Original Article

Incidence Rate of Acute Encephalitis Syndrome without Specific Treatment in India and Nepal

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ABSTRACT

Background: A performance target (PT) for the incidence rate (IR) of acute encephalitis syndrome (AES) was not defined by the World Health Organization (WHO) due to lack of data. There is no specific treatment for ~90% of the AES cases. **Objectives:** (1) To determine the IR of AES not having specific treatment (AESn) in two countries, India and Nepal. (2) To suggest the PT. **Subjects and Methods:** This was a record-based study of the entire population of India and Nepal from 1978 to 2011. The WHO definition was used for inclusion of cases. Cases that had specific treatment were excluded. IR was calculated per 100,000 population per annum. Forecast IR was generated from 2010 to 2013 using time-series analysis. **Results:** There were 165,461 cases from 1978 to 2011, of which 125,030 cases were from India and 40,431 were from Nepal. The mean IR of India was 0.42 (σ 0.24) and that of Nepal was 5.23 (σ 3.03). IRs of 2010 and 2011 of India and that of 2011 of Nepal were closer to the mean IR rather than the forecast IR. IR of 2010 of Nepal was closer to the forecast IR. The forecast IR for India for 2012 was 0.49 (0.19-1.06), for 2013 was 0.42 (0.15-0.97) and for Nepal for both 2012 and 2013 was 5.62 (1.53-15.05). **Conclusions:** IRs were considerably different for India and Nepal. Using the current mean IR as PT for the next year was simple and practical. Using forecasting was complex and, less frequently, useful.

Keywords: Performance target, minimum surveillance standards, record-based study, time-series analysis, Japanese encephalitis, forecasting, epidemic brain attack, epidemic stroke, chandipura encephalitis

Highlights:

1. The mean IRs were different for India and Nepal. In India, it was 0.42 (σ 0.24) and in Nepal, 5.23 (σ 3.03).
2. IRs of AESn differed widely with the region. Therefore, PT for AES must preferably be different at least for different countries.
3. Using the current mean IR as PT for the next year is simple and practical. Using forecasting is complex, time consuming, requires sophisticated statistical software and expert statisticians, and is less frequently useful.

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Introduction

Fever with altered sensorium and/or seizure is acute encephalitis syndrome (AES). It is caused by several different viruses, bacteria, fungi, parasites, spirochetes, etc. More than 100 different pathogens have been recognized as causative agents of AES. Japanese encephalitis (JE), herpes simplex, varicella-zoster, epstein barr virus, mumps, measles, enteroviruses, influenza, adeno virus, echo virus, mycoplasma pneumonia are the most frequent pathogens. Bacterial, fungal, parasitic (like cerebral malaria) and some viral encephalitides (like Herpes simplex, Varicella-zoster) have specific treatment. The majority of cases of viral Acute encephalitis syndrome (~90%) have no specific treatment (AESn).[1] JE/AESn was reported from 171 endemic districts in 17 states of India. 375 million population is at risk of developing AES in India alone. Seventy percent to 75% of disease burden was in Uttar Pradesh.[2] In 2011, incidence of AESn in Nepal was 2.599 times that of UP but CFR of UP was 8.527 times that of

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Nepal.[3] When UP data from 1994 to 2011 were analyzed, IR per 100,000 population in UP ranged from 0.23 (in 1997) to 3.33 (in 2005).[3]

The etiology of AES in 68-75% cases remains unknown.[1,4,5] Syndromic surveillance of the World Health Organization (WHO) aims to identify patients with AES, and, among these, confirm JE using standardized laboratory techniques.[6] AES cases that have specific treatment are managed but not reported by clinicians. Therefore, only AES cases without any available specific treatment are ultimately reported and collected in the data (AESn). JE constitutes about 15% of AES. Adding 10% to the number of AESn (75% unknown +15% JE) will approximately give us the total number of AES.

As with all surveillance standards, the WHO document usually includes performance target (PT) that indicates the quality and completeness of the surveillance. For example, in the polio eradication surveillance standards, an IR of ≥2 non-polio acute flaccid paralysis cases is the minimum that should be reported to show that surveillance is active.[7,8] A PT for the minimum IR of AES was not defined in the field-test version of the JE surveillance standards, pending further information about the likely minimum IR of AES.[6]

There were no studies that specifically addressed the incidence of AES. However, there were studies from various countries that mentioned the incidence of encephalitis in different settings. Those studies suggested an IR of 1.77 (±0.32) to 6.34 for tropical countries and an IR of 0.51-7.4 for Western industrialized countries [Table 1].[9-21] An IR of 145-185 was recorded during an epidemic in Nepal in 1997.[11] A hospital-based study from Andhra Pradesh, India, suggested an IR of 1.[22] A review article suggested that the minimum IR must be fixed at 6.0 based on earlier studies.[23]

The objectives of this study were:

1. To determine the IR of AES not having specific drug treatment (AESn) (antibacterial/antifungal/antiprotozoal/antiviral etc) in India and Nepal.
2. To suggest the performance target (PT).

Subjects and Methods

This was a record-based study of the entire population of India and Nepal from 1978 to 2011. The WHO case definition was used for inclusion of cases [Figure 1] [Annexure I].[6,24-26] AES Cases that had specific treatment were excluded [Figure 1] [Annexure I].[27-30]

Intervention to strengthen surveillance included opening more encephalitis management centers so that a patient could reach a hospital within 30 min. Ambulance services, medical/nursing facilities and diagnostic facilities were improved with the help of State and Central Governments and international organizations. Training-of-trainers programs (TOT) were organized since 1996 at the national and state level in India, and at the national and districts level in Nepal with the help of Governments of India and Nepal and various national and international organizations.[22,31-34] Simple ways of diagnosis with clinical symptoms and signs and management were demonstrated to doctors and nurses using multimedia presentations made by the author. Mass media was utilized for information, education and communication activities.

