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Assessing the burden of human rabies in India: results of a national multi-center epidemiological survey

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Summary
Objective: Human rabies has been endemic in India since time immemorial, and the true incidence of the disease and nationwide epidemiological factors have never been studied. The main objectives of the present study were to estimate the annual incidence of human rabies in India based on a community survey and to describe its salient epidemiological features.
Methods: The Association for Prevention and Control of Rabies in India (APCRI) conducted a national multi-center survey with the help of 21 medical schools during the period February—August 2003. This community-based survey covered a representative population of 10.8 million in mainland India. Hospital-based data were also obtained from the 22 infectious diseases hospitals. A separate survey of the islands of Andaman, Nicobar, and Lakshadweep, reported to be free from rabies, was also undertaken.
Results: The annual incidence of human rabies was estimated to be 17 137 (95% CI 14 109—20 165). Based on expert group advice, an additional 20% was added to this to include paralytic/atypical forms of rabies, providing an estimate of 20 565 or about 2 per 100 000 population. The majority of the victims were male, adult, from rural areas, and unvaccinated. The main animals responsible for bites were dogs (96.2%), most of which were stray. The most common bite sites were the extremities. The disease incubation period ranged from two weeks to six months.

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Hydrophobia was the predominant clinical feature. Many of the victims had resorted to indigenous forms of treatment following animal bite, and only about half of them had sought hospital attention. Approximately 10% of these patients had taken a partial course of either Semple or a cell culture vaccine. The islands of Andaman, Nicobar, and Lakshadweep were found to be free of rabies.

Conclusion: Human rabies continues to be endemic in India except for the islands of Andaman, Nicobar, and Lakshadweep. Dogs continue to be the principal reservoir. The disease is taking its toll on adult men and children, the majority from rural areas, due to lack of awareness about proper post-exposure immunization. The keys to success in the further reduction of rabies in India lies in improved coverage with modern rabies vaccines, canine rabies control, and intensifying public education about the disease.

Introduction

Rabies is one of the oldest and deadliest diseases known to man, and still continues to cause significant human mortality in Asian, South American, African, and Eurasian countries. This fatal viral encephalitis is a zoonotic disease transmitted to man by bites/licks/scratches from rabid animals. While dogs are the major vectors of transmission in Asian countries, transmission by bats and other animals poses a significant threat in America, Africa, and Eurasia.[1] On the other hand, most of the developed western countries are free of human rabies, though wild rabies is still a major problem.

In recent times, some Asian countries such as Thailand, Philippines, and Sri Lanka, have been able to reduce human rabies deaths to a great extent, but India and neighboring Pakistan and Bangladesh report thousands of human deaths every year. There are several reasons for continued human rabies deaths in these countries. Rabies is a disease of low public health priority and there is no national program for its control and elimination. The main vectors of transmission are street dogs, and these are responsible for over 95% of human rabies deaths. In India, there has never been a nationwide epidemiological survey, and early estimates of rabies mortality have been based on regional hospital data projected to the total population of the country. The World Health Organization (WHO) has been using these data in their official publications.[1]

From 1990 to 2002, India has been quoted as reporting 30 000 human rabies deaths, accounting for nearly 60% of global mortality.[2] Even if this figure is considered reasonably accurate, the situation would have changed in the past decade and half as a result of the overall socioeconomic development, availability of potent cell culture vaccines (like human diploid cell vaccine (HDCV), purified chick embryo cell vaccine (PCEC), and purified verocell rabies vaccine (PVRV)), and the increasing public awareness of post-exposure prophylaxis in the urban areas. In India, modern cell culture vaccines were introduced in the early 1980s, and from 1995 onwards there has been a significant increase in the use of these vaccines. Presently, almost 60% of rabies exposed people take one of the modern cell culture vaccines[3] and nearly 5 million doses of these vaccines are sold every year.[4] The production of nerve tissue vaccine (NTV) was discontinued in India in January 2005 and currently only modern cell culture vaccines (CCVs) are used for rabies prophylaxis. With these developments, one can predict a decrease in the incidence of human rabies deaths during the past decade. This has certainly been reflected in the decline in the number of rabies patients admitted to the infectious diseases hospitals situated in urban areas. However, as the majority of rabies cases occur in rural areas, this apparent decrease may not truly reflect the country situation as a whole.

