Measuring effectiveness and impact of Japanese encephalitis vaccination
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Acknowledgements

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<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
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<tbody>
<tr>
<td>AES</td>
<td>Acute Encephalitis Syndrome</td>
</tr>
<tr>
<td>CDIBP</td>
<td>Chengdu Institute of Biological Products</td>
</tr>
<tr>
<td>CSF</td>
<td>cerebrospinal fluid</td>
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<tr>
<td>DALY</td>
<td>disability-adjusted life years</td>
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<tr>
<td>ELISA</td>
<td>enzyme-linked immunosorbent assay</td>
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<tr>
<td>EPI</td>
<td>Expanded Programme on Immunization</td>
</tr>
<tr>
<td>GMP</td>
<td>Good Manufacturing Practice</td>
</tr>
<tr>
<td>IRB</td>
<td>institutional review board</td>
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<tr>
<td>IRR</td>
<td>incidence rate ratio</td>
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<tr>
<td>JE</td>
<td>Japanese encephalitis</td>
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<tr>
<td>JEV</td>
<td>Japanese encephalitis virus</td>
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<tr>
<td>LP</td>
<td>lumbar puncture</td>
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<tr>
<td>OR</td>
<td>odds ratio</td>
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<tr>
<td>PIE</td>
<td>Post-Introduction Evaluation</td>
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<tr>
<td>RCT</td>
<td>randomized controlled trial</td>
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<tr>
<td>RR</td>
<td>relative risk</td>
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<tr>
<td>UNICEF</td>
<td>United Nations Children’s Fund</td>
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<tr>
<td>VPD</td>
<td>vaccine-preventable disease</td>
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<td>WHO</td>
<td>World Health Organization</td>
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Japanese encephalitis (JE) is a vector-borne zoonotic viral disease. JE virus (JEV) is the leading cause of viral encephalitis in Asia. As JE surveillance is not well established in many countries, and laboratory confirmation is challenging, the true extent and prevalence of the virus and burden of disease are not well understood. It is estimated that 67,900 clinical cases of JE occur annually with approximately 13,600 to 20,400 deaths, and an overall incidence rate of 1.8/100,000 in the 24 countries with JE risk (1). In areas where JE is a public health priority, the World Health Organization (WHO) recommends the use of JE vaccine in one-time catch-up campaigns in the primary target population, as defined by local epidemiology (typically children aged <15 years), followed by incorporation of JE vaccine in routine childhood immunization programmes.

Recent years have seen an unprecedented worldwide increase in the introduction of new vaccines, such as JE vaccine, into routine childhood immunization programmes. WHO recommends that the effectiveness and impact of vaccination on disease occurrence be assessed in countries that introduce vaccines, such as JE vaccine, in line with the WHO-recommended standards for surveillance of selected vaccine-preventable diseases (2). Demonstrating vaccine effectiveness and impact on disease occurrence can provide evidence to: inform and sustain vaccine policy decisions; allow parents, health-care providers and decision-makers to appreciate the benefits of vaccination, and decide on which JE vaccine/s to use; assess the programmatic use of vaccines; and monitor progress towards national and international child health goals. Though the cost of some JE vaccine products is comparatively low, the addition of new and underutilized vaccines to national immunization programmes can be challenging and expensive. There may also be competing priorities for scarce human and financial resources. There is, therefore, substantial interest among decision-makers regarding the value of JE vaccination and, importantly, the impact on health outcomes and cost-effectiveness.