Cerebro spinal fluid (CSF), sera, blood and other samples (depending on the clinical picture) of all AESn cases reported by PHC doctors, private doctors and nursing homes were sent in a reverse cold chain to medical college laboratories for analysis. To avoid missing the

Table 1: Summary of AES incidence rates in published studies

Study (publication year)	Year of study	Setting[$]	Design[%]	Incidence rate
Kamei *et al.* (2000)[9]	1989-1991	Japan (T)	R	1.77 *(± 0.32)
Henrich *et al.* (2003)[10]	1993-1998	Thailand (T)	P	6.34
Akiba (1997)[11]	1997	Nepal (T)	R	145-185[#]
Khetsuriani *et al.* (2007)[12]	1988-1997	USA (W)	R	0.51-0.53*
Mailles *et al.* 2007)[13]	2000-2002	France (W) R	R	1.9
Klemola *et al.* (1965)[14] Kaeaeriaeinen *et al.* (1964)[15]	1945-1963	Finland (W)	L	2-3
Ponka *et al.* (1982)[16]	1980	Finland (W)	R	3.5
Trevejo (2004)[17]	1990-1999	USA (W)	R	4.3 (CI 4.2-4.4)
Pedersen (1956)[18]	1952-54	Jutland (W)	R	6.75-9.25†
Khetsuriani *et al.* 2002)[19]	1988-1997	USA (W)	R	7.3
Beghi *et al.* (1984)[20]	1950-1981	USA (W)	P	7.4
Nicolosi (1986)[21]	1950-1981	USA (W)	R	7.4
Nagabhushana Rao Potharaju (2003)[22]	1993-2000	India (T)	R	1

[$]T- tropical country , W- western country; [%]L- longitudinal, P-prospective, R-retrospective. *incidence converted to per 100,000 per annum, [#]During an epidemic, †Incidence calculated from data in paper. CI: Confidence interval

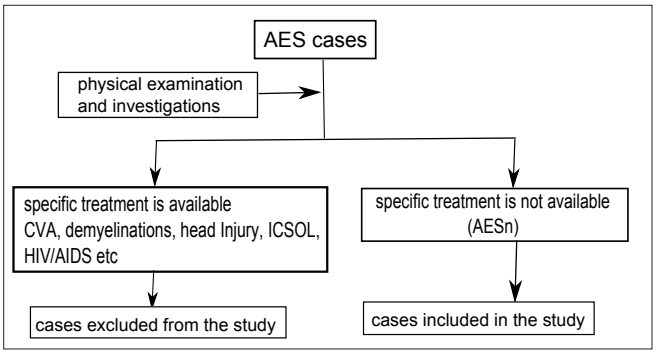

Figure 1: Patient flow

diagnosis of a treatable AES, all cases were thoroughly reviewed by senior specialists and further investigations like neuroimaging, if indicated, were carried out in medical colleges. Medical colleges, regional/district hospitals and private hospitals with laboratories and ventilator facilities functioned as tertiary care centers and were designated as Sentinel Surveillance Sites with laboratory facilities (SSSL). (Currently, there are 73 sentinel sites distributed in 16 states in India). Each SSSL had a designated nodal officer for coordination of JE/AES surveillance activities. Line list of AESn and confirmed JE cases was maintained by the nodal officer and submitted to the District Malaria Officer (DMO)/State Program Officer (SPO) or the designated officer in charge of AES/JE surveillance in the district. Sentinel Surveillance Sites without laboratory facilities (SSSs) were linked to the nearest facility or SSSL with capacity to perform investigations. All reported cases were verified by the DMO/District Medical and Health Officer (DMHO) in India and the Rapid Response Teams (RRT) and Surveillance Medical Officer (SMO) of the World Health Organization Program for Immunization Preventable Diseases (WHO-IPD) in Nepal within 48 h after notification. They obtained laboratory (CSF, serum, etc.) specimens from the case and confirmed AESn. After an outbreak was investigated, the surveillance unit reviewed all reported cases and assigned them a final classification based on clinical history/signs and laboratory results. Line listing of cases was done by the DMHO in India and District Health Officer/District Public Health Officer (DHO/DPHO) in Nepal and conveyed to the national authorities, Director, National Vector Borne Disease Control Programme (NVBDCP) in India and to the Director, Child Health Division, Department of Health Services, Ministry of Health and Population, Teku, Kathmandu, Nepal and WHO-IPD in Nepal. The information was sent monthly during an interepidemic period, weekly during a transmission season and daily during an outbreak. Even when there was no AESn case, "nil case report" was sent. For analysis of doubtful cases, services of 12 apex laboratories including NVBDCP and the National Institute of Virology (NIV), were utilized in India. For Nepal, the National Public Health Laboratory (NPHL) and Armed Forces Research Institute of Medical Sciences (AFRIMS), Bangkok, were the national-level laboratories.

AES/suspected JE case investigation form and JE laboratory request and report form of NVBDCP and WHO-IPD were used for data collection. The data collection was done in India and Nepal with the help of State and Central Governments, WHO South-East Asia Region (WHO-SEAR), WHO-IPD, the Program for Appropriate Technology in Health (PATH) and NVBDCP. Both active and passive surveillances were used. This "GREY LITERATURE" of data was produced by the Governments of India and Nepal, and was not controlled by commercial publishing interests and publishing was not the primary activity of these Governments. The Government of India received help from the WHO-SEAR[6,31] and PATH[22] and Government of Nepal from WHO-IPD.[6,32] Various professional bodies of India and Nepal also participated.[33,34]

The ethics committees of various hospitals in both countries and WHO expert committees have accepted the management.

