A shorter post-exposure prophylaxis regimen for rabies, Pakistan

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Objective To assess the cost and effectiveness of the two-site, 1-week, intradermal rabies post-exposure prophylaxis regimen recommended by the World Health Organization (WHO) in 2018.

Methods We compared the number of rabies vaccine and rabies immunoglobulin ampoules consumed at The Indus Hospital in Karachi, Pakistan and their cost before and after implementing WHO’s 2018 recommendations. In 2017, patients with suspected rabies-infected bites were treated using the two-site, 4-week, Thai Red Cross regimen, which involved administering four rabies vaccine doses intradermally over 4 weeks and infiltrating immunoglobulin into serious wounds, with the remainder injected into a distant muscle. In 2018, patients received three vaccine doses intradermally over 1 week, with a calculated amount of immunoglobulin infiltrated into wounds only. Remaining immunoglobulin was saved for other patients. The survival of patients bitten by apparently rabid dogs was used as a surrogate for effectiveness.

Findings Despite treating 8.5% more patients in 2018 (5370 patients) than in 2017 (4948 patients), 140 fewer ampoules of rabies vaccine and 436 fewer ampoules of rabies immunoglobulin were used, at a cost saving of 4202 United States dollars. Of 56 patients bitten by apparently rabid dogs, 50 were alive at 6-month follow-up. The remaining six patients could not be contacted but did not present to any hospital with rabies.

Conclusion The new regimen was more economical than the two-site, 4-week regimen and was equally effective. This regimen is recommended for preventing rabies in countries where the disease is endemic and rabies vaccine and immunoglobulin are in short supply.

Introduction

Globally, rabies kills approximately 59 000 people annually, with the greatest disease burden falling upon the poorest regions, where few dogs are vaccinated and access to post-exposure prophylaxis is very limited. Although many mammals transmit rabies, 99% of disease in low- and middle-income countries is transmitted by unvaccinated dogs.

Rabies is an acute, progressive encephalitis caused by Rabies lyssavirus. The disease is fatal if not treated effectively soon after a bite from a rabid dog, whose saliva contains rabies virions. Once inoculated into the skin or mucous membranes, the virus travels gradually along nerve axons towards the central nervous system and results in acute, progressive encephalitis. The average incubation period from being bitten to the appearance of symptoms is 6 weeks. Classically, hydrophobia and aerophobia develop and death follows from neuronal and autonomic dysfunction.

In low- and middle-income countries, free-roaming dogs pose a danger both to people, especially children, and animals: financial loss can result from the death of livestock. Unfortunately many health-care providers have not kept pace with new developments in post-exposure prophylaxis, and unsafe home remedies in rural areas in many low- and middle-income countries increase the risk of death. Several studies found that some emergency department physicians in these countries were unaware of recent changes in rabies vaccine administration, whereas others were either afraid to infiltrate rabies immunoglobulin into wounds or considered it too expensive to be used. Moreover, many physicians did not even wash wounds thoroughly before referring victims to rabies prevention centres in distant towns or cities.

Human rabies prophylaxis has improved considerably since the nineteenth century. During the 1970s, the introduction of tissue culture vaccines created a gold standard for human rabies post-exposure prophylaxis, as we describe in the data repository. For many years, the five-dose, Thai Red Cross intradermal regimens was the preferred option for high-throughput clinics in low- and middle-income countries where rabies is endemic, whereas the intramuscular Essen regimen was prescribed in developed countries with few patients. Intradermal administration of rabies vaccine allowed smaller doses to be given without compromising efficacy or safety. Also, one ampoule could be shared among several patients, thereby decreasing the cost and improving vaccine availability in high-incidence areas. Researchers observed, however, that many patients skipped the final 90-day dose. Over the years, studies proved that missing this dose did not increase mortality. Thus, in 2006, the regimen was shortened to the updated two-site, 4-week, Thai Red Cross, intradermal schedule, which was applied in several countries where it mitigated vaccine supply shortages and reduced costs by 60–80%.

