**Special Report:**

# World Health Organization's Latest Position Paper on Rabies

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The World Health Organization [WHO] has published its Latest Position Paper on Rabies, in the Weekly Epidemiological Record dated 6th August, 2010, [No. 32, 2010, 85, pages 309-320]. This Position Paper on Rabies, gives the WHO's latest position on the subject, for the benefit of those APCRI members and readers of the APCRI Journal, who did not have access to it.

## Rabies vaccines: WHO position paper

In accordance with its mandate to provide guidance to Member States on health-policy matters, WHO issues a series of regularly updated position papers on vaccines and combinations of vaccines against diseases that have an international public health impact. These papers are concerned primarily with the use of vaccines in large-scale immunization programmes; they summarize essential background information on diseases and vaccines, and conclude with the current WHO position on the use of vaccines in the global context. The papers have been reviewed by a number of experts within and outside WHO, and since 2006, they have been reviewed and endorsed by the WHO Strategic Advisory Group of Experts on Immunization. The position papers are designed for use mainly by national public health officials and managers of immunization programmes. However, they may also be of interest to international funding agencies, the vaccine manufacturing industry, the medical community, scientific media and the public.

This article incorporates the most recent developments in the field of human rabies vaccines, in particular with regard to immunization schedules, and replaces the position paper on rabies vaccines published in the *Weekly Epidemiological Record* in December 2007. Footnotes provide a limited number of core references; abstracts of these references as well as a more comprehensive list of references can be found at http: / / www. Who.int / immunization / documents / positionpapers / en / index.html.

Grading tables that assess the quality of scientific evidence for key conclusions are Also available through this link and are referenced in the position paper.

## Background

### Epidemiology

Rabies is a viral zoonosis that occurs in >100 countries and territories. Although a number of carnivores and bat species serve as natural reservoirs, rabies in dogs is the source of 99% of human infections and poses a potential threat to >3.3 billion people.[1] In humans, rabies is almost invariably fatal once clinical symptoms have developed. In a number of countries, human deaths from rabies are likely to be grossly underreported, particularly in the youngest age groups. The vast majority of the estimated 55 000 deaths caused by rabies each year occur in rural areas of Africa and Asia. In India alone, 20 000 deaths (that is, about 2/100 000 population at risk) are estimated to occur annually; in Africa, the corresponding figure is 24 000 (about 4/100 000 population at risk). Although all age groups are susceptible, rabies is most common in children aged <15 years; on average 40% of post-exposure immunizations are given to children aged 514 years, and the majority of those immunized are male.[2] In the northwestern part of the United Republic of Tanzania, the incidence of rabies was up to 5 times higher in children aged <15 years than in adults. In industrialized countries and in most urbanized areas of Latin America, human rabies is close to being eliminated owing to the vaccination of domestic dogs and the implementation of other control measures. In Asian countries such as Thailand, mass vaccination of dogs and widespread immunization of humans following exposure have significantly reduced the number of human deaths from rabies.

The internal market data of vaccine manufacturers suggest that at the global level, ≥15 million people receive rabies prophylaxis annually, the majority of whom live in China and India. It is estimated that in the absence of post-exposure prophylaxis, about 327 000 persons would die from rabies in Africa and Asia each year.[1]

## The pathogen and the disease

The rabies virus (RABV) belongs to the genus *Lyssavirus* in the family *Rhabdoviridae*. According to the International Committee on Taxonomy of Viruses, 11 species were classified under the *Lyssavirus* genus as of 2009. The RNA of RABV encodes 5 proteins, including the G glycoprotein that carries the main antigenic sites. Beside RABV, viruses belonging to all other known lyssavirus genotypes have been shown, or are expected, to cause an

acute progressive encephalitis in humans. Hence, rabies is a form of encephalitis caused by a lyssavirus, and RABV is the major viral species representative of the genus.

Human infection usually occurs following a transdermal bite or scratch by an infected animal. Transmission may also occur when infectious material, usually saliva, comes into direct contact with the victim's mucosa or with fresh skin wounds. Human-to-human transmission by bite is extremely uncommon. Rarely, rabies may be contracted by inhalation of virus-containing aerosol or via transplantation of an infected organ. Ingestion of raw meat or other tissues from animals infected with rabies is not a known source of human infection.