The WHO has shown serious concern over the continuing large numbers of rabies deaths in Asian countries, particularly India. An inter-regional meeting was organized by the WHO in July 2002 to develop strategies to reduce rabies deaths in these countries. Of note during the deliberations of this meeting was the lack of data on the incidence of human deaths, particularly from the Indian subcontinent. It was decided to strengthen surveillance systems in these countries in order to obtain accurate data before applying appropriate control measures. A decision was taken to conduct a nationwide epidemiological survey on the rabies situation in India and this task was assigned to a non-governmental specialized organization — The Association for Prevention and Control of Rabies in India (APCRI).

The APCRI conducted a nationwide multi-center survey during February to August 2003. This paper reports the salient features of the survey focusing on the incidence of human rabies from both rural and urban areas of the country. As this survey is the first of its kind conducted in India, it has revealed some hard facts and figures, which we believe should convince national health authorities to establish a comprehensive national rabies control program. The data in this survey will also form the basis from which the WHO can evolve strategies to reduce the number of human rabies deaths, and eventually plan for its elimination from India and other Asian countries.

Methods

Setting

India is a vast country in Southeast Asia with a population of about 1027 million (National Census 2001) and a land area of 3.2 million sq. km. It shares its borders with Nepal, China, Bhutan, Bangladesh, Myanmar, and Pakistan. It is predominantly dependant on agriculture and nearly two-thirds of the population lives in rural areas. Following independence from Great Britain in 1947, and in the last 58 years, good progress has been made in the fields of medical and veterinary services. Life expectancy has improved from 46.5 years in 1950 to 64 years in 2001; the infant mortality rate has dropped from 146 per 1000 live births in 1960 to 70 per 1000 live births in 1999.

India is now the number one milk producer in the world and has surplus food grain availability. Many diseases in livestock including foot and mouth disease are controlled, and Rinderpest has been eliminated. Despite all these developments, both animal and human rabies continue to be a significant public health problem. As rabies is not a notifiable disease, there is no organized system of surveillance of rabies cases, and hence reliable data are not available.[3] For the first time, a survey of this magnitude has been conducted to assess the burden of rabies in India.

Determining rabies endemicity and human rabies incidence

For establishing the endemicity of human rabies, available data from the records of 22 infectious diseases hospitals from all regions of the country were obtained for the period 1992—2002.

For assessing the annual human rabies incidence, a community-based survey was conducted. A survey population of 10 million was considered, based on the earlier reported incidence of 30 000 deaths annually,[2] keeping in mind the survey standards of 90% confidence level and 10% limit of error.

A multi-center approach was used and 21 medical schools representing different regions of the country were chosen. The principal investigators from the departments of community medicine of these medical schools were oriented to the survey methodology at a two-day meeting in February 2003. Subsequently, these principal investigators trained their field team (4—6 medical personnel) in their respective medical schools.

These medical teams initially collected the hospital data for the past 10 years from the infectious diseases hospitals affiliated to them to establish human rabies endemicity as detailed above. From this data they identified the most recent human rabies deaths both from rural and urban areas as 'index cases'. Subsequently the medical team visited the families of these cases along with the respective urban or rural health center staff. At the household level, rabies death information was obtained by interviewing a reliable, responsible, adult respondent (over 18 years of age, surviving spouse, parent, sibling, and others). The medical team determined the confirmation of a death due to rabies based on clinico-epidemiological information provided by the respondents; there was no laboratory confirmation in any of the rabies deaths. In brief, a verbal autopsy exercise was done for each identified human rabies death at the household level.

Each medical school covered a target population of 125 000 in urban areas and 375 000 in rural areas based on the national demographic ratio of 1:3 for urban:rural areas. In view of this large population coverage, it was stipulated that a three-year memory recall (reference) period for urban areas, and a five-year memory recall (reference) period for rural areas should be used. This enabled households to report human rabies deaths that had occurred during these reference periods.