In 2012, researchers showed that a two-site, 1-week, intradermal schedule was associated with a robust antibody response for up to 180 days in healthy volunteers and suggested further studies on dog bite victims. During 2017, in response to evidence from several studies that the fourth dose of the Thai Red Cross, intradermal vaccine schedule given on day 28 offered no additional benefits, the World Health Organization (WHO) constituted a Strategic Advisory Group of Experts working group to consider further improvements in the dosing schedule that could make post-exposure prophylaxis even more affordable and convenient without compromising safety or efficacy. In 2018, based on discussions by the Strategic Advisory Group of Experts, WHO published a position paper on post-exposure prophylaxis that proposed a shorter two-site, 1-week, intradermal vaccine regimen.

Another problem was that rabies immunoglobulin, an important biological agent for treating severe wounds, is costly and frequently in short supply. Previously, the recommendation

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was that rabies immunoglobulin be infiltrated into the wound as much as anatomically possible and that any remaining immunoglobulin be injected into distant muscle. This recommendation, too, has been revised to eliminate the intramuscular injection because evidence showed that injected immunoglobulin did not increase protection and that precious rabies immunoglobulin could be saved without compromising efficacy.15–18

Even before 2018, there was strong support for, “improved access to post-exposure prophylaxis (PEP) for exposed persons, as well as extended dog vaccination… and clear, simplified PEP regimens utilizing modern WHO pre-qualified vaccines and, in case of category-III exposures, appropriate administration of rabies immunoglobulin (RIG).”39

The aim of our study was to compare the cost, effectiveness and treatment adherence of two rabies post-exposure prophylaxis regimens: (i) the two-site, 1-week, intradermal vaccine schedule recommended by WHO in 2018, with infiltration of rabies immunoglobulin into serious wounds only; and (ii) the two-site, 4-week, intradermal vaccine schedule, with infiltration of immunoglobulin into wounds and distant muscle.

Methods

We performed an implementation study at The Indus Hospital in Karachi, Pakistan, a tertiary care hospital that provides free care to all. The Rabies Prevention Center at the hospital is a high-throughput clinic that operates around the clock, is run by trained nurses and receives dog bite victims from all over Karachi and other districts of Sindh and Balochistan provinces.

At the Rabies Prevention Center, the severity of dog bite wounds is assessed in accordance with WHO definitions and all bite victims are provided with the full range of rabies post-exposure prophylaxis recommended by WHO.3 Rabies exposure is classified using three categories. Category I indicates no exposure to rabies and no post-exposure prophylaxis is required; category II indicates a moderate risk of exposure, which requires rabies vaccine only; and category III indicates a severe wound, which necessitates both rabies vaccine and rabies immunoglobulin. Wound lavage is performed for all bites (see data repository).39

Treatment

Before 2018, all patients with dog bite wounds and category-II or –III rabies exposure were given intradermal injections of IndiRab® rabies vaccine (Bharat Biotech, Hyderabad, India) – a cell culture-derived, inactivated vaccine supplied in 0.5 mL reconstituted ampoules – on days 0, 3, 7 and 28 of a 1-month schedule. In patients with category-III exposure, wounds were infiltrated with equine rabies immunoglobulin (Equirab®, Bharat Serums and Vaccines Ltd, Mumbai, India) at a standard dose of 40 IU per kg body weight, with any remaining immunoglobulin injected into a muscle distant from the wound.

After the 2017 meeting of WHO’s Strategic Advisory Group of Experts, one study author, who took part in the working group on rabies vaccine and immunoglobulin, apprised management at The Indus Hospital about the amended rabies post-exposure prophylaxis schedule and provided supportive evidence from clinical trials. Subsequently, in January 2018, the new schedule was implemented after management approval (see data repository).38

First, we made sure hospital staff understood the new regimen and felt comfortable answering queries from patients. Staff members at the Rabies Prevention Center were already trained in intradermal vaccine administration and in infiltrating rabies immunoglobulin into wounds. We obtained feedback on their perceptions of the new regimen and, accordingly, placed information leaflets in the patient waiting areas to allay patients’ anxiety and to counter misinformation. In addition, we held information sessions on the new regimen for emergency department staff and hospital physicians.