**The incubation period** is typically 1-3 months, but may vary from <1 week to >1 year. The length of the incubation period depends upon factors such as the amount of virus inoculated, the degree of innervation at the site of viral entry, and the proximity of the bite to the central nervous system (CNS). Inoculated virus is transported to the CNS via the peripheral nerves. On arrival in the brain, it replicates and disseminates rapidly, again via the nervous system, to many different tissues including the salivary glands. Rabies virus is widespread throughout the body at the time of clinical onset, but usually without induction of a detectable immune response at that point.

**The initial symptoms of rabies** are fever and often pain or paraesthesia at the wound site. As the virus spreads through the CNS, progressive fatal encephalomyelitis develops, characterized by hyperactivity and fluctuating consciousness and, in cases of furious rabies, hydrophobia or aerophobia, or both. Death occurs by cardiorespiratory arrest within a few days.[3,4,5] Paralytic rabies, which may represent as much as 30% of the total number of human cases, runs a less dramatic and usually longer course than the furious form, although it is still ultimately fatal. The paralytic form of rabies is often misdiagnosed and this contributes to the underreporting of the disease.

**During infection**, the rabies virus is concealed from immune surveillance by its intraneuronal location, and antibody responses in serum and cerebrospinal fluid (CSF) are unpredictable and rarely detected before the second week of illness.[6,7,8,9]

**No tests are available to diagnose rabies** infection in humans before the onset of clinical disease, and unless the rabies-specific signs of hydrophobia or aerophobia are present, the clinical diagnosis may be difficult. At the stage of clinical manifestations, saliva, urine, extracted hair follicles and CSF may be tested by virus isolation or by polymerase chain reaction, and serum and CSF may be tested for antibodies to rabies virus.[10] Skin biopsy specimens may be examined for rabies antigen in the cutaneous nerves at the base of hair follicles.[8]

**Postmortem**, the standard diagnostic technique is to search for rabies virus antigen in brain tissue by fluorescent antibody test. A rapid tissue culture isolation test may also be used[11]. More recently, a direct rapid immunohistochemical test to detect rabies virus antigen in frozen or glycerol-preserved brain samples has been shown to be 100% sensitive and specific compared to the fluorescent antibody test.[12]

**Rabies differs** from many other infections in that the development of clinical disease can be prevented through timely immunization even after exposure to the infecting agent.

## Rabies vaccines

Since their development more than four decades ago, concentrated and purified cell-culture and embryonated eggbased rabies vaccines (here jointly referred to as CCVs) have proved to be safe and effective in preventing rabies. These vaccines are intended for pre-exposure prophylaxis as well as post-exposure prophylaxis, and have been administered to millions of people worldwide. In a few countries, mainly in Asia and Latin America, populations at high risk of rabies may still depend on rabies vaccines derived from animal nerve tissues for post-exposure prophylaxis. Nerve tissue vaccines induce more severe adverse reactions and are less immunogenic than CCVs; therefore their production and use is not recommended by WHO.[2] In Africa and Asia, post-exposure rabies prophylaxis at its present level prevents approximately 272 000 deaths each year.[1]

### Cell-culture-based vaccines available internationally

CCVs consist of rabies virus that has been propagated in cell substrates such as human diploid cells (embryonic fibroblast cells), fetal rhesus diploid cells, Vero cells (kidney cells from the African green monkey), primary Syrian hamster kidney cells, primary chick embryo cells or in embryonated duck eggs.[13] The more recently developed vaccines based on chick embryo cells and Vero cells have safety and efficacy records comparable to those of the human diploid cell vaccines and are less expensive. Following growth in the respective cell cultures, the viral harvest is concentrated, purified, inactivated and lyophilized. Some of the CCVs use human albumin or processed gelatine as a stabilizer. No rabies vaccines are supplied in multidose vials for intramuscular injection. Rabies vaccines prequalified by WHO do not contain

preservatives such as thimerosal. The shelf-life of these vaccines is ≥3 years, provided they are stored at +2°C to +8°C and protected from sunlight. Following reconstitution with the accompanying sterile diluent, the vaccines should be used immediately, or within 68 hours if kept at the correct temperature.

**All CCVs should comply** with the WHO recommended potency of ≥2.5 IU per single intramuscular dose (0.5 mlor 1.0 ml volume after reconstitution, depending on the type of vaccine).