The author is a member (since 1996) and chairman (2006 and 2009) of the national expert committee on JE/AES, Government of India, core committee member of Joint ICMR- NCDC- NVBDCP-CDC Workshop on Public Health and Research Priorities on JE/AES, and short-term consultant to WHO-IPD, Nepal, and is permitted by both Governments to use this data. The data of India were provided to the author by The Director, NVBDCP, Government of India and the data of Nepal were provided by The Director, Child Health Division, Department of Health Services, Ministry of Health and Population, Teku, Kathmandu, Nepal.

Statistics

IR per 100,000 population per annum was calculated using the general population as the denominator.

$$\text{Incidence rate} = \frac{\text{Number of new cases of AESn in 1 year}}{\text{Population}} \times 100,000$$

For descriptive statistics, time-series analysis and forecasting, IBM SPSS version 20 was used. Both exponential smoothening models and autoregressive integrated moving average (ARIMA) models were examined. Outliers were detected and prevented from influencing parameter estimates. Maximum number of lags in autocorrelation function (ACF) and partial autocorrelation function (PACF) output checked was 24 [Figure 2]. Stationary R-square (larger values indicate a

better fit) was the goodness of fit measure for selecting the best-fitting model to generate forecast IRs. Best-fitting models were different for different regions and different periods. For India, simple model was the best-fitting model for forecasting 2010 and 2011 and ARIMA (1,0,0) was the best-fitting model for 2012 and 2013. ARIMA (0,0,0) was the best-fitting model for Nepal [Figure 2] for 2010 to 2013. IR from 1978 to 2009 was used for forecasting IR along with 95% confidence limits for the year 2010. IR from 1978 to 2010 was used for forecasting IR of 2011 and IR from 1978 to 2011 was used to forecast IR of 2012 and 2013. Observed IR of 2010 and 2011 were compared with mean IR up to the preceding year and also with forecast IR.

Results

There were 165,461 cases from 1978 to 2011, of which 125,030 cases were from India,[1] and 40,431 were from Nepal.[4] The mean IR in Nepal (5.23 {σ 3.03}) was 12.56-times that of the mean IR of India (0.42 {σ 0.24}) [Figure 3 and Table 2]. IR in India ranged from 0.14 (1994) to 1.13 (1978) and in Nepal from 0.36 (1981) to 12.78 [Figure 4].[1,4] IR of AESn in both India and Nepal showed epidemics recurring every 2-4 years [Figure 4]. There was a gradual increase in IR in this millennium in both countries [Figure 4].

Indian states that reported AESn cases were Andhra Pradesh, Assam, Bihar, Delhi, Goa, Haryana, Jharkhand, Kerala, Karnataka, Maharashtra, Manipur, Nagaland, Punjab, Tamil Nadu, Uttar Pradesh, Uttarakhand and West Bengal.[1] Many states in India and many districts in Nepal have not reported any AESn so far [Figure 5].[1,4] The states of India that did not report AESn were Arunachal Pradesh, Chhattisgarh, Gujarat, Himachal Pradesh, Jammu and Kashmir, Madhya Pradesh, Meghalaya, Mizoram, Odisha, Rajasthan, Sikkim and Tripura. The Union Territories of India that did not report even one case of AESn were Andaman and Nicobar

Table 2: Fixing PT. Comparison of Mean, forecast and observed IRs of 2010 and 2011. Forecast for 2012 and 2013 also are depicted. IR in bold italics are closer to the observed IRs

Country	Year	Mean till preceding year	Forecast with CI	Observed
India	2010	**0.41 (σ 0.24)**	0.34 (0-0.80)*	0.45
Nepal		5.24 (σ 3.12)	**5.58** (1.21-16.92)#	5.55
India	2011	**0.41** (σ 0.23)	0.38 (0-0.82)*	0.65
Nepal		**5.25** (σ 3.07)	5.65 (1.5-15.39)#	4.55
India	2012	0.42 (σ 0.24)	0.49 (0.19-1.06)@	
Nepal		5.23 (σ 3.03)	5.62 (1.53-15.05)#	
India	2013		0.42 (0.15-0.97)@	
Nepal			5.62 (1.53-15.05)#	

*Best-fitting forecast model was Simple. #Best-fitting forecast model was ARIMA (0,0,0). @Best fitting model was ARIMA (1,0,0). CI: Confidence intervals