From January 2018, the new post-exposure prophylaxis regimen for patients with category-II or –III rabies exposure comprised intradermal administration of 0.1 mL of vaccine at two sites (i.e. each deltoid muscle) on days 0, 3 and 7 of a 1-week schedule. As the Rabies Prevention Center functions on a 24-hour basis, each 0.5 mL ampoule was usually used up; if a small volume was left over, a hospital employee was vaccinated as pre-exposure prophylaxis. In addition, patients with category-III rabies exposure had immunoglobulin infiltrated into wounds only. The amount of immunoglobulin administered was calculated by body weight and, depending upon the number and severity of bites, an entire ampoule may have been needed. If the calculated volume of rabies immunoglobulin was less than the amount required to inject into wounds, it was diluted with normal saline before injection.3 If there were several small wounds, the calculated amount was drawn into two or three syringes and infiltrated into each wound. Any unused immunoglobulin was refrigerated for up to 12 hours and saved for the next category-III patient. Wastage of rabies vaccine and immunoglobulin was kept to a minimum and each ampoule was used to treat the maximum number of patients, which saved on cost and obviated the need for extra procurement of consumables.

Outcomes

To assess the effectiveness of treatment, we investigated survival in patients who were bitten by an apparently rabid dog. As diagnostic evidence of rabies virus infection in dogs was not available, we accepted the affected community’s characterization of an apparently rabid dog as one that displayed highly aggressive behaviour and hypersalivation. In addition, if five or more people were bitten without provocation by the same dog on the same day, we assumed that the bites carried a high risk of rabies. Documented survival of anyone bitten in this way 6 months after being treated was taken as indirect evidence of the effectiveness of treatment. In 2017, 61 people were bitten by apparently rabid dogs compared with 56 in 2018.

Patients were followed up by monthly phone calls for 6 months even though the average incubation period of the virus is 6 weeks. If there was no response the first time, a second call was placed at a different time within 1 week of the first. On average, two calls were made per patient each month during the follow-up period of 6 months. If a patient did not respond for two consecutive months, the patient’s home was visited by a member of the team.

Data on patients treated between 1 January and 31 December in both 2017 and 2018 were obtained from the health management information system at The Indus Hospital. Information on the number of ampoules of rabies vaccine and immunoglobulin consumed was obtained from the pharmacy department at the hospital and details of costs were...
Table 1. Demographic characteristics, dog bite victims, The Indus Hospital, Karachi, Pakistan, 2017 and 2018

| Patient characteristic | Year, no. (%) | 2017 (n = 4998) | 2018 (n = 5465) |
|------------------------|--------------|----------------|----------------|
|                         | Male         | Female        |                |
| Age, years              | 0–5          | 675 (13.5)    | 884 (16.2)     |
|                         | 6–15         | 1699 (34.0)   | 1522 (27.9)    |
|                         | > 15         | 3075 (61.5)   | 3672 (67.2)    |
| Rabies exposure categorya | I            | 50 (1.0)      | 95 (1.7)      |
|                         | II           | 2699 (54.0)   | 2761 (50.6)   |
|                         | III          | 2249 (45.0)   | 2609 (47.7)   |

a Category I indicates no exposure to rabies, category II indicates a moderate risk of exposure and category III indicates a severe dog bite wound.

Table 2. Cost of rabies treatment, The Indus Hospital, Karachi, Pakistan, 2017 and 2018

| Treatment characteristic | Year | Difference between years |
|--------------------------|------|-------------------------|
| Rabies vaccine           | 2017 | 2018                    |
| Patients treated, no.    | 4948 | 4581                    |
| Ampoules consumed, no.   | 7174.6 | 7034.7                  | -139.9 |
| Cost per ampoule, US$b   | 5.65  | 5.65                    | 0.00   |
| Cost per patient, US$    | 8.19  | 7.40                    | -0.79  |
| Total vaccine costs, US$ | 40536.50 | 39746.00                | -790.50|

| Rabies immunoglobulin    | Year | Difference between years |
|--------------------------|------|-------------------------|
| Patients treated, no.    | 2249 | 2365                    | +116   |
| Ampoules consumed, no.   | 2431 | 1995                    | -436   |
| Cost per ampoule, US$    | 7.285 | 7.285                   | 0.00   |
| Cost per patient, US$    | 8.45  | 6.60                    | -1.85  |
| Total immunoglobulin costs, US$c | 19022.60 | 15610.90                | -3411.70|