A vaccine effectiveness study measures the extent by which the incidence of the target disease is reduced among vaccinated persons compared to similar unvaccinated persons when the vaccine is delivered in the context of a public health programme (i.e. it is the programmatic equivalent to vaccine efficacy measured in a clinical trial). In contrast, a vaccine impact study measures the reduction in the incidence of the target disease in a population as a consequence of a vaccination programme, compared to what the incidence would have been in the absence of the programme. Thus, vaccine effectiveness reflects vaccine performance among vaccinated individuals, while vaccine impact reflects changes in disease in a population due to a vaccination programme. Bearing in mind the pressing need for vaccine effectiveness and impact assessments, public health officials and researchers should be aware that it is essential to choose a method that takes into account clinical, lab, and surveillance capacity in any given country. The choice of design of such a study should be carefully considered.
Furthermore, the interpretation of the possible outcomes of a study or surveillance should be considered in advance of data collection. Failure to do so could result in inaccurate conclusions, or uninterpretable data, that could mislead or confuse rather than resolve or clarify the local situation.

This manual describes approaches to measuring JE vaccine effectiveness and impact on disease occurrence and a framework for determining the best methodology for measurement for different country or epidemiologic settings. The document is divided into four sections containing (i) a brief description of JE virus infections and recommended vaccines, (ii) the use of case-control studies to evaluate vaccine effectiveness and the need for laboratory confirmation for proper diagnosis in suspected JE cases, (iii) approaches to assessing JE vaccine impact using surveillance data, and (iv) conclusions summarizing recommended approaches to JE vaccine assessments. Additional tools are available in the form of draft protocols and data-collection instruments that would accompany the studies described in the main body of the document, and specifically a generic protocol for a case-control study to assess JE vaccine effectiveness against confirmed JE. This prototype protocol can be adapted, submitted to institutional review boards (IRBs) and implemented following site-specific modifications.
1. Introduction

JE virus (JEV), a mosquito-borne flavivirus, is the leading cause of viral encephalitis in Asia. JE occurs in nearly all Asian countries, whether temperate, subtropical, or tropical, and has intruded into new areas through importation of infected vectors. Currently, an estimated 3 billion people live in the 24 countries, mainly in the WHO South-East Asia and Western Pacific Regions, considered at risk of JE (3). As JE surveillance is not well established in many countries, and laboratory confirmation is challenging, the true extent and prevalence of the virus and burden of disease are not well understood and likely under-reported. It is estimated that 67 900 clinical cases of JE occur annually, with approximately 13 600 to 20 400 deaths, and an overall incidence rate of 1.8/100 000 in the 24 countries with JE risk (1). Although infection is common, severe disease is rare but can be devastating with a high rate of residual disability [709 000 disability-adjusted life years (DALY)] (4).

Approximately 15 JE vaccines are currently in use. In areas where JE is a public health priority, WHO recommends the use of JE vaccine in one-time catch-up campaigns in the primary target population, as defined by local epidemiology (typically children aged <15 years), followed by incorporation of JE vaccine in routine childhood immunization programmes in all countries where JE is endemic (5). Other than vaccination of humans, there is little evidence to support a reduction in JE disease burden from interventions such as vaccination of pigs, environmental management for vector control, and chemical control of vectors (6). Data on the population impact of vaccination programmes show significant reductions in JE cases (7). When high coverage is achieved and sustained in populations at risk of disease, JE can be greatly reduced despite the fact that the virus remains in circulation: with humans being dead-end hosts, vaccination has no impact on the zoonotic transmission cycle, hence susceptible individuals will continue to be at risk of disease even when few cases are observed.

WHO has highlighted the need for an assessment of the effectiveness of JE vaccines as well as robust and sustained disease surveillance data to monitor impact (5). These assessments are important for evaluating how well JE vaccines prevent new JE cases and for monitoring the epidemiologic patterns of JE disease after vaccine implementation and comparing the overall number of cases to the number expected had a JE vaccination programme not been implemented. This information may be useful to country health leaders and public health officials in countries where JE vaccines will be introduced in the near future, or where JE vaccines have recently been introduced.