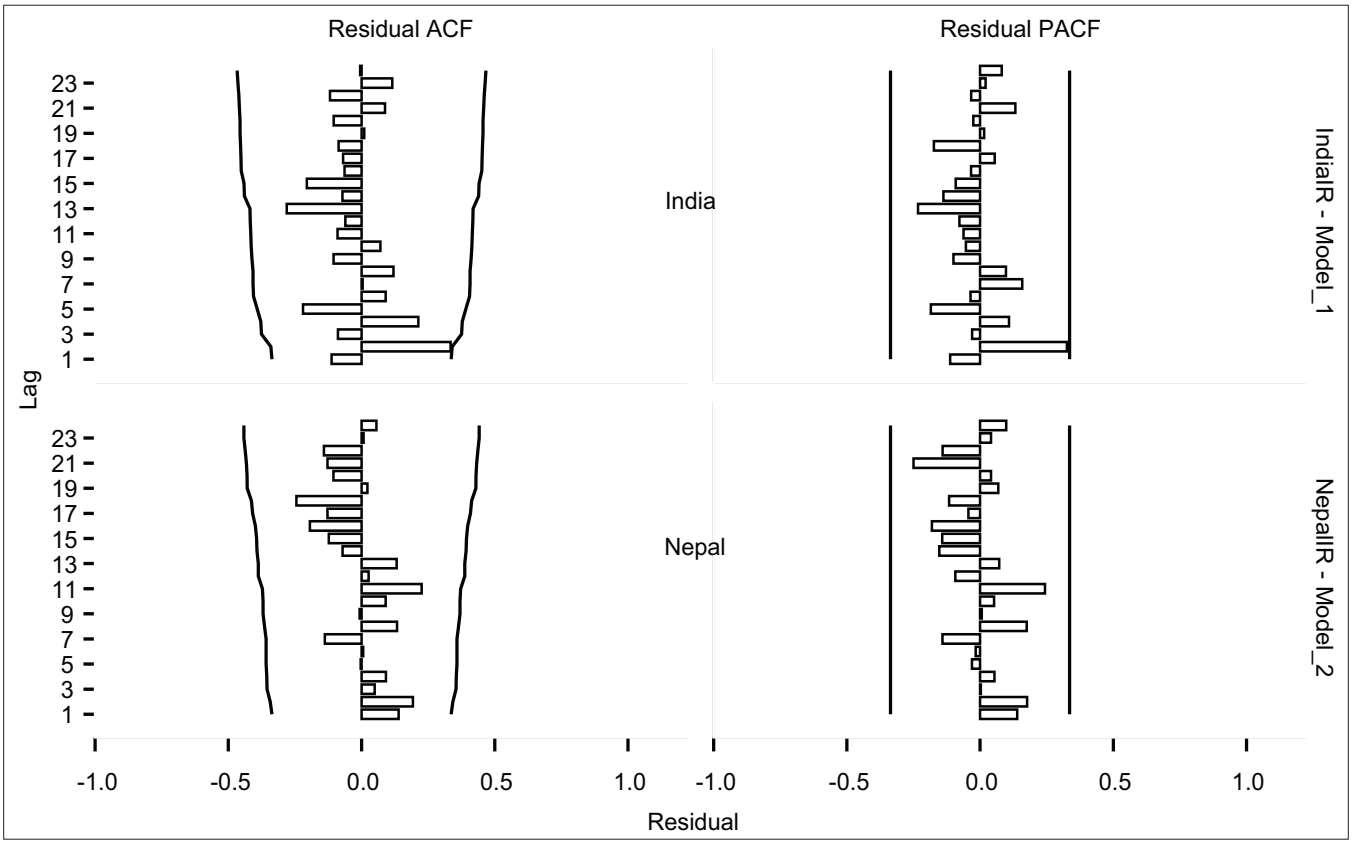

Figure 2: Residual ACF and PACF of AESn in India and Nepal

Islands, Chandigarh, Dadra and Nagar Haveli, Daman and Diu and Puducherry.[1]

The districts of Nepal like Kathmandu, Jhapa, Morang, Bara, Lalitpur, Parsa, Nawalparasi and Kailali have reported AESn, but districts like Taplejung, Manang, Mustang, Jajarkot, Jumla, Mugu, Bajhang, Bajura, Darchula and Doti have not reported any AESn [Figure 5].[4]

IRs of 2010 and 2011 of India and that of 2011 of Nepal were closer to the mean IR rather than the forecast IR. IR of 2010 of Nepal was closer to the forecast IR. Forecast IR for India for 2012 was 0.49 (0.19-1.06), for 2013 was 0.42 (0.15-0.97) and for Nepal for both 2012 and 2013 was 5.62 (1.53-15.05) [Table 2].

