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MINIREVIEW

# Zagreb Regimen, an Abbreviated Intramuscular Schedule for Rabies Vaccination

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**The Zagreb regimen, an abbreviated intramuscular schedule for rabies vaccination, was developed by I. Vodopija and colleagues of the Zagreb Institute of Public Health in Croatia in the 1980s. It was recommended by WHO as one of the intramuscular (IM) schedules for rabies vaccination in 2010. We reviewed the literature on the immunogenicity, safety, economic burden, and compliance of the Zagreb 2-1-1 regimen. Compared to Essen, another IM schedule recommended by WHO, Zagreb has higher compliance, lower medical cost, and better immunogenicity at an early stage.**

Rabies is a viral zoonosis that is known to be present in more than 150 countries, including territories of all continents except Antarctica (1). Rabies virus is a member of the genus *Lyssavirus* of the *Rhabdoviridae* family. The RNA of this virus encodes 5 proteins, including the G glycoprotein that carries the main antigenic site (2). Typically, the incubation period of rabies is 1 to 3 months, but it may vary from <1 week to >1 year (2). Factors that influence the length of the incubation period include the amount of the viral inoculum, the degree of innervation at the site of viral entry, and the proximity of the bite to the central nervous system (CNS). Unfortunately, an effective therapy for rabies has not been developed; once symptoms begin, rabies is almost invariably fatal. Consequently, pre- and postexposure prophylaxis are the main mode for controlling rabies, and these are usually quite effective when properly administered. Postexposure prophylaxis (PEP) includes thorough washing and flushing of the bite wound site (for about 15 min, if possible) with soap or detergent and copious amounts of water, immediate vaccination with rabies vaccine, and passive immunization with human rabies immunoglobulin (HRIG) when appropriate. Lack of a standardized PEP regimen for rabies has been the major reason for the morbidity and mortality associated with rabies in China (3). Globally, it is estimated that ≥15 million people receive rabies prophylaxis annually, and the majority live in China and India (2, 4). Further estimates suggest that without PEP, approximately 327,000 persons would die from rabies in Africa and Asia each year (2, 4).

Guidelines from the World Health Organization (WHO) published in 2010 indicated that active immunization with rabies vaccine after exposure (i.e., PEP) can be administered via either the intradermal or intramuscular (IM) routes (2). For intradermal administration, 0.1 ml of vaccine is administered into each of 2 sites (deltoid and thigh) on days 0, 3, 7, and 28. Compared with traditional IM vaccination, intradermal vaccination appears to be equally safe and immunogenic and is a more economical alternative for PEP. The intradermal route has been introduced for PEP in countries such as India and Thailand. Unfortunately, the logistics of switching to this regimen require significant staff training to ensure correct vaccine storage, reconstitution, and injection; this has impeded its acceptance in many countries, including China (5).

Vaccination via the traditional IM route requires the injection of either 1.0 or 0.5 ml of vaccine (depending on the vaccine used) into the deltoid muscle (or anterolateral thigh for children) in either a 5-dose (days 0, 3, 7, 14, and 28) or 4-dose regimen (2 doses on day 0 [one in each of the 2 deltoid or thigh sites], followed by 1 dose on days 7 and 21). The 5- and 4-dose IM regimens are known as the Essen and Zagreb regimens, respectively. The Zagreb regimen has been widely adopted in China recently, as it can reduce the number of clinic visits to three, compared with the Essen regimen, which requires five visits.

## EPIDEMIOLOGY OF RABIES IN ASIA AND AFRICA

Approximately 60,000 people die annually from rabies worldwide (95% of the deaths occur in Asia and Africa), with 84% of the deaths occurring in rural areas. Children represent a high-risk population, with 4 of every 10 rabies-associated deaths occurring in children under the age of 15 (1). More deaths attributable to rabies occur in Asia (including India and China) than anywhere else in the world (30,000 deaths/year), and most of these occur in India (20,565 deaths/year) (6). The death toll from rabies in Africa is estimated at 23,700 deaths/year. Dogs are the main host animal and transmitter of rabies around the world, including Asia and Africa. Bats are a major source of human rabies deaths in the Americas, Australia, and Western Europe, but the incidence of rabies is comparatively low in these regions (1).