$US$: United States dollar.

a In 2017, patients received intradermal rabies vaccine over 1 month plus rabies immunoglobulin injections into wounds and muscle; in 2018, patients received intradermal rabies vaccine over 1 week plus rabies immunoglobulin injections into wounds only.

b Pakistani rupees were converted into United States dollars (US$) at the 2018 conversion rate of US$1 to 130 Pakistani rupees.

c Of 2609 patients with category-III rabies exposure, 244 did not receive immunoglobulin for the following reasons: (i) the dog that bit them was vaccinated or was kept under observation for 10 days; (ii) the patient had previously received rabies vaccine; (iii) the patient presented > 1 week after receiving rabies vaccine elsewhere; or (iv) the patient presented several weeks or months after the dog bite and the dog was still alive.

We report descriptive statistics for all patients treated during 2017 and 2018 and compare the cost of rabies post-exposure prophylaxis in these 2 years.

Results

In 2017, 4998 patients with dog bites were registered at The Indus Hospital. In 2018, the number was 5465, 9.3% (467/4998) more than in 2017. The demographic characteristics of these patients were similar in the 2 years (Table 1). In both years, more than 80% of people bitten were male and over 30% were younger than 15 years. Almost all patients presented with category-II or -III rabies exposure and were given rabies vaccine: 99.0% (4948/4998) in 2017 and 98.3% (5370/5465) in 2018. Patients with category-III exposure also received rabies immunoglobulin: 45.0% (2249/4998) in 2017 and 43.3% (2365/5465) in 2018. Category-I victims received neither vaccine nor immunoglobulin.

We also computed the difference in the number of ampoules of rabies vaccine and immunoglobulin consumed in these years. Costs are expressed in United States dollars (US$) and were derived using the exchange rate for 2018, during which US$1 equaled 130 Pakistani rupees. The cost of consumables, such as needles, swabs and supplies for wound washing, were the same in both years and had no implications for expenditure.

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The study was submitted to an institutional review board registered with the Office for Human Research Protections at the United States Department of Health and Human Services (registration number IRB 00005148). As the study involved a chart review and data were analysed anonymously, it was declared exempt from review by the institutional review board.

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Statistical analysis

We report descriptive statistics for all patients treated during 2017 and 2018 and compare the cost of rabies post-exposure prophylaxis in these 2 years.
to treat 2249 patients at a total cost of US$ 19,022.60. In 2018, despite the fact that the number of patients who received rabies immunoglobulin increased to 2365, an increase of 5.2% (116/2249), 436 fewer ampoules were consumed and the total cost was US$ 15,610.90. Hence, more patients were treated for US$ 3411.70 less. Overall, had we continued with the 2017 regimen in accordance with WHO 2005 guidelines, we would have used 612 more vaccine ampoules and 559 more rabies immunoglobulin ampoules in 2018 than with the new regimen. However, we were able to treat more patients in 2018 for US$ 4202.20 less.

In 2017, 71.8% (3587/4998) of patients completed the vaccine course over 1 month. In 2018, 78.5% (4290/5465) of patients completed the course over 1 week, which suggests that adherence to the shorter schedule was better. In 2018, there were six occasions reported to The Indus Hospital on which five or more people were bitten without provocation by the same dog on the same day and the dog was assumed to be rabid. Of the 56 patients bitten, 50 (89%) were alive at follow-up. The remaining six (11%) could not be contacted because they and their families had moved out of the locality. However, as none of the six patients presented to The Indus Hospital or any other hospital with signs of rabies during follow-up, we felt confident in assuming they were alive.

Discussion
Timely and complete treatment of people bitten by rabid animals is important for reducing mortality due to the rabies virus. In countries with scarce resources and a chronic shortage of vaccine, shorter treatment protocols will save money and enable more people to be treated. In our study, we found that treatment with the abridged, three-dose, 1-week version of the previously updated Thai Red Cross regimen, which was recommended by WHO in 2018, was effective and associated with lower costs and good treatment adherence.