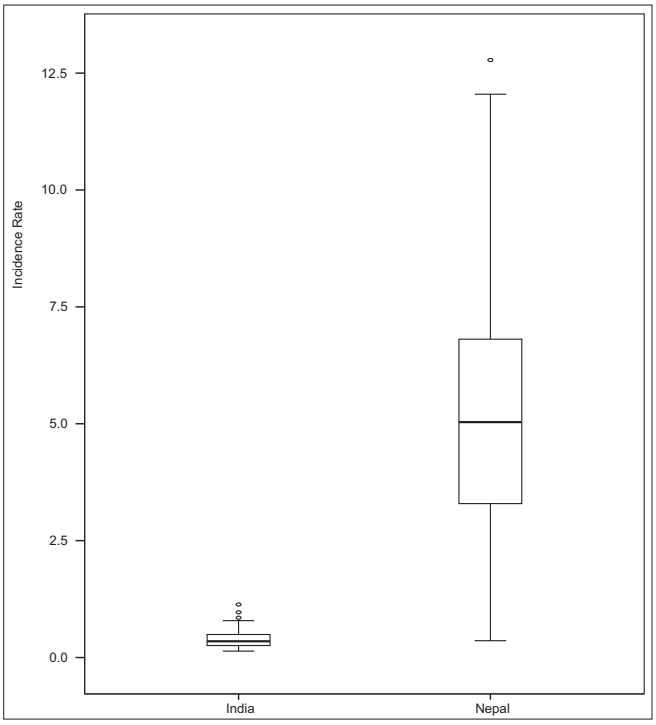

Figure 3: Boxplot of IR of AESn in India and Nepal

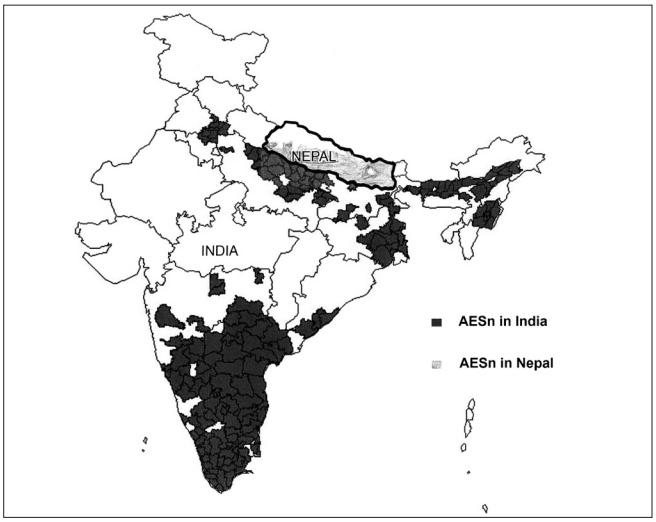

Figure 5: Distribution of AESn in India and Nepal

Data analysis from 2006 to 2011 revealed that the percentage of JE cases among AESn cases varied between 10.74 to 14.72 in India and between 8.73 and 26.74 in Nepal [Figure 6].[1,4]

Discussion

Although there were no studies that specifically addressed the incidence of AES, there were studies that mentioned the incidence of encephalitis in different settings. Earlier studies from various countries between 1989 and 2000 suggested an IR of 1.77 (±0.32) to 6.34 for tropical countries and an IR of 0.51-7.4 for Western industrialized countries [Table 1].[9-21] An IR of 145-185 was recorded during an epidemic in Nepal in 1997 [Table 1].[11] A hospital-based study from the Andhra Pradesh state of India suggested an IR of 1.[22] For ease of use in protocols

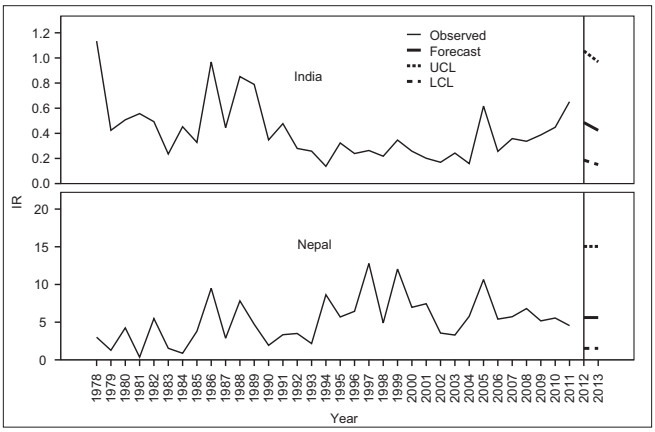

Figure 4: IR of AESn in India and Nepal. Observed values from 1978 to 2011 and forecast values up to 2013 with Upper and Lower Confidence Limits (UCL, LCL)

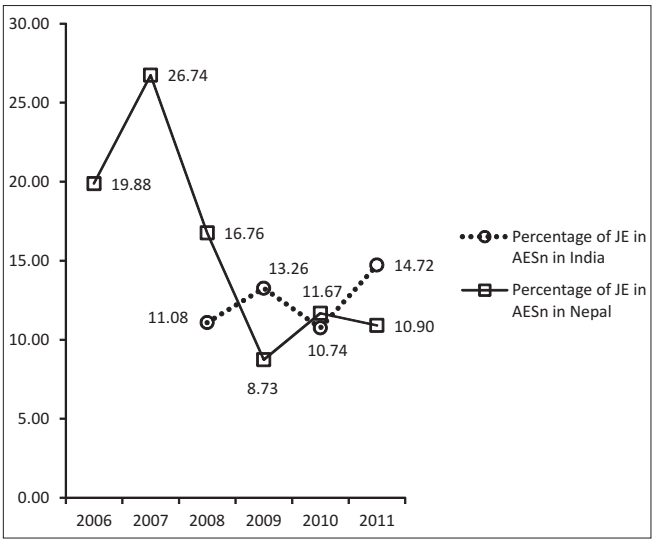

Figure 6: Percentage of JE among AESn cases from 2006 to 2011

and as the benchmark, an IR of 6 was suggested for use in the future WHO AES surveillance standards.[23] Fixing PT based on one to two-decade old data, based on many different countries, is unlikely to yield correct results because many epidemiological variations and confounding variables could have occurred and altered IR over the last 20 years.

The present study was the first study that specifically addressed the IR of AESn. Additional strengths of the study were that it included the entire population of two countries over a period of 34 years; the data was drawn from grey literature and as there was no financial benefit to anybody or recommendation of a particular medicine, there was no bias for personal gains.