Although the incidence of rabies in China has been declining since 2007, China is still a high rabies burden country. Data issued by the Chinese Center for Disease Control and Prevention showed that the incidence of rabies was 0.1058 per million population, with 1,425 deaths attributable to rabies in 2012. Within China, the three provinces with the highest incidence of rabies were Guangxi, Guizhou, and Hainan, with 0.4995, 0.3257, and 0.3077 cases/million, respectively (3, 7). The 2012 Chinese Yearbook of Health Statistics revealed that, in 2011, rabies was the fourth most common cause of death among category A and B notifiable infectious

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**TABLE 1** Studies on the immunogenicity of rabies vaccines with Essen and Zagreb regimens

| Yr(s) of publication | Author(s) (reference[s]) | Vaccine | Regimen | SCR rate (%) on day[a]: | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | 7 | 14 | 15 | 20 | 21 | 28 | 30 | 42 | 45 | 90 | 365 |
| 1986, 1988 | Vodopija et al. (15, 16) | HDCV | Zagreb | 65.38 | 100 | — | — | 100 | 100 | — | — | — | 100 | — |
| | | FBKC vaccine | | 38.10 | 100 | — | — | 95.24 | 100 | — | — | — | 95.24 | — |
| | | PCECV | | 82.61 | 100 | — | — | 100 | 100 | — | — | — | 100 | — |
| | | PVRV | | 78.26 | 100 | — | — | 100 | 100 | — | — | — | 100 | — |
| | | PDEV | | 92.86 | 100 | — | — | 100 | 100 | — | — | — | 100 | — |
| 1995 | Zanetti et al. (17) | Suckling mouse brain vaccine | Zagreb | — | 100 | — | — | — | 100 | — | 100 | — | — | — |
| 2011 | Lv et al. (18) | PVRV | Essen | — | — | — | 64.60 | — | — | — | — | 97.80 | — | — |
| | | | Zagreb | — | — | — | 69.30 | — | — | — | — | 98.60 | — | — |
| 2011 | Liu (19) | PVRV | Essen | — | — | — | — | — | — | 94.47 | — | — | — | — |
| | | | Zagreb | — | — | — | — | — | — | 95.63 | — | — | — | — |
| 2011 | Liu et al. (20) | PVRV | Essen | 46.67* | 100 | — | — | — | — | — | — | 100 | — | — |
| | | | Zagreb | 69.39* | 100 | — | — | — | — | — | — | 100 | — | — |
| | | PCECV | Zagreb | 68.75 | 100 | — | — | — | — | — | — | 100 | — | — |
| 2012 | Li et al. (21) | PVRV | Essen | — | — | 96.27 | — | — | — | — | — | — | — | — |
| | | | Zagreb | — | — | 97.23 | — | — | — | — | — | — | — | — |
| 2014 | Hu et al. (22) | PCECV | Essen | 57.33** | 100 | — | — | — | — | — | — | 100 | — | 95.90 |
| | | | Zagreb | 71.33** | 100 | — | — | — | — | — | — | 100 | — | 89.47 |

[a] *, $P = 0.045$; **, $P = 0.014$.

diseases, following AIDS, infant tetanus, and tuberculosis (8). Summer and autumn represent high-incidence seasons for rabies, with 66% of annual cases occurring during this period. Males are more likely to develop rabies than females (the male/female ratio is 2.32:1). Farmers represent a high-risk population, accounting for 66.27% of all rabies cases in China, and rabies is most commonly seen in individuals between the ages of 5 and 15 years and 35 and 70 years (3, 7). Canines (88.53% to 95.00%) remain the primary source of rabies infection in China, followed by cats (1% to 7%) (3, 9, 10), and Chinese ferret-badgers play an important role as a reservoir and in the transmission of rabies in the southeast of China (11). Yu et al. (11) examined brain specimens from dogs and cats for the presence of rabies virus. Overall, 78 (2.59%) of the 3,007 dog brains examined were positive for rabies virus by reverse transcription-PCR (RT-PCR). For 93 brains recovered from dogs and cats that attacked humans, rabies virus was detected by RT-PCR in 63 specimens (67.74%). The maintenance of relatively high endemic rates of rabies in China appears to be due to unsuccessful control of rabies in dogs, the existence of healthy carrier dogs, and inadequate, improper, or complete absence of rabies PEP for individuals at risk for recent exposure to rabies (3, 9, 12–14). Epidemiological investigation recently demonstrated that only 6.0% of rabies cases in China received a full course of PEP; 27.6% received inadequate PEP, and 66.3% did not receive any PEP (9).