Following the index case enquiry, a community search was activated for identification of other rabies deaths in the health center area. This search process was initiated through the medical officer of the health center by involving community informants such as health staff, lady health volunteers, schoolteachers, postmen, village accountants, priests, washermen, barbers, village leaders, and others. At the same time, information was also obtained from other sources such as sub-registrar offices (for births and deaths), burial grounds and crematoria, nursing homes, private hospitals, veterinary centers, the Indian Medical Association, and other professional and social services groups.

All the information from the survey was collected with simple, standardized, pretested and structured schedules. All the 21 teams conducted the survey simultaneously for a six-week period from March to May 2003. An independent monitor from the WHO visited four randomly chosen centers of survey, verified the survey process through field visits, and checked the data collected. In addition, an inbuilt mechanism of internal validation was in place both at the medical school level and at the headquarters level.

The islands of Andaman, Nicobar, and Lakshadweep, which are historically rabies-free, were surveyed during the period July—August 2003. The data available from the medical and veterinary services, airports, and seaports in these islands were verified by site visits from one of the principal investigators.

Data analysis

The data were analyzed using the software SPSS version 10.0.

Results

Rabies endemicity and profile of human rabies

Rabies was found to be endemic during the 10-year period 1992—2002 as all 22 infectious diseases hospitals included in the study reported cases throughout this period (Table 1).

From the population, 235 human rabies deaths were reported based on the community survey conducted by the

Table 1 Hospital incidence of human rabies[a] during the decade 1992—2002

Year	Cases	Deaths	LAMA[b]
1992	876	413	456
1993	908	373	525
1994	924	374	527
1995	933	380	526
1996	730	340	390
1997	886	339	545
1998	791	318	472
1999	782	313	466
2000	802	301	493
2001	707	297	405
2002	728	304	418

Source: from 22 infectious diseases hospitals/medical college hospitals of 18 states.

[a] All probable cases based on clinico-epidemiological diagnosis.

[b] LAMA: left against medical advice. The totals are not correct due to possible errors in recording among those who left against medical advice after knowing the prognosis of the disease.

Table 2 Socio-demographic profile of human rabies cases

Details	Urban	Rural	Total
Human rabies deaths (*n* (%))	56 (24%)	179 (76%)	235
Age distribution (%)			
Children (≤14 years)	25.5	38.3	35.3
Adults (>14 years)	74.5	61.7	64.7
Sex distribution (%)			
Male	72.7	70.6	71.1
Female	27.3	29.4	28.9
Economic level (%)			
Poor and low income	81.9	89.3	87.6
Middle income	14.5	7.8	9.4
Upper income	1.8	1.7	1.7
Not assessed/reported	1.8	1.2	1.3

teams from the medical schools. The majority of human rabies victims (76%) were from rural areas, and adult men constituted 71%. The majority (87.6%) had poor and low socioeconomic status (Table 2).

The animal mainly responsible for human rabies deaths was the dog (96.2%) (Table 3). The majority of these were stray dogs (75.2%), followed by pets (11.1%), wild animals (3.5%), and others/unknown (10.2%). Cats accounted for 1.7% of deaths. Among the wild animals, two deaths were due to bites from jackals.

Table 3 Human rabies incidence: details of bites, treatment, and incubation period

Details	Urban (%)	Rural (%)	Total (%)
Biting animal			
Dog	98.2	95.6	96.2
Cat	1.8	1.7	1.7
Others	—	2.7	2.1
Site of bite[a]			
Head and face	—	—	11.5
Trunk	—	—	1.7
Upper limb	—	—	20.9
Hands	—	—	17.0
Lower limb	—	—	56.2
Others	—	—	2.1
Anti-rabies treatment (yes)	30.9	17.6	20.9
NTV	20.0	8.3	11.1
CCV	14.5	8.3	9.8
RIG	3.6	0.6	1.3
Incubation period			
0—14 days	—	—	5.1
15—30 days	—	—	17.9
31—90 days	—	—	53.2
91—180 days	—	—	14.0
181—365 days	—	—	5.1
366+ days	—	—	4.7

NTV: nerve tissue vaccine; CCV: cell culture vaccine; RIG: rabies immunoglobulin.
[a] Includes multiple bites/responses.