Factors which might have increased IR of AESn

1. Overcrowding with resultant worsening of environmental sanitation and difficulty in getting protected water supply might have resulted in infections spreading rapidly.
2. Some cases of AES with specific treatment might have died before a diagnosis was made and so were not removed from the AESn study group. Lack of facilities for urgently required advanced investigations (e.g., magnetic resonance imaging scan in a case of Acute disseminated encephalomyelitis [ADEM]) might have played a role in such cases.
3. Some febrile convulsions were reported as JE for financial gains by private hospitals. Some doctors labeled cases of gastroenteritis with electrolyte imbalance and resultant coma as encephalitis to avoid being blamed of medical negligence in the event of death. The DMHO/DMO/DHO/DPHO/SMO was assigned the responsibility to confirm AESn to eliminate this error.
4. Malnutrition is an important factor contributing to illness, and is the most common cause of immune deficiency worldwide. It might have been responsible for the high incidence in Nepal and in some states of India. The incidence of malnutrition in Nepal was 48%.[35] According to a World Bank report, India has the largest child development program in the world; however, progress on malnutrition has been limited. The prevalence of underweight children in India was among the highest in the world, and was nearly double that of sub-Saharan Africa. Forty-seven percent of the children were underweight in 2000: 50% in the rural and 38% in the urban areas were underweight.[36,37] Approximately 60 million children are underweight in India.[38] Strangely, Madhya Pradesh, which has an "extremely alarming" hunger index, has not reported any AESn case.
5. Coma epidemics continue to pose considerable challenges to doctors in establishing the diagnosis and unraveling the pathogenesis. During epidemics, mass hysteria of parents of hundreds of cases overloads the few available rural basic doctors. Media, bureaucratic, political and public criticism is always less if a diagnosis is made and something is done to show that doctors are taking all possible measures to contain the epidemic and treat the cases. This results in the tendency of medical personnel to label any acute epidemic coma as epidemic encephalitis or Reye's syndrome to tide over the crisis as other neurological diseases that can cause coma were never reported to have presented in an epidemic form.[28] Report of epidemic brain attack (EBA) (stroke in epidemics) as Chandipura encephalitis by some virologists is a classical example.[39] Misdiagnosis of epidemic brain attack (stroke in epidemics) (EBA) as Chandipura encephalitis was responsible for the apparent increase in IR in some areas.[28-30] Treating clinicians were not involved in the discussion and description of the new epidemic when a diagnosis of Chandipura encephalitis was made by virologists based on a single brain biopsy. Bilateral papilledema at admission and many other findings excluded the possibility of encephalitis in the patient from whom brain biopsy was done, Chandipura virus (CHPV) was demonstrated and the diagnosis of Chandipura encephalitis was made.[28] When the outbreak of EBA was reported as Chandipura encephalitis, clinicians critically argued against the diagnosis of encephalitis and a pathogenic role of CHPV as the linkage between CHPV and EBA was not proven.[28] In their subsequent papers, virologists avoided arguing against the ischemia hypothesis or defending the diagnosis of encephalitis or the etiological role of CHPV by ignoring that report, and did not even reference the EBA articles in their subsequent publications.[40] Such biased publications resulted in falsely elevated IR of AESn. Clinicians suspected fecal-oral infection by Enteroviruses to be responsible for some of the recurrent coma epidemics in their article in 2004,[28] which has gained evidence now after 7 years of investigations.[41] The outbreak in UP in 2011 is proven to be caused mainly by enteroviruses, which are water borne.[41] Transmission of enterovirus infections is increased by poor hygiene and overcrowded living conditions. Around four to five enteroviruses work in tandem, in clusters, in particular areas. It is difficult to identify the deadliest virus among them.[2]
6. Another reason for inaccurate incidence rates of encephalitis in some regions of India is the tendency of some virologists to publish a paper about a new disease at the earliest without proper confirmation or correlation with the clinical picture (which may be named as "paper publication syndrome") to avoid concerned clinicians being included as authors in the paper. One should not make the diagnosis

of particular viral encephalitis without the patient clinically having symptoms and signs of encephalitis just because his blood shows evidence of a virus that could as well be a contamination. There have been various instances of a national-level laboratory claiming discovery of a new disease and publishing in national or international journals without discussing the possibility with the clinicians who have referred the cases for investigation. Such claims or publications were never confirmed by any other laboratory in the world. Claims of atypical measles encephalitis by a national virological laboratory were later found to have been due to contamination of the serum samples with a vaccine virus in its laboratory.[42]

7. Lack of vaccines against most pathogens to prevent AES is an important reason. Currently, vaccines are available for only a few diseases like JE, measles, mumps and rubella, etc.
8. Genetic variation resulting in susceptibility to AESn had to be considered. Avoiding consanguineous marriages will minimize this risk.

Factors which might have decreased IR

1. Improved environmental sanitation, health education and availability of more specialists might have resulted in early diagnosis and prevention of spread of AESn.
2. Improved communication and transport systems, methods of detection of treatable etiologies and availability of multimedia teaching facilities might have supplemented the diagnostic efficiency of medical and nursing personnel resulting in early specific treatable diagnosis.
3. Although utmost care was taken to report every case, there was a possibility that some cases of AESn might have died before being seen by a doctor, thereby reducing the number of cases of AESn. Part of the low IR might have been due to lack of staff[43] or timely diagnostic facilities for making a diagnosis before death of the patient or lack of awareness among doctors that they have to report AESn cases.

Epidemics recurring every 2-4 years in both India and Nepal suggested that falling herd immunity might have been the responsible factor [Figure 4].

There was an increase in IR of AESn in this millennium in both countries in spite of vaccination against JE [Figure 4].[1,4] This could have been due partly to increased facilities for transport and spread of infections to new areas and increasing awareness of AESn. Alternately, some other agent(s) may be responsible for AESn in recent years, like emerging (Nipah virus, enteroviruses-EV-89 and EV-76) and re-emerging viruses such as dengue and chikungunya. The diagnosis of Nipah viral encephalitis, which attacked West Bengal state of India in 2001 was missed initially by the national virology laboratory. The diagnosis was made by WHO when it investigated a simultaneous epidemic in a neighboring country, Bangladesh. Five years later, the etiology of the epidemic was confirmed to be Nipah virus by National Institute of Virology, India, retrospectively.[44]

The fact that many areas in both India and Nepal did not report AESn was surprising, because, by definition, AESn was expected to occur everywhere. Politicians, bureaucrats and DMHOs in India feel that high IR of AESn reflects badly about the functioning of the health care system. Therefore, the real Figures are not being projected. There are multiple examples of one state reporting AESn cases in a border village, and, the neighboring state across its border, saying that there was no case in its villages. In one state, doctors were told to diagnose AESn as "viral infection of the brain" to avoid public reaction. Another state did not sanction funds for purchase of laboratory reagents for confirmation of JE just to reduce the reported number of JE. The chikungunya pandemic of 2006 could have been averted had the officials reacted immediately to the initial reports from Andhra Pradesh state in India. Red-tapism is responsible for many epidemics in India.