This document outlines different methods to measure the effectiveness and impact of JE vaccine on disease occurrence. It is important to remember that data analysis and studies must be conducted using data of the highest possible quality and with the best possible epidemiological and statistical oversight. Ensuring high quality of data,
analysis and interpretation can avoid the problem of misleading or uninterpretable studies. Thus, it is essential to understand the quality of surveillance data available and to establish surveillance of the highest possible quality. If further studies are needed to provide additional information, then the appropriate study design should be judiciously selected for each given setting and purpose. The primary objective of this guide is to provide a systematic and standardized framework for measuring the effectiveness and impact of JE vaccine on disease burden, and relevant to settings with a range of surveillance, epidemiologic study capacities and financial resources. It is divided into five sections with additional tools available online (http://www.who.int/immunization/diseases/japanese_encephalitis/en/).

Section 1 is an introduction that contains a brief description of the JE disease burden, JE vaccines, and approaches to assessing their effectiveness and impact, and also a framework for deciding the most appropriate methods for the setting.

Section 2 discusses methods to measure JE vaccine effectiveness.

Section 3 describes how to measure JE vaccine impact using surveillance data.

Section 4 provides the conclusion and summary of the methods described.

1.1. Target audience and scope of the manual

This manual is primarily targeted at public health officials and scientists in countries where JE vaccines have recently been introduced or will be introduced in the near future. In these countries, this document should be useful for programme managers and technical staff in ministries of health and other agencies working in national disease surveillance and immunization services. Its purpose is to help country health planners and public health officials identify the most appropriate methods to measure the impact of JE vaccine in their particular settings, and to understand the advantages and disadvantages of each method. The manual does not provide a comprehensive description of how to carry out each method. Country officials considering a vaccine effectiveness and/or impact assessment should discuss their plans with local and regional experts, including research partners, and WHO and UNICEF colleagues. For example, if a country has no existing JE surveillance, there are resources available, through WHO and other partners, that describe how to set up such a system (7). Laboratory methods to be used to diagnose JE can be found in WHO guidance (8). If country public health officials wish to conduct a surveillance analysis or an epidemiological study (such as a case-control study), they may need to consult with an epidemiologist, statistician or other appropriately experienced person, to develop a comprehensive protocol. Interpretation of surveillance findings is particularly challenging when surveillance begins around the time of vaccine introduction. Detailed description of the interpretation of surveillance findings, or an epidemiological study, is beyond the scope of this document, but should be recognized as essential for understanding and meaningfully interpreting the impact of JE vaccine programmes.

The methods discussed in this document can be applied to a range of settings, but particular emphasis will be placed on the options for resource-limited countries whose technical capacity may be constrained by limited human and financial resources, limited routine disease surveillance infrastructure, or weak health systems.
This manual is a companion to other WHO documents on approaches to establish and strengthen surveillance systems for JE (2). The manual does not discuss methods for evaluating the impact of JE vaccine introduction on the immunization programme itself; this should be assessed through an EPI programme review. Other tools are also available that describe how to evaluate specific aspects of the immunization programme (9), such as immunization coverage surveys (10) and vaccine management assessments (11).

1.2. Why are effectiveness and impact assessments necessary?

A vaccine effectiveness study measures the extent by which the incidence of the target disease is reduced among vaccinated persons compared to similar unvaccinated persons when the vaccine is delivered in the context of a public health programme. For example, a case-control study might be used to measure the odds of vaccination among individuals with JE disease versus the odds of vaccination among those without JE disease. In contrast, a vaccine impact assessment is a study that measures changes in outcomes that are attributable to a public health intervention or programme. Using surveillance data, changes over time in laboratory-confirmed JE following JE vaccine introduction can be compared to the number of JE cases that would have been expected had a JE vaccination programme not been introduced.