Table 4 Human rabies deaths: site of bite and incubation period

Site of bite	No.	Incubation period (days)			
		Mean	Median	Minimum	Maximum
Head and face	20	42	22	12	180
Trunk only	2	45	45	45	45
Upper limbs only	30	108	60	20	1095
Hands only	30	83	60	8	360
Lower limbs only	116	107	75	15	545
Multiple bites	23	48	43	13	96

Clinical features, medical care, and details of death

The most common site of bite was lower limbs (56.2%), followed by upper limbs (20.9%), hands (17%), and then the head and face (11.5%).

The majority (79.1%) had not received any rabies vaccine. Among those who had received rabies vaccine (20.9%) the use of NTV was slightly higher (11.1%) than that of cell culture vaccine, CCV (9.8%). Only 7.6% of them had received the vaccine within 24 hours of the animal bite. Only 15% of those who received NTV and 21% of CCV recipients had completed their course of vaccinations (10 or 14 injections for NTV and five injections for CCV). The use of rabies immunoglobulins (RIGs) was negligible (1.3%) (Table 3).

In 85% of the cases, the incubation period was between two weeks and six months and in 5.1% of cases it was less than two weeks (Table 3). The incubation period was lowest in bites to the head including the face (mean 42 days and median 22 days), and highest in bites to the lower limbs (mean 107 days and median 75 days) and upper limbs excluding the hands (mean 108 days and median 60 days) (Table 4).

Approximately 60% of victims had resorted to indigenous treatment following animal bite. The approaches most commonly resorted to were magico-religious practices (28.9%) followed by herbal therapy (10.6%) (Table 5).

The majority of victims had hydrophobia (95.7%) followed by aerophobia (66.4%), photophobia (33.2%), and paralysis (21.3%). Among these 55.8% were admitted as inpatients,

Table 5 Details of indigenous treatment undertaken following animal bite

Indigenous treatment	No.	%
Magico-religious (faith healing, witchcraft, etc.)	68	28.9
Herbal therapy	25	10.6
Consulting unqualified local practitioners	14	6.0
Application of red chilli powder	12	5.1
Application of turmeric powder	5	2.1
Other local application/dressings	16	6.8
None	95	40.5
Total	235	100.0

27.6% only had an outpatient consultation, and the remaining 16.6% did not seek any medical consultation.

About 50.6% of victims reportedly died at home, 35.3% in hospital, and 11.9% in transit. However, medical autopsy was not undertaken in any of the cases, and hence no laboratory confirmation was possible.

Criteria of diagnosis

As per WHO criteria[5] only eight (3.4%) were classified as 'suspected cases' (compatible with clinical description only), and the remaining 227 (96.6%) were 'probable cases' (suspected cases plus history of contact with suspected rabid animals) of human rabies. None of the human rabies cases belonged to the 'confirmed' category (i.e., laboratory confirmed), as no autopsies were performed.

Estimating the burden of human rabies in India

A close examination of the 235 human rabies deaths detected from the community survey revealed that, with a recall period of three years for urban and five years for rural areas, there was some influence of memory recall attrition and migration of the affected family on the total number of cases detected by this method. For example, 126 (53.6%) of the total 235 cases detected belonged to the previous 16-month period viz. January 2002 to April 2003. Hence, for precision, only these 123 cases (three cases, outliers, were omitted as their area had an abnormally large population base and could lead to errors in correct estimation) were used for the estimation based on the population as per the 2001 census. Using the natural growth rate factor as per census 2001, the mid-year population was estimated for 2002, and the final population surveyed was estimated to be 10.8 million as on the 30th April 2003.

Subsequently, the actual annual human rabies incidence was calculated on the basis of man-days of exposure. The resultant estimated figure was 17 137 (14 109—20 165 at 95% confidence) or 1.7 per 100 000 population. Based on expert group advice, an additional 20% was added to this to include paralytic/atypical forms of rabies that might have been missed during the survey, providing a final estimate of 20 565 (Table 6).

Rabies free areas

The island groups of Andaman, Nicobar, and Lakshadweep are historically known to be rabies-free (the islands of Lakshadweep are free of dogs). The availability and use of human rabies vaccines is practically nil in these islands. In Port Blair, the capital of Andaman and Nicobar islands, about 5616 cases of dog and other animal bites treated during the period 1998—2003 did not receive any rabies vaccine and all patients survived.