## IMMUNOGENICITY AND SAFETY OF THE ZAGREB REGIMEN

Vodopija et al. (15, 16) studied the immunogenicity of five rabies vaccines in 19- to 25-year-old French volunteers using the Zagreb regimen (the results of all comparative studies are summarized in Table 1). The five vaccines studied included HDCV (human diploid cell vaccine; prepared on human diploid cells), FBKC vaccine (fetal bovine kidney cell vaccine; prepared on primary fetal bovine kidney cells), PCECV (primary chicken embryo cell vaccine; prepared on primary chicken embryo cells), PVRV (purified Vero cell rabies vaccine; prepared on Vero cells), and PDEV (purified duck embryo vaccine; prepared on embryonated duck eggs). The seroconversion rates (SCR) for virus-neutralizing antibody (VNA) on day 7 for HDCV, FBKC vaccine, PCECV, PVRV, and PDEV were 65.38%, 38.10%, 82.61%, 78.26%, and 92.86%, respectively. The SCR on days 14, 21, 28, and 90 were 100% for all vaccines except FBKC vaccine, which was 95% on days 21 and 90. Inoculation with suckling mouse brain vaccine via the Zagreb regimen induced VNA in 100% of 22- to 38-year-old Brazilian volunteers who were never previously vaccinated (tested 14, 28, and 42 days after vaccination) (17). The comparative study carried out by Lv et al. with PVRV (18) revealed SCR of 64.60% and 97.80% on days 20 and 45, respectively, with the Essen regimen, compared to 69.30% and 98.60% on days 20 and 45, respectively, for the Zagreb regimen; there were no significant differences between the two regimens. With outpatients seen at the rabies clinic of the Sichuan Provincial People's Hospital as subjects, Liu (19) explored the effect of different immunization regimens after potential rabies exposures. The SCR on 30 days after vaccination with PVRV were 94.47% and 95.63% for the Essen and Zagreb regimens, respectively, with no significant difference between the two regimens. Liu et al. (20) also compared the immunogenicity of different rabies vaccines using different administration regimens. On day 7, the SCR of subjects receiving PVRV under the Zagreb regimen, PCECV under the Zagreb regimen, and PVRV under the Essen regimen were 69.39%, 68.75%, and 46.67%, respectively. The SCR for PVRV under the Zagreb versus the Essen regimens were significantly different ($P = 0.045$), with the Zagreb regimen producing better results. These differences were no longer evident after 2 weeks; from day 14 on, all subjects in all groups had VNA titers that exceeded protective levels as defined by the WHO. By day 45, all subjects in all groups had antibody levels that were at least 3-fold higher than the WHO-recommended level for seroconversion. Li et al. (21) studied the immunogenicity of PVRV under different regimens for subjects potentially exposed to rabies in the Jinmen district of China. On day 15 after vaccination, SCR were 96.27% and 97.23% for the Essen and Zagreb regimens, with no