**Intramuscular and intradermal administration**

The cost of CCVs for intramuscular administration limits their widespread use in many areas where canine rabies is prevalent. Intradermal administration of these vaccines offers an equally safe and immunogenic alternative that requires only 1-2 vials of vaccine to complete a full course of post-exposure prophylaxis, thereby reducing the volume used and the direct cost of vaccine by 60-80% compared with standard intramuscular vaccination.[14,15,16,17,18]

**There is no evidence that intradermal administration requires vaccines with potency higher than that recommended for intramuscularly-administered rabies vaccines.** [19,20,21]

Intradermal regimens have been successfully introduced for post-exposure prophylaxis in countries such as India, the Philippines, Sri Lanka and Thailand.[16,17]

However, in addition to using vaccines explicitly authorized for the intradermal route, proper delivery of the vaccine requires sufficient staff training to ensure correct storage, reconstitution and injection.

## Vaccine efficacy and immunogenicity

Because rabies is a fatal disease, randomized controlled human trials involving untreated comparison groups could not be carried out for ethical reasons. Direct assessment of vaccine-induced protection is based on the efficacy of post-exposure prophylaxis following category II or III exposure to animals confirmed to be rabid through laboratory analysis. (For information on exposure categories, see *Post-exposure prophylaxis* below).

Furthermore, animal models serving as human surrogates have been used to demonstrate the protective efficacy of CCVs after experimental infection.[22] An indirect assessment of vaccine efficacy can be made through immunogenicity studies. All CCVs induce a prompt and high rabies-virus neutralizing antibody response to the viral G protein. WHO's specified minimum titre of 0.5 IU/ml of serum, measured by the rapid fluorescent focus inhibition test (RFFIT) or the fluorescent antibody virus neutralization test (FAVN), is a widely used reference.[23]

**In healthy vaccinees, this level should be achieved in most individuals by day 14 of a post-exposure regimen, with or without simultaneous administration of rabies immunoglobulin and irrespective of age.**

When new rabies vaccines are introduced, their immunogenicity is evaluated by comparing the rabies-virus neutralizing antibody titres induced by the vaccine being tested with those induced by a vaccine of demonstrated efficacy.[24]

**Studies from Thailand and several other countries** in South-East Asia have established the immunogenicity and effectiveness of CCVs for both pre-exposure and post-exposure prophylaxis. The feasibility of using them either intramuscularly or intradermally in all age groups, including infants, has been clearly demonstrated.[24, 25]

In both pre-exposure and post-exposure use, these vaccines induce an adequate antibody response in almost all individuals. Prompt post-exposure use of CCVs combined with proper wound management and simultaneous administration of rabies immunoglobulin is almost invariably effective in preventing rabies, even following high-risk exposure.[26] However, delays in starting or failure to complete correct prophylaxis may result in death, particularly following bites in highly innervated regions, such as the head, neck or hands, or following multiple wounds.[27] Rarely, true failures have been reported after patients received state-of-the-art treatment.[28]

## Duration of immunity

The development of immunological memory after vaccination with CCVs is critical for the establishment of longlasting immunity against rabies in humans. Individuals who had received their primary series 521 years previously showed good anamnestic responses after booster vaccination.[29] Long-term immunity is also achieved with intradermal immunization[30] and may persist even when antibodies are no longer detectable.[31,32] The ability to develop an anamnestic response to a booster vaccination is related neither to the route of administration of the initial series (intramuscular or intradermal) nor to whether the patient completed a pre-exposure or post-exposure series.[16,33]

For pre-exposure and post-exposure immunization schedules, see the section on the WHO position below.