Discussion

To obtain an estimate of human rabies mortality in Tanzania, a mathematical model was used based on dog bite injuries.[6] However, no other reports of large-scale nationwide epidemiological surveys have been available for assessment of human rabies mortality. Hence, for the first time in India this kind of a large epidemiological survey of human rabies was undertaken. Prior to this survey, some hospital-based, clinico-epidemiological data from infectious diseases hospitals were available,[7—9] and in the absence of other community surveys for human rabies, these hospital-based studies are used in this report to make some relevant comparisons.

Human rabies continued to be an endemic disease in India during the period of 1992—2002, as all 22 infectious diseases hospitals reported cases. The prevalence of the disease appears to be constant without any obvious trend of either gross increase or decrease in numbers (Table 1). It was disturbing to find that many patients left hospital against medical advice, presumably after learning that there is no cure for the disease.

The community survey revealed that the majority of human rabies victims were adult men (71.1%) and from poor sections of the community. As over two thirds of the population lives in rural areas, nearly 76% of the rabies cases were reported from the rural population. A marginally higher proportion of children (38.3%) from rural areas and adults (74.5%) from urban areas had died of rabies. A recent study based on case record analysis in Delhi, also revealed that males (78%) and adults (>15 years old) constituted 55% of cases.[9] An earlier hospital-based study in 1998 had revealed that 80% were adult males and 20% were children less than 15 years of age. A rural preponderance was also reported in this study.[8]

Dog bites were mainly responsible for these deaths and the majority of these were by stray dogs. The remaining few deaths were due to cats and wild animals such as jackals. Similarly, other studies have identified dogs as being the main animal responsible for human rabies deaths in India. Consequently, the key to human rabies prevention and control in India lies in the successful control of canine rabies and the stray dog population.

The lower limbs (56.2%) were the main site of bite, followed by bites to upper limbs, hands, and head or face. These findings are also corroborated by similar observations from other studies.[7—9]

The majority of victims (79.1%) had not received any rabies vaccine. A small proportion that had received rabies vaccine did not complete the full course. The use of RIGs was negligible. This reflects gross negligence on the part of both the bite victim as well as the healthcare system. Though over the years there has been a significant improvement in overall healthcare in this country, prevention and control of rabies has been a low priority for the health authorities and this has been the main reason for the continued use of Semple vaccine. However, the production of NTV was discontinued in January 2005. With the increased use of modern CCVs and rabies immunoglobulins, particularly in the rural areas, it is expected that the incidence of human rabies deaths will decline. For this to happen, it is important that intradermal rabies vaccination with CCVs be approved and popularized, as it is cost-effective and its benefits are already demonstrated in other countries such as Thailand, Philippines, and Sri Lanka.[10] Simultaneously, extensive public education, particularly for the rural community, is equally important for reducing rabies mortality.

It is recommended that all dog bite victims receive the life-saving modern rabies immunization free of cost from the public health institutions. It was also revealed in the study

Table 6 Estimation of human rabies deaths in one year based on the community survey

	Year	Number
Number of rabies deaths reported[a]		
Urban	2002	25
	2003	11 (Up to 30th April 2003)
Rural	2002	58
	2003	29 (Up to 30th April 2003)
Total		123
Estimation of population at risk		
Base or surveyed population (2001)[b]		
Urban		1 298 897
Rural		3 935 290
Total		5 234 187
Estimated population as per natural growth rates as on 1st March of the year[c]		
Urban	2002	1 339 293
	2003	1 380 945
Rural	2002	4 005 732
	2003	4 077 435
Total		10 803 405
Mid-year population for 2002 (1st July 2002) and mid-period population for 2003 (1st March 2003)[d]		
Urban	2002	1 353 177
	2003	1 380 945
Rural	2002	4 029 633
	2003	4 077 435
Total		10 841 190
Man-days of exposure		
Urban	2002	1 353 177 × 365 days = 493 909 605 man-days
	2003	1 380 945 × 120 days = 165 713 400 man-days
Rural	2002	4 029 633 × 365 days = 1 470 816 045 man-days
	2003	4 077 435 × 120 days = 489 292 200 man-days
Total man-days of exposure		2 619 731 250 man-days
Total rabies deaths reported		123
Number of rabies deaths per one million man-days of exposure		123/2 619 731 250 × 1 million = 0.04695138
Number of rabies deaths/one million man-years of exposure		0.04695138 × 365 = 17.13725406
Number of rabies deaths/1000 million (1 billion) population in one year (or 1000 million man-years)		17.13725406 × 1000 = 17 137 (1.7 per 100 000 population)
SE of probability of a rabies death in one year[e]		0.000001545
95% Confidence interval[f] for rabies death estimate in one year per 1000 million (or 1 billion) population		(17137 − 3028) to (17137 + 3028) = 14 109 to 20 165

