

# WHO-recommended standards for surveillance of selected vaccine-preventable diseases\*

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**Vaccine Assessment and Monitoring team**  
of the Department of Vaccines and Biologicals  
(for further information please contact [epidata@who.int](mailto:epidata@who.int))

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**Copies may be requested from:**  
World Health Organization  
Department of Vaccines and Biologicals  
CH-1211 Geneva 27, Switzerland  
• Fax: + 41 22 791 4227 • Email: [vaccines@who.int](mailto:vaccines@who.int) •

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## Japanese Encephalitis

*(Updated August 2008)*

### **Rationale for surveillance**

Japanese encephalitis (JE) is a mosquito-borne viral encephalitis that occurs in temperate and tropical regions of Asia and is maintained in a cycle of virus transmission between vertebrate amplifying hosts (e.g., pigs, herons, egrets) and several *Culex* mosquito species. The greatest transmission to humans occurs in rural settings, particularly those in which agricultural practices increase the potential for breeding of vectors or infection of vertebrate hosts. In urban settings, the potential for an outbreak of JE is low, although transmission can occur. In recent decades, JE outbreaks have occurred in areas previously non-endemic for the disease. The high case fatality rate (20%-30%) and frequent residual neuropsychiatric damage in survivors (50%-70%) make JE a major public health problem.

JE is the leading form of viral encephalitis in Asia where about 50 000 cases and 10 000 deaths are reported each year, mostly among children. However, officially reported cases of JE greatly under-represent the true impact, due to incomplete surveillance in many affected areas. Among the control strategies, human vaccination has proven to be the single most effective control measure.

Infection with Japanese encephalitis virus (JEV) may be asymptomatic, or may cause febrile illness, meningitis, myelitis or encephalitis. Encephalitis is the most commonly recognized presentation, and is clinically indistinguishable from other causes of an acute encephalitis syndrome (AES). Syndromic surveillance therefore aims to identify patients with AES, and among these confirms JEV infection using standardized laboratory techniques.

In many JE affected countries, the epidemiology and public health burden of JE are poorly understood. The primary goal of disease surveillance in these countries is to characterize the epidemiology and burden of JE so as to advocate for and guide programmatic interventions.

Where JE immunization is already ongoing, the primary purpose of surveillance is to identify high-risk populations or geographical areas in need of improved vaccination coverage and areas with new disease transmission, and to document the impact of control measures.

In summary, JE surveillance is critical to characterize the epidemiology and burden of the disease, identify high risk areas for appropriate public health response and document the impact of control measures.

## *Japanese encephalitis (continued)*

### **Recommended case definition**

#### **Clinical case definition**

Clinically, a case of Acute Encephalitis Syndrome (AES) is defined as a person of any age, at any time of year with the acute onset of fever **and at least one of**: a) change in mental status (including symptoms such as confusion, disorientation, coma, or inability to talk); b) new onset of seizures (excluding simple febrile seizures<sup>1</sup>). Other early clinical findings may include an increase in irritability, somnolence or abnormal behaviour greater than that seen with usual febrile illness<sup>2</sup>.

#### **Case classification**

**AES (Suspected JE) Case:** A case that meets the clinical case definition for AES. AES cases should be classified in one of the following four ways (see Figure 1):

**Laboratory-confirmed JE:** An AES case that has been laboratory-confirmed as JE.

**Probable JE:** An AES case that occurs in close geographical and temporal relationship to a laboratory-confirmed case of JE, in the context of an outbreak.

**AES - other agent:** An AES case in which diagnostic testing is performed and an etiologic agent other than JE virus is identified.

**AES - unknown:** An AES case in which no diagnostic testing is performed or in which testing was performed but no etiologic agent was identified or in which the test results were indeterminate.

### **Laboratory criteria for confirmation**

Clinical signs of JE are indistinguishable from other causes of AES. Laboratory confirmation is therefore essential for accurate diagnosis of JE. Detection of IgM antibody by capture ELISA in cerebrospinal fluid (CSF) or serum reaches  $\geq 95\%$  sensitivity 10 days after onset of first symptoms (see note below).

The recommended method for laboratory confirmation of a JE virus infection is:

1. Presence of JE virus-specific IgM antibody in a single sample of CSF or serum, as detected by an IgM-capture ELISA specifically for JE virus<sup>3</sup>.