Measuring the effects of newly introduced vaccines can, in principle, demonstrate vaccine effectiveness in reducing incidence of JE disease and impact on morbidity and sequelae, as well as on mortality in the field, and establish epidemiologic patterns of JE disease after vaccine implementation (Table 1). JE vaccine is not yet widely used in all endemic settings, but vaccines have had dramatic effects on disease burden in countries that have introduced JE vaccine. In Nepal, mass vaccination campaigns were conducted between 2006 and 2009 among those aged 1–15 years in some districts and among all persons ≥1 year of age in other districts, with high coverage (94% of the target population) achieved (12). Surveillance data from 2004–2009 showed the incidence of laboratory-confirmed JE following the campaigns was 1.3 per 100 000, i.e. 72% lower than the expected incidence of 4.6 per 100 000 had no campaigns had taken place (12). The greatest difference in incidence was seen in the high-risk districts and where vaccination targeted the entire population ≥1 years of age (12).

Approximately 15 JE vaccines are currently in use globally. All current vaccines are based on genotype 3 virus strains. The four major types of JE vaccines are:

1) Inactivated Vero cell-derived vaccines,
2) Live attenuated vaccines,
3) Live recombinant (chimeric) vaccines,
4) Inactivated mouse brain-derived vaccines.

The 2015 WHO JE vaccine position paper stated that mouse brain-derived vaccines should be gradually replaced by new generation JE vaccines, which have multiple advantages including with respect to reactogenicity, cost, and dose requirements (5). For the other JE vaccine types available internationally, limited vaccine effectiveness data exist. To date, effectiveness data are only available for the live attenuated
vaccine manufactured prior to the establishment of a Good Manufacturing Practice (GMP)-compliant facility. Vaccine effectiveness for the non-GMP-manufactured live attenuated vaccine was generally above 90% up to five years post-vaccination (13–16), although one study estimated vaccine effectiveness at 84% at 0–38 months post-vaccination (17). All of these studies were based on a relatively small number of cases (20–35) and used the non-GMP-manufactured product. No vaccine effectiveness data yet exist for WHO prequalified GMP-manufactured live attenuated vaccines, inactivated Vero cell vaccines, and live recombinant (chimeric) vaccines.

There is clear evidence of significant impact on JE disease of high coverage with live attenuated and inactivated mouse brain-derived JE vaccines (12, 18–23); as yet no such data are available for the inactivated Vero cell-derived and live recombinant vaccines.

**Table 1: Objectives and rationales for assessing JE vaccine effectiveness and impact**

<table>
<thead>
<tr>
<th>Objective</th>
<th>Rationale</th>
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<tbody>
<tr>
<td>Measure vaccine effectiveness on incidence of JE disease</td>
<td>• JE vaccines are licensed based on immunogenicity and not with disease endpoints. Therefore, it is important to demonstrate effectiveness against JE disease when used in routine settings.</td>
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<td>• The performance of JE vaccine from randomized trials may not be applicable to the real-world setting where limited resources may lead to immunization programme problems, such as breaks in the cold chain, alternative immunization schedules and delayed or incomplete vaccination.</td>
</tr>
<tr>
<td></td>
<td>• The effectiveness of some JE vaccines, including alternative schedules and over time, is not well characterized.</td>
</tr>
<tr>
<td></td>
<td>• Effectiveness data do not yet exist for inactivated Vero cell-derived and live recombinant vaccines.</td>
</tr>
<tr>
<td>Measure vaccine impact on JE morbidity and mortality in a routine use setting</td>
<td>• Post-introduction impact data are missing or limited in regions and settings where these vaccines have not been widely used.</td>
</tr>
<tr>
<td></td>
<td>• Economic evaluations using health impact data provide the evidence base that allows for informed decision-making and priority setting.</td>
</tr>
<tr>
<td></td>
<td>• Measured impact can form the basis for rational decisions on whether to sustain or enhance JE vaccination coverage. Such studies can also contribute to decisions on whether to introduce JE in neighbouring countries.</td>
</tr>
<tr>
<td></td>
<td>• Evidence of ongoing disease after introduction of new vaccines can reveal new or pre-existing weaknesses in vaccine-delivery systems, such as compromises in the cold chain that could reduce vaccine potency (i.e. freezing vaccines), and logistical challenges that reduce coverage (e.g. inadequate microplanning and inadequate monitoring of vaccine introduction).</td>
</tr>
<tr>
<td>Establish epidemiologic patterns of JE disease after vaccine implementation</td>
<td>• Following vaccine introduction, patterns of disease by age distribution can change. While traditionally considered a childhood disease, as cases in children decrease due to successful vaccination programmes, there is frequently a shift to a greater proportion of cases in older, unvaccinated age groups.</td>
</tr>
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</table>
WHO currently recommends one dose of live attenuated and of live recombinant JE vaccines in endemic areas (with additional doses per manufacturer recommendations for inactivated vaccines). Different dosing schedules exist across countries, where concern for vaccine failures or programmatic considerations motivates use of a second dose. However, the WHO position paper acknowledges that the need for a booster (2nd dose) of live attenuated or live recombinant has not yet been established and that vaccine effectiveness and impact studies, including vaccine failure monitoring, are needed to confirm this dosing schedule and its lasting protection (or conversely to document waning immunity). Additionally, for inactivated Vero cell-derived vaccines, further evidence is required to identify whether a booster dose may be needed in JE endemic settings.