[a] A 16-month recall period of the survey was used to get a better, precise, and valid estimate of the human rabies incidence.
[b] Base or surveyed population referred to is 2001 census population.
[c] The natural growth rate of 3.11% for the urban and 1.79% for the rural population is applied as per the 2001 Census of the Government of India.
[d] For 2002, the mid-year population (as on 1st July) is estimated, while for 2003, the mid-period population (as on 1st March) is estimated.
[e] SE = $\sqrt{(pq/n)}$ where p = 123/7 177 346 = 0.000017137, $q = (1 - p)$ = 0.999982863, n = 2 619 731 250 man-days ÷ 365 days = 7 177 346 man-years exposure.
[f] 95% Confidence interval: $p \pm 1.96$ SE (p).

that incomplete treatment had resulted in some rabies deaths. It is very important that people are also educated about the need for a full course of vaccination in order to prevent deaths due to rabies.

In the vast majority (about 90%), the incubation period was less than six months and among these, in a small proportion (5.1%), it was less than two weeks. The incubation periods were short in those cases with bites to the head and face and were longer in those cases with bites to the upper limbs (excluding hands) and lower limbs. This aspect of the disease is already an established fact.

The cases with bites to the head and face and having short incubation periods had received incomplete, delayed, and irregular anti-rabies vaccination, and none had received RIGs. The cases with bites to the upper and lower limbs and having long incubation periods had not received any rabies vaccine except for one case, which had received one dose of NTV. This suggests that in addition to site of bite, incomplete, delayed, and irregular anti-rabies immunization also influences the incubation period.

In another study based on case record analysis in an infectious diseases hospital in Delhi, India, in about 212 or 63% of the cases the incubation period was about 1–3 months.[9] A similar study from the city of Bangalore, India, revealed that in nearly 95% of cases the incubation period was less than six months.[7]

It was also disturbing to note that the majority of bite victims had resorted to different indigenous treatment practices. This could be an act of desperation due to poor prognosis associated with this disease. In addition, it is well known that availability and affordability of modern rabies immunization still needs to improve, and that the facilities and services are poor in infectious diseases hospitals where rabies patients are to be managed. In this survey, it was found that only 50% of the patients were actually hospitalized; the remainder of the rabies cases died at home or during transit.

The present survey has some limitations. Most importantly there was no laboratory confirmation of the disease in any case. However, as most human rabies cases present with clear clinical manifestation of hydrophobia that is not found in any other disease, diagnosis based on epidemiological and clinical findings should suffice for a large-scale epidemiological study such as this. However, there is a need to establish a system of laboratory diagnosis of human rabies, preferably post-mortem, by overcoming the prevailing socio-cultural objections to ensure wider acceptance of diagnosis of human rabies made in this country.

The islands of Andaman, Nicobar and Lakshadweep continued to be rabies free. There is a need to strengthen the surveillance of rabies in the canine population in Andaman and Nicobar and to ensure better screening of dogs and cats during their entry into these islands so that these islands continue to remain rabies-free.

The new estimate of about 20 000 (or 2 per 100 000 population) annual human rabies incidence based on this community survey[11] shows a decline of about 30% from the earlier incidence of 30 000 (3 per 100 000 population) reported during the period 1990–2002.[2] This could be due to improvement in the socioeconomic condition of the people and increased usage of modern rabies vaccine, particularly in urban areas. This new survey estimate of 20 565 cases is concurrently validated by another independent study based on mathematical modeling, which also assessed the incidence of human rabies in India to be 19 700.[12] Thus, this survey provides the much-needed valid data from the field to both the Government of India and the WHO for more concerted actions in the future for prevention and control of rabies in India.

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