In addition, any of the following laboratory criteria is confirmatory for JE:

2. Detection of JE virus antigens in brain tissue by immunohistochemistry or immunofluorescence assay; OR

<sup>1</sup> A simple febrile seizure is defined as a seizure that occurs in a child aged 6 months to less than 6 years old, whose only finding is fever and a single generalized convulsion lasting less than 15 minutes, and who recovers consciousness within 60 minutes of the seizure.

<sup>2</sup> JE virus infection can also sometimes present with a meningitis syndrome or an acute limb paralysis syndrome, which are not covered in these clinical case definitions.

<sup>3</sup> Further confirmatory tests (e.g., looking for cross-reactivity with other flaviviruses circulating in the geographical area) should be carried out when: a) There is an ongoing dengue or other flavivirus outbreak; b) when vaccination coverage is very high; c) or in cases in areas not having epidemiological and entomological data supportive of JE transmission.

## *Japanese encephalitis (continued)*

### **Laboratory criteria for confirmation** *(continued)*

3. Detection of JE virus genome in CSF, serum, plasma, blood<sup>4</sup>, or brain tissue by reverse transcriptase Polymerase chain reaction (PCR) or an equally sensitive and specific nucleic acid amplification test; OR
4. Isolation of JE virus in CSF, serum, plasma, blood<sup>4</sup> or brain tissue; OR
5. Detection of a four-fold or greater rise in JE virus-specific antibody as measured by hemagglutination inhibition (HI) or plaque reduction neutralization assay (PRNT) in serum collected during the acute and convalescent-phase of illness. The two specimens for IgG should be collected at least 14 days apart. These should be performed in parallel with other flaviviruses as indicated in footnote 3.

#### **Note:**

- CSF is the preferred sample for diagnosis of JE.
- The large majority of JE infections are asymptomatic. Therefore, in areas that are highly endemic for JE, it is possible to have AES due to a cause other than JE virus and have JE virus-specific IgM antibody present in serum. To avoid implicating asymptomatic JE as the cause of other AES illnesses, sterile collection and testing of a CSF sample from all persons with AES is recommended when feasible.
- A serum sample should be obtained at admission. Because it may not yet be positive in a JE-infected person, a second serum sample should be collected at discharge or on the 10th day of illness onset (usually around 7 days after admission) or at the time of death and tested for presence of JE virus specific IgM.
- It is not necessary to test all specimens in a normal seasonal outbreak of JE after the outbreak has been confirmed by laboratory testing. If the outbreak is not an expected seasonal outbreak, or there are unusual epidemiological features (e.g. age distribution of cases not consistent with pattern of JE infection), testing of CSF is especially important, as an encephalitis outbreak could be due to other etiologies.

### **Recommended types of surveillance**

JE surveillance should be conducted year-round. Where feasible, surveillance for and reporting of JE should be performed within the context of integrated disease surveillance, and linked synergistically with similar surveillance activities such as those for acute flaccid paralysis (AFP) or meningitis.

#### **A. In all Asian countries:**

Comprehensive syndromic surveillance for acute encephalitis syndrome (AES) with aggregate reporting is recommended. In sentinel hospitals, surveillance should be case-based with specimens collected for laboratory confirmation. The number of sentinel hospitals can be gradually increased if feasible logistically.

<sup>4</sup> Detection of virus genome or virus isolation in serum, plasma, or blood is very specific for JE diagnosis; however, it is not sensitive as virus levels are usually undetectable in clinically ill JE cases. Therefore a negative result by these methods should not be used to rule out JE in a suspected case. Similarly detection of virus genome or virus isolation in CSF is usually only found in fatal cases and therefore not very sensitive and should not be used for ruling out a diagnosis of JE.

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## *Japanese encephalitis (continued)*

### **Recommended types of surveillance** *(continued)*

#### **B. In Asian countries where a high level of JE control has been achieved:**

Surveillance should be case-based throughout the country and include laboratory confirmation of all suspect cases.

Regardless of the type of surveillance, reporting should be weekly or monthly and include "zero-reporting" (i.e. no blanks should be left in the reporting forms, a zero should be indicated when there are no cases detected). Outbreak investigations should be initiated if there is a sudden increase in cases or if cases reported are different from historical information, in terms of season, geographical area, age group, or case fatality.