**TABLE 2** Studies on the immunogenicity of rabies vaccines plus HRIG with Zagreb regimen

| Yr of publication | Authors (reference) | Vaccine | SCR rate (%) on day: | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | | | 7 | 14 | 21 | 28 | 35 | 90 | 360 | 1,100 |
| 1991 | Chutivongse et al. (23) | PVRV + HRIG | — | 100 | — | — | — | 80.00 | 50.00 | — |
| 1997 | Vodopija et al. (24) | HDCV/PCECV/PDEV/PVRV/+ HRIG | — | — | — | — | 100 | — | — | 56.82 |
| 1988 | Vodopija et al. (15) | HDCV | 65.38 | 100 | 100 | 100 | — | 100 | — | — |
| | | HDCV + HRIG | 50.00 | 100 | 100 | 100 | — | 100 | — | — |
| | | FBKC vaccine | 38.10 | 100 | 95.24 | 100 | — | 95.24 | — | — |
| | | FBKC vaccine + HRIG | 70.00 | 100 | 100 | 100 | — | 100 | — | — |
| | | PCECV | 82.61 | 100 | 100 | 100 | — | 100 | — | — |
| | | PCECV + HRIG | 27.27 | 100 | 100 | 100 | — | 100 | — | — |
| | | PVRV | 78.26 | 100 | 100 | 100 | — | 100 | — | — |
| | | PVRV + HRIG | 60.00 | 100 | 100 | 100 | — | 100 | — | — |
| | | PDEV | 92.86 | 100 | 100 | 100 | — | 100 | — | — |
| | | PDEV + HRIG | 92.31 | 100 | 100 | 100 | — | 100 | — | — |
| 1999 | Vodopija et al. (26) | Rabipur | 82.60 | 100 | 100 | 100 | — | 100 | — | — |
| | | Rabipur + HRIG | 27.27 | 100 | 100 | 100 | — | 100 | — | 69.23 |

significant difference between the two regimens. Hu et al. (22) compared the immunogenicity of PCECV on days 0, 7, 14, 45, and 365, using the Essen and Zagreb regimens in patients with category II exposure to rabies in Wuhan, China. The SCR for the Zagreb regimen was significantly higher than for the Essen regimen on day 7 (71.33% versus 57.33%, $P = 0.014$), but all patients in both groups seroconverted by day 14 and this was sustained until day 45. However, on day 365, seropositivity had decreased to 95.90% and 89.47% for the Essen and Zagreb regimens, respectively. Hu et al. (22) also demonstrated that the rabies VNA levels were significantly higher in subjects immunized using the Zagreb (versus the Essen) regimen on days 7 and 14 (0.733 versus 0.542 and 7.144 versus 5.672, respectively, $P < 0.0001$), whereas the VNA levels were higher in subjects immunized using the Essen (versus the Zagreb) regimen on days 45 and 365 (23.34 versus 37.46, 2.333 versus 5.353, $P < 0.0001$).

In addition to thorough cleaning of wounds and active immunization, passive immunization with HRIG is extremely important for PEP following grade III exposure. Administration of HRIG, however, may impact the antibody response to active immunization. One hundred Thai patients who were treated with HRIG after high-risk exposure to rabies were vaccinated with PVRV using the Zagreb regimen (the results of studies showing the effects of HRIG on seroconversion following active rabies immunization using the Zagreb regimen are summarized in Table 2). None of the patients died within a year of exposure, and all 10 of the subjects tested for antibodies on day 14 had a satisfactory antibody response (titer of $>0.5$ IU ml$^{-1}$); this response was only sustained in 8 and 5 of the 10 patients at days 90 and 360, respectively (23). Vodopija et al. (24) also studied the immunogenicity of the Zagreb regimen when administered in conjunction with HRIG. The SCR were 100% and 56.82% on days 35 and 1,100, respectively. Vodopija et al. (15) also tested the five rabies vaccines (HDCV, FBKC vaccine, PCECV, PVRV, and PDEV) applied alone or combined with HRIG in 161 volunteers, using the Zagreb immunization schedule. Although HRIG had an apparent effect on seroconversion to some of the vaccines on day 7, most notably PCECV, no effect was seen by day 14; seroconversion occurred in all vaccine recipients by day 14 and was sustained in all but one recipient until day 90 (Table 2). Vodopija et al. (15) also analyzed the effects of passive immunization with HRIG on the kinetics of the response to active rabies immunization using VNA levels (data not shown) and concluded that passive immunization delayed antibody induction by PCECV, PVRV, and PDEV. In contrast, the overall kinetics of the immune response to HDCV and FBKC vaccine was not influenced by passive immunization with HRIG (15). The effect of passive immunization with HRIG on the immune response to PVRV was also evaluated in a multicenter study conducted in Indonesia (25). The results indicated that HRIG negatively impacted the SCR and geometric mean titers (GMT) on day 28 and the GMT (but not SCR) on day 90 (25). HRIG similarly suppressed seroconversion on day 7 in subjects vaccinated with Chiron Behring's (formerly Behringwerke) Rabipur, prepared on primary chicken embryo cells (82.60% seroconversion for Rabipur only versus 27.27% for Rabipur plus HRIG). HRIG did not affect seroconversion on days 14, 21, 28, and 90, and 69.23% of subjects vaccinated with Rabipur plus HRIG remained seropositive on day 1,100; subjects receiving Rabipur alone were not tested at that time (26).