In 2019, researchers demonstrated through mathematical modelling that the abridged regimen can be used to treat more patients at less cost. In our study, we found evidence that this new regimen is effective. Moreover, compared with the previous 1-month regimen with immunoglobulin injections into wound and muscle, use of the abridged, two-site, 1-week regimen with dose-sparing immunoglobulin injections was associated with an annual cost saving despite an increase in patient volume.

We followed patients bitten by apparently rabid dogs (i.e. dogs that bit five or more people on a single day without provocation) for at least 6 months, which was similar to the follow-up period in a study by the Institut Pasteur in Cambodia that provided the groundwork for WHO’s 2018 recommendations. Overall, 89% of these patients were confirmed as being well and there were no reports of rabies-suspected deaths among the remaining 11%. Our findings also concur with the results of the RESIST-2 cohort study, which showed that the administration of rabies vaccine beyond day 7 offered no additional benefit. In addition, a clinical trial in Thailand established that a two-site, abridged regimen was noninferior in effectiveness and safety to a four-site, 1-week regimen. Hence, we are confident that the 2018 regimen is effective.

We were encouraged to continue with the rabies post-exposure prophylaxis regimen recommended by WHO in 2018 by our finding that it was effective and economical. This approach helped mitigate rabies vaccine and immunoglobulin shortages at The Indus Hospital. Moreover, patients did not have to travel to the Rabies Prevention Center to receive a vaccine dose on day 28, which not only saved their time and expense but also conserved time for hospital personnel, reduced overcrowding and economized on consumables, such as syringes and swabs. In Pakistan, where an estimated 40% of the population lives below the poverty line and a family of five may have an income of US$ 1.8 per day, people cannot afford to travel from remote areas on numerous occasions (see data repository). Hence, relieving them of even one visit can result in substantial savings to their meagre incomes.

The successful use of the shortened regimen at the Rabies Prevention Center was not without challenges. We presented our study data and experience at different local forums and, although we showed the shortened regimen to be noninferior and more cost-effective than previous regimens, we got a mixed response. Health-care providers were initially reluctant to accept the modified regimen because of concerns over efficacy. Moreover, some were worried about the lack of training on intradermal administration and others expressed reservations about patient safety.

Engaging key stakeholders and building confidence among health-care providers was key to overcoming this initial resistance and to dispelling scepticism. We achieved this by organizing 3-day workshops for small groups twice a year (which expanded to a bimonthly schedule) intended to introduce trainees to the new schedule and to share experience, including analyses of patient outcomes and patients’ adherence to the new regimen (see data repository). We used didactic lectures and instructional videos in local languages to impart practical training on history-taking, washing wounds, proper vaccine dilution, intradermal inoculation and wound injection techniques for rabies immunoglobulin. Since 2018, we have organized over 20 workshops in Karachi and other areas across Pakistan, including Badin in Sindh province, Quetta in Balochistan province and Abbottabad and Mansehra in Khyber Pakhtunkhwa province. In total, we have trained over 150 health-care providers in the abridged regimen and we intend to continue with refresher training. Coverage by mass media led to our efforts being recognized by the Sindh Health Department and we are now training providers in the use of the new regimen across Sindh province.

A limitation of our study was the absence of laboratory diagnostic facilities to confirm rabies infections in dogs. Consequently, we had to rely on indirect evidence that a person had been bitten by a rabid dog based on its behaviour and unprovoked biting of several people. In countries with a high disease burden, increasing rabies diagnostic capability is needed.

Globally, many people are at risk for dog attacks. Safe, affordable and effective biological agents are now available to prevent rabies. We found the abridged regimen, recommended by WHO in 2018, is cost-effective and noninferior to the 28-day regimen. We suggest the...
The abridged regimen’s implementation in low- and middle-income countries where there is a high patient volume and erratic access to rabies vaccine and immunoglobulin. In the long run, rabies could be eliminated by educating the public, by risk assessment and by implementing the One Health approach through mass dog vaccination.\textsuperscript{4,44} Together, these strategies can help achieve the global vision of zero human deaths due to rabid dogs by 2030.\textsuperscript{45–48}

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Résumé

Raccourcissement du schéma de prophylaxie post-exposition à la rage au Pakistan

Objectif Évaluer le coût et l’efficacité du schéma de prophylaxie post-exposition à la rage par voie intradermique en deux sites sur une semaine, tel que recommandé par l’Organisation mondiale de la Santé (OMS) en 2018.