### **Recommended minimum data elements**

#### **Aggregated data**

- Number of cases and deaths by week/month
- Number of cases by age group, sex and immunization status
- Number of cases by state/province

#### **Case-based data**

- Unique identifier
- Age
- Sex
- Geographical area
- Travel history over the past 2 weeks
- Ever immunized against JE; 1 = yes; 2 = No; 9 = unknown.
- If yes, number of doses administered.
- If yes, type of JE vaccine (most recently received).
- Date of last JE immunization
- Date of onset of first symptoms
- Fever: 1 = yes; 2 = No; 9 = unknown.
- Change in mental status: 1 = yes; 2 = No; 9 = unknown.
- Seizure: 1 = yes; 2 = No; 9 = unknown.
- Date CSF sample taken
- Date serum sample 1 taken
- Date serum sample 2 taken
- Autopsy specimen taken; 1 = yes; 2 = No; 9 = unknown.
- Clinical diagnosis: \_\_\_\_\_

## *Japanese encephalitis (continued)*

### **Recommended minimum data elements** *(continued)*

Depending on which laboratory tests used for serum or CSF:

- IgM serum 1 results: 1 = positive; 2 = negative; 3 = not tested; 9 = unknown.
- IgM serum 2 results: 1 = positive; 2 = negative; 3 = not tested; 9 = unknown.
- IgM CSF results: 1 = positive; 2 = negative; 3 = not tested; 9 = unknown.
- Virus detection (PCR, virus isolation, immunohistochemistry) results: 1 = positive; 2 = negative; 3 = not tested; 9 = unknown.
- HI or PRNT results on acute and convalescent sera: 1 = positive (4 fold rise or greater); 2 = negative (<4 fold rise); 3 = not tested; 9 = unknown.
- Date serum 1 results reported.
- Date serum 2 results reported.
- Date CSF results reported.
- Date virus detection results reported.
- Final classification: 1= laboratory confirmed JE; 2= probable JE; 3 = AES unknown; 4 = AES other agent
- Status at discharge: 1 = alive; 2 = dead; 9 = unknown.
- Date of death or discharge

### **Recommended data analyses, presentations, reports**

#### **Aggregated data**

- Number and incidence of suspected cases by week, month, year, age group, and geographical area
- Number and incidence of confirmed cases by week, month, year, age group, and geographical area
- JE vaccine coverage by year and geographical area.
- Percentage of cases vaccinated and unvaccinated
- Completeness/timeliness of monthly reporting by geographical area.

**Case-based data** – same as aggregated data plus the following:

- Suspected JE (AES) and confirmed cases age-specific, gender-specific, geographical area-specific, and immunization status-specific incidence
- Percentage of suspected cases with CSF and/or serum specimens
- Percentage of cases with serum ten or more days after onset of illness (when the testing methodology is IgM-capture ELISA)
- Case fatality ratio
- Final classification of all suspect JE (AES) cases.
- Proportion of AES attributed to JE.

#### **Performance indicators of surveillance quality**

The following targets are for countries with a well established AES surveillance system (Table 1 and Table 2). Countries commencing with JE surveillance may set intermediate targets.

## Japanese encephalitis (continued)

### Recommended data analyses, presentations, reports (continued)

**Table 1: Targets for countries with established surveillance systems**

Indicator	Target
Completeness of monthly reporting	≥ 90%
Timeliness of monthly reporting	≥ 80%
Minimal AES rate per 100,000 population	> 2/100,000
Percentage of serum samples taken a minimum of 10 days after onset (when the testing methodology is IgM-capture ELISA)	≥ 80%

In countries where a high level of JE control has been achieved, the following indicators can be helpful as managerial tools to identify areas where corrective action is needed (Table 2).

**Table 2: Indicators to assist corrective action**

Indicator	Target
Percentage of all AES cases for which specimens were collected	≥ 80% <sup>a</sup>
Percentage of CSF/serum samples reaching laboratory in adequate <sup>b</sup> condition	≥ 80%
For all tests, laboratory results reported < 1 month after receipt specimen	≥ 80%

<sup>a</sup> Only applicable for countries doing nationwide case-based surveillance.  
<sup>b</sup> "Adequate condition" means the specimen is transported using reverse cold chain and is greater than 100ul volume.