Surveillance for vaccine-preventable diseases (VPDs) should be linked to introduction of new vaccines as part of strengthening health systems and research capacity. Rigorous measurement of the degree to which laboratory-confirmed JE cases is reduced due to JE vaccine introduction can provide reliable information to guide priorities and policy decisions. Impact assessments are most valuable when complementary programmatic information is gathered in addition to data on the reduction in disease occurrence. For example, information on challenges in vaccine delivery and cold-chain capacity provides reasons why the measured vaccine impact in terms of disease reduction may be lower than anticipated (24). Furthermore, capturing timely and valid epidemiological information to control VPDs is one of the aims of WHO (7).

1.3. Epidemiology of Japanese encephalitis

Japanese encephalitis (JE) is a mosquito-borne viral disease and the most common cause of viral encephalitis in Asia. In countries where JE is endemic, JE is thought to be a childhood disease where infection usually occurs before adolescence and confers lifelong immunity. Most infections are asymptomatic; however, clinical cases can rapidly progress to severe symptoms with an estimated 30% of survivors experiencing long-term neurologic abnormalities and serious disabilities. Of all clinical cases, 20–30% die, and the risk of severe disease and death in children younger than 10 years is even higher. Across affected Asia-Pacific countries, approximately 67 900 clinical cases of JE are documented per year; of these, an estimated 13 600 to 20 400 deaths occur annually (1). These figures are likely underestimates due to the challenges in differentiating causes of encephalitis and poor surveillance in these countries.

JE is caused by a flavivirus that is related to the West Nile, Murray Valley encephalitis and St. Louis encephalitis viruses. Five different genotypes have been identified with genotype 3 having historically been the most common; however, genotype 1 is becoming a more common circulating genotype. The JE virus circulates in zoonotic cycles in mosquitoes, pigs and birds. Culex mosquitoes, the primary vectors found in most Asian countries, breed in stagnant pools of water and bite at night. Pigs and birds serve as animal reservoirs for the virus, making elimination of JE not feasible and vaccination the most effective method for preventing the spread of disease. Transmission from human-to-mosquito-to-human is not possible because of low levels of viraemia found in humans, making humans dead-end hosts. Because of this, JE vaccine introduction does not offer any indirect protection benefits.
The actual burden of JE is not known. Reliable diagnosis of JE is challenging in rural settings, where JE predominantly circulates. In addition, the estimate of 67,900 cases of JE per year may be an underestimate due to insufficient surveillance data gathered from the few numbers of participating sentinel hospitals. Other issues that contribute to producing uncertain estimates include (i) a lack of standardized laboratory testing methods (ii) incomplete collection of clinical samples; and (iii) the co-circulation of other cross-reactive flaviviruses (especially dengue viruses) in some JE-endemic areas (3). More extensive surveillance systems utilizing laboratory diagnostic techniques that are highly specific for JE are needed to generate a more accurate estimate of the burden of disease. Improved surveillance data are needed to better capture the burden of JE and to characterize all areas at risk of disease. Some countries have detected JE cases in some rural settings where it has not been documented before and even in some urban areas, including Kathmandu, Nepal, and New Delhi, India, which is evidence that JE transmission patterns seem to be extending into cities (25, 26). Tracking the changing epidemiology of JE in neighboring areas and countries with similar ecological profiles may be useful to determine true JE disease burden (3).