## Adverse events following immunization

In general, CCVs have been shown to be safe and well tolerated.[16,34] However, in 35-45% of vaccinees, minor and

transient erythema, pain and/or swelling may occur at the site of injection, particularly following intradermal administration of a booster.[16,35,36]

Mild systemic adverse events following immunization (AEFI), such as transient fever, headache, dizziness and gastrointestinal symptoms, have been observed in 515% of vaccinees.[17,36,37]

Serious AEFIs (for definition, see http://www.who.int/vaccinesdocuments/DocsPDF05/815.pdf), mainly of allergic or neurological nature, rarely occur.[38,39]

### Contraindications and precautions

For pre-exposure prophylaxis, previous severe reaction to any components of the vaccine is a contraindication to further use of the same vaccine. Because rabies is a lethal disease, no contraindications exist to post-exposure prophylaxis following high-risk exposure. This is also the case for post-exposure prophylaxis during infancy or pregnancy, and for immunocompromised individuals, including children with HIV/AIDS.[40]

People taking chloroquine for malaria treatment or prophylaxis may have a reduced response to intradermal rabies vaccination.[41] These patients should receive the vaccine intramuscularly.

As with all other immunizations, vaccinees should if possible be kept under medical supervision for at least 15-20 minutes following vaccination.

## Rabies immunoglobulin

Rabies immunoglobulin should be administered in all people with category III exposure and to those with category II exposure who are immunodeficient. (For information on exposure categories, see *Post-exposure prophylaxis* below.)

**Human rabies immunoglobulin** has a relatively slow clearance (the half-life is about 21 days), so it is the preferred product, particularly in cases of multiple severe exposures and bites on the head, face and hands. However, human rabies immunoglobulin is in short supply and available mainly in industrialized countries.

Where it is not available or affordable, equine immunoglobulin or F(ab´)2 products of equine immunoglobulin should be used, although the F(ab´)2 have a faster clearancenthan human rabies immunoglobulin. Most of the new equine immunoglobulin preparations are potent, highly purified, safe and considerably less expensive than human rabies immunoglobulin. However they are of heterologous origin and carry a small risk of anaphylactic reaction (1/45 000 cases).[42,43]

There are no scientific grounds for performing a skin test prior to administering equine immunoglobulin because testing does not predict reactions, and it should be given whatever the result of the test. The treating physician should be prepared to manage anaphylaxis which, although rare, could occur during any stage of administration.

### Economic and societal aspects of rabies

Model outputs on mortality and morbidity associated with rabies have been used to calculate an improved disability-adjusted life year (DALY) score for the disease in Africa and Asia.[1] Human mortality from endemic canine rabies was estimated to be 55 000 deaths/year (90% confidence interval [CI], 24 00093 000). The authors estimated that deaths due to rabies would be responsible for 1.74 million DALYs lost each year (90% CI, 0.752.93) and that an additional 0.04 million DALYs were lost through morbidity and mortality following side-effects from nerve-tissue vaccines. The estimated annual cost of rabies including costs for post-exposure prophylaxis and rabies control in dogs was calculated at US$ 583.5 million (90% CI, US$ 540.1626.3 million). Patient-borne costs for postexposure treatment form the bulk of expenditure, accounting for nearly half the total cost of rabies.

In 2005, the estimated global expenditure for rabies prevention exceeded US$ 1 billion. The frequency and costs of post-exposure prophylaxis are expected to rise dramatically in all countries where rabies is present in dogs, particularly in countries that are replacing nerve-tissue vaccines with the safer and more potent CCVs.[1,19]

### WHO position on the use of rabies vaccines

### Replacing nerve-tissue vaccines with CCVs

Despite the development of more-affordable CCVs and administration schedules that use less vaccine, a few countries mostly in Asia and Latin America are still producing and using nerve-tissue vaccines. These vaccines induce more-severe adverse reactions and are less immunogenic than CCVs. It is therefore imperative that production and use of nerve-tissue vaccines be discontinued as soon as possible and replaced with CCVs.

### Intradermal administration of CCVs

For administration by the intradermal route, CCVs should meet the same WHO requirements for production and control as required for rabies vaccines delivered intramuscularly. In addition, the immunogenicity and safety of intradermally administered vaccines should be demonstrated in appropriate clinical trials using the WHO recommended post-exposure prophylaxis regimen and a volume of 0.1 ml per intradermal site.[19]

**New post-exposure regimens**, particularly those using intradermal administration, even if shown to be safe and efficacious, must have clear practical or economical advantages, or both, over existing regimens if they are to be endorsed.

In countries where intradermal administration is an approved route for post-exposure prophylaxis, manufacturers of vaccines proved to be safe and efficacious by this route should be requested to state that their vaccine can be used intradermally.