### Principal uses of data for decision-making

- Guide policy and strategies on JE control
- Assess the impact of vaccination
- Identify geographical areas or populations at high risk to further guide where immunization coverage should be improved
- Monitor the performance of surveillance
- Monitor the performance of the laboratory

## Japanese encephalitis (continued)

### Special aspects

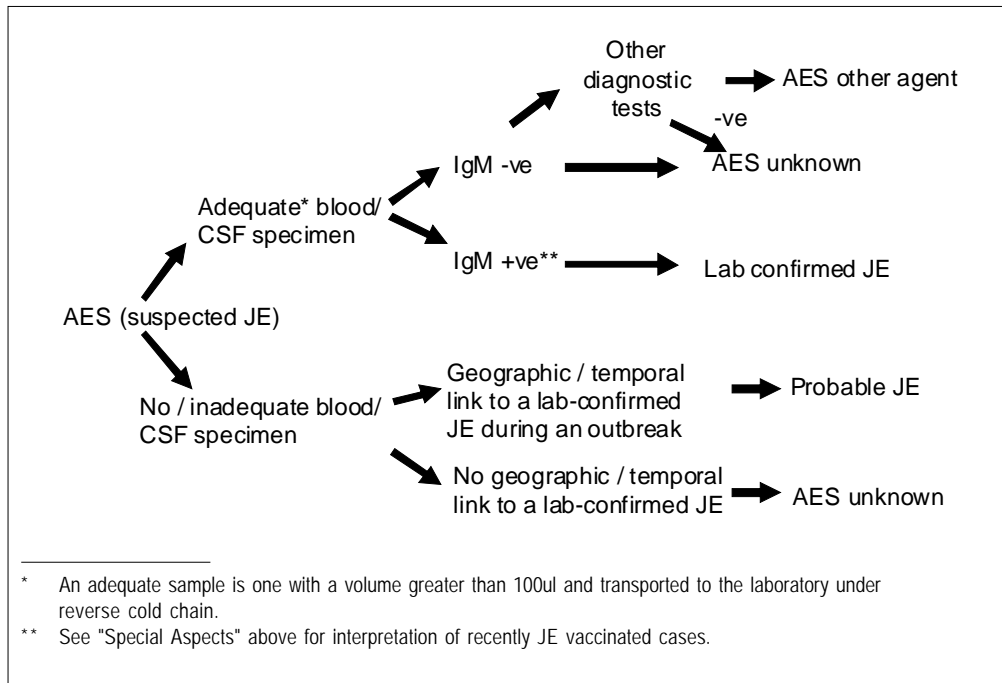
For persons vaccinated with JE vaccine within six months of illness onset, testing a single serum sample for JE IgM may not be diagnostic because any IgM detected may be vaccine-related and not disease-related. In such cases, a diagnosis can only be confirmed by demonstrating JE IgM in the CSF, JE virus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

Efforts should be made to identify other causes of AES. As a general rule, persons with acute encephalitis should undergo a lumbar puncture to obtain CSF to identify other treatable agents that may result in an illness that manifests as acute encephalitis syndrome. CSF with WBC  $\geq 1000/\text{mm}^3$  are unlikely to be due to JE or any other Arbovirus; in these cases, bacterial causes of purulent meningitis such as *Haemophilus influenzae*, *Neisseria meningitidis*, or *Streptococcus pneumoniae* should be considered. In malaria transmission areas, malaria testing should be carried out to rule out cerebral malaria. Health care providers should also rule out Herpes encephalitis, if possible, as it is a treatable cause of AES.

In patients with central nervous system (CNS) disease, there is a clear overlap between those that meet the case definition for "acute encephalitis syndrome" and those that meet the case definition for "bacterial meningitis". It is well recognized that patients with JE can present with signs of meningism. Approaches to encephalitis and meningitis surveillance are also similar, with collection of a CSF specimen for definitive diagnosis. Integration of surveillance for meningitis and encephalitis may be appropriate to help streamline program logistics, ensures case detection is as complete as possible, and to make the best use of available resources. Integrated meningoencephalitis surveillance, for example, could enable data collection for a variety of CNS diseases for which an effective public health control measure - (immunization) is available (e.g. JE, *Haemophilus influenzae* type b, *Streptococcus pneumoniae*, *Neisseria meningitidis*). Public health priorities in country, availability of viral and bacterial diagnostics, and access to testing may all determine the appropriateness of an integrated approach.

*Japanese encephalitis (continued)*

**Figure 1: Final classification scheme for AES cases**



A suspected JE (AES) can also be a suspected case of bacterial meningitis (see bacterial meningitis section for definitions). In this event, a CSF/blood sample should be sent to both a bacteriology and a virology laboratory to allow rapid and appropriate case management and classification.