Méthodes Nous avons comparé le nombre d’ampoules de vaccin antirabique et d’immunoglobuline antirabique consommées à l’Indus Hospital à Karachi, au Pakistan, ainsi que leur coût avant et après l’application des recommandations émises en 2018 par l’OMS. En 2017, les patients présentant une morsure avec suspicion de rage étaient traités selon le schéma de la Croix-Rouge thaïlandaise d’injection en deux sites sur quatre semaines, ce qui impliquait l’administration intradermique de quatre doses de vaccin en l’espace de quatre semaines et l’infiltration d’immunoglobuline dans les blessures graves, avec injection du reste dans un muscle distant. En 2018, les patients ont reçu trois doses par injection intradermique en l’espace d’une semaine, avec une quantité précise d’immunoglobuline infiltrée uniquement dans les blessures. Le reste de l’immunoglobuline était conservé pour d’autres patients. La survie des patients mordus par des chiens infectés a servi d’indicateur d’efficacité.

Résultats Malgré une hausse de 8,5% des patients traités en 2018 (5370 patients) par rapport à 2017 (4948 patients), l’hôpital a utilisé 140 ampoules de vaccin antirabique et 436 ampoules d’immunoglobuline
Carcinoma of endometrium is the most common gynecological cancer by the WHO. The rising incidence of endometrial cancer in women is occurring in both high- and low-resource settings. This cancer is usually asymptomatic until it has spread to other organs. The disease is often diagnosed late, after it has metastasized. Globally, endometrial cancer is responsible for 122,843 deaths per year, with the majority occurring in low-resource countries.

Conclusion: The new regimen has demonstrated to be less costly compared to the regimen of injections in two sites for four weeks, always in line with the same level of efficacy. It is thus recommended to fight against the rage in the countries where the disease is endemic, but also where the vaccines antirabies and the immunoglobulin antirabies are very scarce.

Resumen

Acortamiento del régimen de profilaxis postexposición a la rabia en Pakistán

Objetivo Evaluar el coste y la eficacia de la pauta de profilaxis postexposición a la rabia intradérmica de dos sitios, con una semana de duración, según recomendó la Organización Mundial de la Salud (OMS) en 2018.

Métodos Se comparó el número de vacunas para la rabia y de ampollas de inmunoglobulina antirrábica utilizadas en el Hospital Indus de Karachi ( Pakistán) y su coste antes y después de aplicar las recomendaciones de la OMS de 2018. En 2017, los pacientes con mordeduras presuntamente infectadas por la rabia fueron tratados con el régimen de la Cruz Roja tailandesa de dos sitios y 4 semanas, que implicaba la administración de cuatro dosis de vacuna antirrábica por vía intradérmica durante 4 semanas y la infiltración de inmunoglobulina antirrábica en las heridas graves, y el resto se inyectaba en un músculo distante. En 2018, los pacientes recibieron tres dosis de vacuna por vía intradérmica durante 1 semana, con una cantidad calculada de inmunoglobulina antirrábica infiltrada solo en las heridas. La inmunoglobulina restante se guardó para otros pacientes.

La supervivencia de los pacientes mordidos por perros apareentemente con la rabia se utilizó como sustituto de la eficacia.

Resultados A pesar de tratar un 8,5% más de pacientes en 2018 (5370 pacientes) que en 2017 (4948 pacientes), se utilizaron 140 ampollas menos de vacuna antirrábica y 436 ampollas menos de inmunoglobulina antirrábica, con un ahorro de costes de 4202 dólares estadounidenses. De 56 pacientes mordidos por perros apareentemente con la rabia, 50 estaban vivos a los 6 meses de seguimiento. Los seis pacientes restantes no pudieron ser contactados, pero no se presentaron en ningún hospital con rabia.

Conclusión: El nuevo régimen ha demostrado ser menos costoso que el régimen de inyecciones de dos sitios y cuatro semanas, mientras que proporciona el mismo nivel de eficacia. Por lo tanto, se recomienda para el control de la rabia en los países donde la enfermedad es endémica, pero también donde las vacunas antirrábicas y la inmunoglobulina antirrábica son escasas.
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