Incidence of disease can fluctuate as JE transmission varies from year to year. Historically thought to be a childhood disease, the annual incidence of JE in those younger than 15 years of age is an estimated 5.4 per 100,000 while approximately 0.6 cases per 100,000 is observed in the ≥15 year age group (1). Due to a large variation across regions, incidence in those younger than 15 years of age may be as high as an estimated 12.6/100,000 in some high incidence areas in China and the Democratic People’s Republic of Korea. With the introduction of JE vaccines, the numbers of cases in children decrease and a shift toward a greater proportion of cases in older, unvaccinated age groups is often observed. In some countries even without vaccination programs, such as Bangladesh, a substantial proportion of cases are in those older than 15 years of age (27). In Thailand, 69% of individuals 20–24 years had protective levels of neutralizing antibody, and by 40 years of age, approximately 90% of the population had protective levels of antibody titers (28). Among a sample of unvaccinated 12–18 year-olds in the Philippines, the seroprevalence rate was just 44% (29). These data suggest an important proportion of adults are still susceptible. How severity differs by age group is not well understood, in part because of the lack of follow up of many cases. The age-specific incidence may be considered when designing immunization programs, and some countries, such as Nepal, have chosen to conduct campaigns in which all individuals over one year of age were vaccinated in select areas.

1.4. Japanese encephalitis vaccines

1.4.1. Inactivated Vero cell-derived vaccines

In recent years, a variety of inactivated Vero cell JE vaccine products have been developed and licensed. An inactivated Vero cell vaccine, IXIARO® in the US and Europe and JESPECT® in Australia and New Zealand, was first licensed in 2009 and is the most widely available JE vaccine (3). This alum-adjuvanted vaccine is based on the SA 14-14-2 strain derived from Vero cells and contains phosphate buffered saline as excipient and protamine sulphate in residual amounts (3, 5). Production of this vaccine was transferred by technology agreement to another manufacturer and was licensed in
India (JEEV®) in 2012 (3, 5). JEEV® was first WHO prequalified in July 2013 (3), for limited age groups, and since January 2016 has been prequalified for 1–49 year-olds. Other available inactivated Vero cell-derived products are produced in Japan, China, and India, which use different viral strains and are not widely distributed (5).

1.4.2. Live attenuated vaccines

The live attenuated SA 14-14-2 vaccine is derived from primary hamster kidney (PHK) cells and has been licensed in China since 1988 (CD.JEVAX®) (3, 5). It is now licensed and used in several countries in Asia (5). It contains gelatin, saccharose, human serum albumin, and sodium glutamate as excipients (3). In partnership with PATH, the manufacturer, Chengdu Institute of Biological Products (CDIBP) built a new GMP-compliant facility (approved by the Chinese Food and Drug Administration in 2011), and in October 2013, the CDIBP live attenuated vaccine was WHO prequalified for individuals starting at 8 months of age (3). Two other live attenuated vaccines are manufactured in China but are not exported (3).