Cooperation of various specialists is necessary for proper diagnosis and management of AESn. One virology laboratory is known to collect information from concerned public health doctors, case sheets and photographs from the treating clinicians, samples from patients and publish papers before informing the results to the concerned departments or doctors. Concerned clinicians and public health personnel who sought help from the laboratory knew the results only when they were published in a journal. This resulted in many clinicians not seeking virological investigation and not reporting AESn.

Intervention at various levels is required to improve surveillance. In the government setup, all the crucial positions in the health sector are handled by bureaucrats and ministers who do not have the training or experience[45] or expertise in public health. Some of them also have a tendency to downplay the incidence of encephalitis by various ways to avoid public wrath. Creation of awareness and administrative reforms are needed to improve surveillance. The Chief Secretary of one state was not willing to permit the epidemic investigating team to wear masks during their investigation of an unknown epidemic because he felt that it will create public panic. In terms of making a real difference to policy, the researchers/faculty members of medical colleges need to be much more proactive.[46] There is a need for a paradigm shift in the style of the postgraduate teaching in public health in India.[47]

Nepal had IR 12.56-times higher than in India. This could have been multifactorial and might have been due to poverty, poor environmental sanitation, lack of health education or increasing awareness in Nepal and/or under or lack of reporting in some states of India. In addition, IR could have been confounded by all the ways in which the countries could differ (genetic, epidemiological, nutritional, vaccinations, health care facilities, environmental sanitation, social, political, etc.). An important reason for low IR in India is lack of efficient cross-checking mechanisms and inadequate and poorly supervised surveillance. NVBDCP coordinates its work with the health ministries of various states. Whatever reports are submitted by the state are accepted and recorded by the NVBDCP. Most private hospitals, especially in the corporate sector, do not report AESn, and no action is taken against them. Active surveillance must be strengthened to eliminate this error. In Nepal, there is a complementary surveillance mechanism supported by the WHO-IPD, which made surveillance successful in >90% of the cases.

The question that haunts us is whether the surveillance was active at all in the areas that never reported any AESn. What is the minimum IR of AESn that should be reported to show that there is active surveillance taking place? Fixing minimum IR or PT based on short period studies or old studies or another country's studies would be misleading and is unlikely to yield reliable results because many epidemiological variations and confounding variables could have occurred and altered IR over the years. So Fixing minimum IR or PT may better be based the entire data available for the region. With the data available, PT may be fixed based either on the mean IR till the preceding year or using forecasting statistical software.

Forecast IR using the time-series analysis and best-fitting model is highly complex, time-consuming and requires experienced statisticians, but sounds impressive as it considers all variables and outliers and uses robust statistical methods. However, in practice, the situation was different. The observed IR was closer to the current mean IR rather than the forecast IR for both India and Nepal in 2011 and for India in 2010 (three times out of four) [Table 2]. The forecast IR was closer to the observed IR for Nepal in 2010 (one time out of four) [Table 2]. This suggests that we require a better statistical model than the best fitting model that is currently available for forecasting.

A universal target for AES IR looks simple and attractive, but ignores regional epidemiological variations in the diseases causing AES. Establishing country-wise/state-wise/district-wise PTs depending on the situation is more appropriate for their needs, as has been proven here. Similarly age-specific and sex-specific PT may be generated. Using the current mean IR as PT for the next year rather than forecast IR seems to be simpler and practical about 75% of times. Forecasting is not only complex and time-consuming but also requires the expert statistician's services and is close to the observed IR only 25% of the times.

PT for IR of AESn in India may be fixed at 0.42 and for Nepal, at 5.23 for the year 2012. AESn forms about 90% (75% unknown etiology+15% JE) of all AES cases.[1,4,5] Therefore, AESn IR+10% will give approximate IR of all AES with and without specific treatment put together. Thus, the PT for IR of AES for India would be 0.46 and for Nepal these would be 5.75 for the year 2012. The fact that the etiology of acute encephalitis remains unknown in the majority of patients[1,4,5] continues to be a laboratory diagnostic challenge.

Limitations of the study and steps taken to minimize the possibility of bias

Some officers tried to avoid reporting AESn as they felt the Government might take action against them for not being able to prevent the epidemic. This was overcome by highlighting the fact that it was not doctors but the municipal administration that is responsible for not maintaining environmental sanitation and the resultant epidemics.

All mass media reports of AES were investigated to eliminate the risk of not including a case.

Because tens of thousands of doctors and nurses of two countries participated in the detection of cases, it was quite likely that all participants could not have had the same caliber of knowledge, efficiency and dedication. This would have altered the IR to some extent. This problem was minimized by explaining to them the importance of the study, training them with multimedia demonstrations, giving handouts to all participants and giving them the mobile phone numbers of senior specialists for seeking advice as and when necessary.

India and Nepal share the open border policy. Indian currency is a legal tender in Nepal. Many Indian and Nepali families are related. When an Indian Tertiary Care Hospital (TCH) (e.g., in Uttar Pradesh, Bihar, Sikkim or West Bengal) was closer to a Nepali village in the border, there was a likelihood that a Nepali case would have gone there with an Indian relative's address. Similarly, an Indian case residing in the border village could have got admission in one of the TCH of Nepal giving a Nepali relative's address. These cases were included by the respective region only if they attended the surveillance sites before crossing the border. Because there was no cross-border reporting mechanism, there

was a possibility that few such cases might have been missed by the surveillance units. This was a limitation of the study. Because the numbers of such cases is likely to be small, the ultimate effect on the results was unlikely to be very significant.