## Pre-exposure prophylaxis

Pre-exposure prophylaxis is recommended for anyone who will be at continual, frequent or increased risk of exposure to the rabies virus, either as a result of their residence or occupation (for example, laboratory workers dealing with RABV and other lyssaviruses, veterinarians and animal handlers).

Travellers with extensive outdoor exposure in rural high-risk areas where immediate access to appropriate medical care may be limited should also be vaccinated regardless of duration of stay. Children living in or visiting rabies-affected areas are at particular risk.

WHO encourages the implementation of carefully designed studies on the feasibility, cost-effectiveness and long-term impact of incorporating CCVs into the immunization programmes of infants and children where canine rabies is a public health problem.

## Intramuscular administration for pre-exposure prophylaxis

Pre-exposure prophylaxis requires intramuscular doses of 1 ml or 0.5 ml (volume depending on the type of vaccine) to be given on days 0, 7 and 21 or 28. For adults and children aged ≥2 years, the vaccine should always be administered in the deltoid area of the arm; for children aged <2 years, the anterolateral area of the thigh is recommended.

***Rabies vaccine should not be administered in the gluteal area, as the induction of an adequate immune response may be less reliable.***

## Intradermal administration for pre-exposure prophylaxis

Intradermal administration of 0.1 ml volume on days 0, 7, and 21 or 28 is an acceptable alternative to the standard intramuscular route. To lead to significant savings, intradermal immunization sessions should involve enough individuals to utilize all opened vials within 6-8 hours.

## Requirements for booster injections

Booster doses of rabies vaccines are not required for individuals living in or travelling to high-risk areas who have received a complete primary series of pre-exposure or post-exposure prophylaxis with a CCV.

Periodic booster injections are recommended as an extra precaution only for people whose occupation puts them at continual or frequent risk of exposure. If available, antibody monitoring of personnel at risk is preferred to the administration of routine boosters. For people who are potentially at risk of laboratory exposure to high concentrations of live rabies virus, antibody testing should be done every 6 months.

Those professionals who are not at continual risk of exposure through their activities, such as certain categories of veterinarians and animal health officers, should have serological monitoring every 2 years.

Because vaccine-induced immunity persists in most cases for years, a booster would be recommended only if rabiesvirus neutralizing antibody titres fall to <0.5 IU/ml.

## Post-exposure prophylaxis

The indication for post-exposure prophylaxis depends on the type of contact with the suspected rabid animal:

**Category I** touching or feeding animals, licks on intact skin (that is, no exposure);

**Category II** nibbling of uncovered skin, minor scratches or abrasions without bleeding;

**Category III** single or multiple transdermal bites or scratches, contamination of mucous membrane with saliva from licks, licks on broken skin, exposures to bats.

**For Category I exposures**, no prophylaxis is required.

**For Category II exposures**, immediate vaccination is recommended.

**For Category III exposures**, immediate vaccination and administration of rabies immunoglobulin are recommended.

**For Categories II and III**, thorough washing and flushing (for about 15 minutes, if possible) with soap or detergent and copious amounts of water of all bite wounds and scratches should be done immediately, or as early as possible.

Where available, an iodine-containing, or similarly viricidal, topical preparation should be applied to the wound.

When it is impossible to complete post-exposure prophylaxis with the same CCV, another CCV should be used instead. However, since no study has been done yet on vaccine immunogenicity following changes in the route of vaccine administration (for example, from intramuscular to intradermal) during post-exposure prophylaxis, such changes should be the exception.

**Post-exposure prophylaxis may be discontinued** if the suspect animal is proved by appropriate laboratory examination to be free of rabies or, in the case of domestic dogs, cats or ferrets, the animal remains healthy throughout a 10-day observation period starting from the date of the bite.

**Factors that should be taken into consideration when deciding whether to initiate post-exposure prophylaxis** include the epidemiological likelihood of the implicated animal being rabid, the category of exposure (I-III) and the clinical features of the animal, as well as its availability for observation and laboratory testing.

