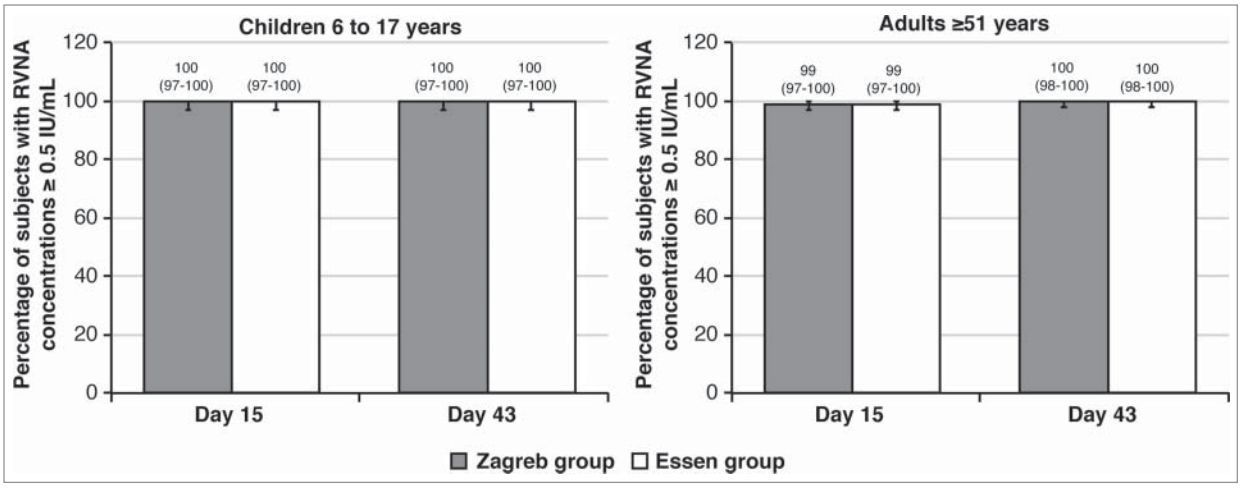

Figure 3. Percentage of subjects with RVNA concentrations ≥0.5 IU/mL in the Zagreb and Essen regimens (PP set) on Days 15, and 43, by age cohort. Error bars and values in parenthesis represent 95% CI.

Zagreb or Essen regimen, and immune responses following Zagreb regimen were found to be non-inferior to those induced by 5-dose Essen regimen in all age cohorts.

All subjects at the end of the study, in both PEP regimens and in both age cohorts achieved RVNA concentrations ≥0.5 IU/mL. These results are in agreement with previous results obtained with healthy adult subjects (18 to 50 years) vaccinated under the Zagreb PEP regimen with PCECV or other licensed vaccines.[9,11,19,23] As expected, RVNA concentrations resulted higher in the children than in older adults, especially after the fifth dose of vaccine received following Essen regimen.

The results suggested a lower overall rate of AEs after the first vaccination among subjects ≥51 years compared to the children and adolescents. However, there were no significant differences in the frequency and nature of reported AEs between either post-exposure regimens in any of the age cohorts. The incidence of AEs resulting in premature withdrawal from the study was low and was observed at a similar frequency for both regimens.

In China, 90% of human rabies cases occur in rural areas,[5,33] and besides difficult or delayed access to public health services, the lack of proper or complete PEP is one of the major causes of treatment failure.[2,6] Indeed, recent epidemiological data indicate that among subjects who sought medical advice and received PEP, only 77% to 78% were actually compliant with the full vaccination course for contact categories requiring vaccination, and the study noted that compliance dropped significantly after the third dose.[34] Therefore, it is foreseeable that beyond strict adherence to standard WHO and ACIP recommendations, compliance with the full vaccine course might be eased by the adoption of the abbreviated Zagreb regimen.

In summary, the results of the present study confirm that post-exposure rabies vaccination with PCECV is well tolerated and immunogenic with an acceptable safety profile in healthy Chinese children and older populations, and that the immune response induced under the abbreviated 4-dose Zagreb IM regimen is non-inferior to the response obtained following the 5-dose Essen regimen in subjects 6-years of age and older.[23]

Disclosure of Potential Conflicts of Interest

Dr. M. Pellegrini is a Novartis Vaccines and Diagnostics employee; F. Xie is a statistical consultant to Novartis Vaccines and Diagnostics. All other authors declare no conflicts of interest.

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Author Contributions

All authors contributed to the content, drafting, critical revision and approval of this manuscript.

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