Data analysis from 2006 to 2011 revealed that the percentage of JE cases among AESn cases varied between 10.74 to 14.72 in India and between 8.73 and 26.74 in Nepal [Figure 6].[1,4] A dedicated study is required to analyze the efficacy (in Indian and Nepalese populations), coverage and logistics of JE vaccination (for any programmatic errors) to guide further reduction of JE incidence.

Conclusions

Unless accurate IR is available, neither WHO nor any Government can plan for the provision of management measures. The disease burden of AES has to be defined based on evidence. Once PT is fixed, performance can be assessed. If the target is not achieved, various reasons responsible may be investigated and rectified.

The IR was different for India and Nepal. Using the current mean IR as PT for the next year is simple, practical and more frequently reliable. Generating forecasting is complex, requires advanced statistical software and expert statisticians and is less frequently reliable.

Many states/districts in India and Nepal have not reported even one case of AESn. Let us not be under the false sense of security that there is no AESn in those areas. Because most pathogens cannot be avoided/eradicated, if some state or district is not reporting, it is time to check for AESn more carefully, search for the reasons and rectify them. Even if there is no JE, there can be other AESn. The Directors of Health of those states must look into the reasons and find solutions.

Public health departments in India and Nepal will have to concentrate more on health education, environmental sanitation, improving laboratory diagnostics, improvement in vaccination coverage against JE and protected water supplies for reducing fecal-oral infections. DMHOs reporting epidemics must be given support to investigate them and not a memo as if they are responsible for the epidemic. Doctors/nurses may be able to reduce the incidence if they are given training, resources and powers. Development of newer laboratory techniques and epidemiological studies might lead to the etiologic diagnosis in a higher number of AESn cases.

This study, being a record-based study of the entire population of India and Nepal (grey literature), supported by various international and national non-profit organizations, presents Category I level of evidence.[48]

Planning the future action

Currently, Government of India constituted a Group of Ministers (GoM) [Health & FW, Drinking Water Supply & Sanitation, Women & Child Development, Social Justice & Empowerment, Rural Development, Urban Development] to look into incidents of AES. Rs 4,000 crores are being allocated[49] for National Encephalitis Control Programme which includes replacement of shallow hand pumps by deep bore hand pumps in acute encephalitis syndrome-affected districts, setting up of Intensive Care Unit wards, especially for JE patients, in all district hospitals and identifying the most undernourished children and providing them better nutrition to fight the virus. It will first be implemented in 60 districts in West Bengal, Bihar, Uttar Pradesh, Tamil Nadu and Assam.[2] This raises the hopes for a better tomorrow.

The Global Disease Detection Program (GDD) is the Centers for Disease Control and Prevention's (CDC's) (USA) principal and most visible program for developing and strengthening global capacity to rapidly detect, accurately identify, and promptly contain emerging infectious diseases that occur internationally. It has started Global Disease Detection India Center (GDDIC) at Delhi recently. A Joint ICMR- NCDC- NVBDCP-CDC Workshop on Public Health and Research Priorities on Japanese Encephalitis / Acute Encephalitis Syndrome was held at Lucknow, UP from 24th – 26th May, 2012 for formulating prospective surveillance for establishing the diagnosis of AES. The author was invited as a core committee member for this meeting. Many points presented in this paper were made note of for planning the future surveillance.[50]

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Annexure I

Case definition

WHO definition was used for the diagnosis of AES [Figure 1].[6,24-26] "A case of AES is defined as a person of any age, at any time of year with the acute onset of fever and a change in mental status (including symptoms such as confusion, disorientation, coma, or inability to talk) and/or new onset of seizures (excluding simple febrile seizures)". Other early clinical findings may include an increase in irritability, somnolence or abnormal behavior greater than that seen with usual febrile illness.

Exclusion criteria were [Figure 1]: 1. Availability of specific treatment like antibacterial, antifungal, antiprotozoal or antiviral drugs,[27-30] 2. Demyelination. 3. Sporadic/ Epidemic Brain Attacks (Cerebrovascular accidents {Stroke, Epidemic Brain Attack-EBA}).[28-30] Fever, alteration of sensorium without rash or meningeal signs of irritation, normal CSF, epidemic within 2 days of heavy rain after a hot summer and neuroimaging features of infarction suggested the diagnosis of EBA,[28-30] 4. Head injuries, 5. Intracranial Space Occupying lesions (ICSOL), 6. Human Immunodeficiency Virus (HIV) and Acquired Immunodeficiency Syndrome (AIDS).

AESn cases=AES cases-AES cases with specific treatment.

Diagnosis of JE:[6,24-26] A patient must have clinical evidence of AES in addition to positive serology. The standard of JE diagnosis in practice is IgM-capture ELISA of CSF (preferred) or serum. Various other tests used included:

1. Four fold or greater rise in JE virus-specific antibody in paired sera through IgM/IgG ELISA, haemagglutination inhibition test or virus neutralization test, in a patient with no history of

recent yellow fever vaccination and where cross-reactions to other flaviviruses have been excluded, or
2. Detection of JE virus, antigen or genome in tissue, blood or other body fluid by immunochemistry or immunofluorescence or PCR.

For persons vaccinated with Japanese encephalitis vaccine within six months of illness onset, testing a single serum sample for Japanese encephalitis IgM may not be diagnostic because it may give a false positive result. In such cases, a diagnosis can only be confirmed by demonstrating JE IgM in the CSF, JE virus isolation, a positive nucleic acid amplification test, immunohistochemistry, or a four-fold or greater rise in antibody titer in acute and convalescent phase serum samples.

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