Studies of adverse local or systemic reactions conducted in China on healthy volunteers and exposed subjects did not detect any significant differences between the Essen and Zagreb regimens (18-22, 27). However, Huang et al. (28) reported that the rate of adverse reactions to Zagreb was higher than that for Essen (2.37% versus 1.75%). Children $<10$ years of age had the highest rates of adverse local or systemic adverse reactions, but the adverse reaction rates were similar for males and females (29). Xie and Qiu (30) compared the safety of domestic (ChengDa, China) and imported (Rabipur, India) rabies vaccines. Overall, there was no significant difference between these two vaccines, but the domestic vaccine had a higher rate of adverse reactions for recipients $<20$ years of age.

## ECONOMIC BURDEN AND COMPLIANCE FOR ZAGREB REGIMEN

Goswami et al. (31) estimated the total costs of different PEP regimens and concluded that utilizing the Zagreb regimen saved approximately 30% of total costs compared to the Essen regimen. Furthermore, an economic burden survey conducted in Beijing indicated that compared to Essen, the Zagreb regimen decreased direct medical costs by 20% (from \$53.65 to \$42.92), direct nonmedical costs by 40% (from \$8.15 to \$4.89), and indirect costs by

40% (from $51.36 to $30.82) (32). Yang et al. (33) conducted an economic burden survey in Meizhou, China, with very similar results. Consequently, adopting the Zagreb instead of the Essen regimen for rabies PEP in China would translate to an estimated annual savings of $483.14 million.

Standardized PEP is critically important for rabies prophylaxis. The incidence of rabies in exposed subjects who received standardized PEP was 0.15%, compared to 13.9% for those failed to complete standardized PEP (34). An investigation conducted in Meizhou, China showed that compliance rates for the Essen regimen were 20.49%, 75.25%, and 90.24% for grade I, II, and III exposures, respectively. In general, patients are fairly compliant for the first three doses. Patients begin to stop returning for their fourth dose, and there is a dramatic decline in the rate of return for the fifth dose (33). The main reasons for noncompliance were the frequency and inconvenience of returning for vaccination (85.29%), failure to understand the importance of completing the vaccination regimen (32.59%), and adverse reactions (11.29%). Yang (35) compared compliance with the Essen and Zagreb regimens. Not surprisingly, given that the Zagreb regimen requires only three visits while the Essen regimen requires five visits, compliance was significant higher for the Zagreb regimen (97.16% versus 87.99%, $P < 0.01$).

**Conclusions.** Compared to the Essen regimen, one vaccine dose and two visits to the clinic are eliminated by the Zagreb 2-1-1 regimen. Consequently, widespread replacement of the Essen regimen with the Zagreb regimen can significantly reduce costs while significantly improving compliance, thereby decreasing the likelihood of developing rabies. Compared to the Essen regimen, the Zagreb regimen appears to induce earlier (7 day) seroconversion, but this difference is essentially abolished at 14 days. There is some concern, however, that HRIG administration may reduce early seroconversion when using the Zagreb regimen, whereas coadministration of HRIG does not lower VNA levels when the Essen regimen is employed. It is uncertain, however, whether this delay in seroconversion is clinically significant. Controversy remains regarding the relative safety of the two regimens, with some suggestion that, compared to Essen, the Zagreb regimen has a higher incidence of adverse reactions in children. Although our review suggests that the early antibody production in response to the Zagreb regimen is delayed by HRIG, further studies are necessary to explore the influence of HRIG on the immunogenicity of the Zagreb regimen. Specifically, all studies cited were conducted before 2000 and the preparative techniques for rabies vaccine and HRIG have changed since then, with potential effects on the impact of passive immunization with HRIG on the immunological response to active immunization with rabies vaccine.

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The authors declare that they have no competing interests.

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