***In most situations in developing countries, the vaccination status of the implicated animal alone should not be considered when deciding whether to give or withhold prophylaxis.***

**Intramuscular administration for post-exposure prophylaxis**

The post-exposure vaccination schedule is based on injecting 1 ml or 0.5 ml (the volume depends on the type of vaccine) into the deltoid muscle (or anterolateral thigh in children aged <2 years) of patients with category II and III exposures. The recommended regimen consists of either a 5-dose or a 4-dose schedule:

**(I) the 5-dose regimen prescribes 1 dose on each of days 0, 3, 7, 14 and 28.**

**(Ii) the 4-dose regimen prescribes 2 doses on day 0 (1 in each of the 2 deltoid or thigh sites) followed by 1 dose on each of days 7 and 21.**

An alternative for healthy, fully immunocompetent, exposed people who receive wound care *plus* high quality rabies immunoglobulin *plus* WHO-prequalified rabies vaccines, is a post-exposure regimen consisting of 4 doses administered intramuscularly on days 0, 3, 7 and 14. [44]

## Intradermal administration for post-exposure prophylaxis

The 2-site regimen prescribes injection of 0.1 ml at 2 sites (deltoid and thigh) on days 0, 3, 7 and 28. [16,17,45] This regimen may be used for people with category II and III exposures in countries where the intradermal route has been endorsed by national health authorities.

## Post-exposure prophylaxis for previously vaccinated individuals

For rabies-exposed patients who can document previous complete pre-exposure vaccination or complete post-exposure prophylaxis with a CCV, 1 dose delivered intramuscularly or intradermally on days 0 and 3 is sufficient. Rabies immunoglobulin is not indicated in such cases.

This 1-site 2-day intradermal or intramuscular regimen also applies to people vaccinated against rabies who have demonstrated rabies-virus neutralizing antibody titres of ≥0.5 IU/ml. As an alternative to this regimen, the patient may be offered a single-visit 4-site intradermal regimen consisting of 4 injections of 0.1 ml equally distributed over left and right deltoids or prescapular areas.[19] Vaccination cards recording previous immunizations are invaluable for making correct decisions.

## Immunization of immunocompromised individuals

In immunocompromised individuals including patients with HIV/AIDS, a complete series of 5 doses of intramuscular CCV in combination with comprehensive wound management and local infiltration with human rabies immunoglobulin is required for patients with category II and III exposures. When feasible, the rabies-virus neutralizing antibody response should be determined 2-4 weeks following vaccination to assess the possible need for an additional dose of the vaccine.

## Rabies immunoglobulin for passive immunization

Rabies immunoglobulin for passive immunization is administered only once, preferably at, or as soon as possible after, the initiation of post-exposure vaccination. Beyond the seventh day after the first dose, rabies immunoglobulin is not indicated because an active antibody response to the CCV is presumed to have occurred.[46]

The dose of human rabies immunoglobulin is 20 IU/kg body weight; for equine immunoglobulin and F(ab')2 products, it is 40 IU/kg body weight. All of the rabies immunoglobulin, or as much as anatomically possible (but avoiding possible compartment syndrome), should be administered into or around the wound site or sites. The remaining immunoglobulin, if any, should be injected intramuscularly at a site distant from the site of vaccine administration. Rabies immunoglobulin may be diluted to a volume sufficient for all wounds to be effectively and safely infiltrated.[19]

## Coordinated efforts towards rabies control

As demonstrated in industrialized countries and in most of Latin America, eliminating rabies from dog populations significantly reduces human exposure to the disease. Mass vaccination of dogs is the single most cost-effective intervention to control and eliminate canine rabies. However, successful rabies control also depends on measures such as managing the dog population, mainly by promoting responsible dog ownership; compulsory notification of rabies in humans and animals; ensuring the availability of reliable diagnostic procedures; conducting postmortem examinations to confirm the cause of death in people suspected to have been infected with rabies; and

improving coordination between all public sectors involved in rabies control.[47]

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## *Announcement*

**The APCRI Journal is published twice a year. Once in January and again in July. The APCRI Journal invites Contributions from the Scientific Community, on All aspects of Rabies and Related Matter, in the form of Original Articles and Review Articles, Brief Reports, Case Reports, Personal Viewpoint, Letters to the Editor, Notes and News, Your Questions and Book Review.**

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## Announcement

**The APCRI Newsletter is published every six monthly, in October and in April. APCRI members and the members of the Scientific Community are requested to contribute News Clippings, Photographs and Reports on Scientific activity on Rabies and Related matter for publication in the Newsletter.**
**Please contact the Convener of the Editorial Board of APCRI.**

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