1.4.3. Chimeric vaccines

A live attenuated, recombinant chimeric JE vaccine, IMOJEV®, was first licensed in Australia in 2010 (3, 5). In September 2014, it was prequalified by the WHO and is now also licensed and in use in several Asian countries (3, 5). At the time of publication of this document, it is licensed for individuals 9 months of age and older (3). It was created using recombinant DNA technology by replacing the premembrane (prM) and envelope (E) coding sequences of the yellow fever live attenuated 17D vaccine virus with the SA 14-14-2 live attenuated JE vaccine virus (3). Mannitol, lactose, glutamic acid, potassium hydroxide, histidine, human serum albumin, and sodium chloride are excipients (3).

1.4.4. Inactivated mouse brain-derived vaccines

First developed in the 1960s, many countries have produced or continue to produce their own inactivated mouse brain-derived vaccine products (3). In 2015, the WHO JE vaccine position paper stated that mouse brain-derived vaccines should be gradually replaced by newer generation JE vaccines (5, 30). Given this, evidence of vaccine effectiveness and impact for inactivated mouse brain-derived vaccines is not a priority.

1.5. How to approach JE vaccine assessment in the context of routine immunization and mass immunization campaigns

JE vaccine assessments include both vaccine effectiveness and impact studies. WHO recommends an assessment of the effectiveness and impact of introduction of JE vaccines coupled with strong JE disease surveillance.

1) A vaccine effectiveness study measures the extent by which the incidence of laboratory-confirmed JE disease is reduced among vaccinated persons compared to similar unvaccinated persons when the vaccine is delivered in the context of a public health programme.
2) A vaccine impact assessment is a study that measures changes in outcomes that are attributable to a public health intervention or programme utilizing robust surveillance data (e.g. changes in JE incidence following JE vaccine introduction).

In other words, vaccine effectiveness reflects vaccine performance among vaccinated individuals, while vaccine impact reflects changes in disease in a population due to a vaccination programme. Within these two analytical strategies, there are a number of common study designs that are used and these will be discussed in Sections 2 and 3 (Table 2).

Vaccine effectiveness studies estimate the proportion of a given outcome preventable by vaccine when used in an endemic setting. Many study design options exist, but based on the rarity of JE disease, the case control study design is the preferred approach and highlighted in this manual. As laboratory-confirmation of JE disease is required, vaccine effectiveness studies may include cases from either hospitals involved in ongoing active surveillance or sentinel hospitals recruited for the purpose of the study.

Surveillance of laboratory-confirmed JE is recommended to assess vaccine impact by evaluating trends in disease burden data over time. As a general rule, population-based or sentinel hospital surveillance is conducted based on laboratory-confirmation of the causative organism from clinical specimens. Using surveillance data to assess vaccine impact on disease outcomes requires consistent and reliable surveillance data, ideally for at least two years before and at least three years after vaccine introduction, for accurate measurement of disease burden changes. Passive national surveillance systems that are laboratory-based can also be used; however, passive surveillance is likely to underestimate disease occurrence.

Vaccine effectiveness and impact assessments are not meant to be exclusive, and countries may choose to do both, since these two strategies have different functions. Choosing the strategy most appropriate for a country depends on the chosen outcome and the data sources that are available. Choice of which health impact to be measured will be discussed in Section 4, and the sources of data that can be used will be discussed in the sections on each respective study design.

<table>
<thead>
<tr>
<th>Assessing vaccine effectiveness</th>
<th>Assessing vaccine impact by evaluating trends in disease burden data</th>
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<tbody>
<tr>
<td>• Case-control study</td>
<td>• Population-based, active surveillance</td>
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<td></td>
<td>• Sentinel site surveillance</td>
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<td></td>
<td>• Periodic surveys</td>
</tr>
<tr>
<td></td>
<td>• Laboratory-based passive national surveillance</td>
</tr>
</tbody>
</table>
1.6. Summary and key points

1) In areas where JE is a public health priority, JE vaccine is recommended for use in one-time catch-up campaigns in the primary target population, as defined by local epidemiology (typically children aged <15 years), followed by incorporation of JE vaccine in routine childhood immunization programmes.

2) Public health officials are encouraged to assess the vaccine effectiveness and/or impact of JE vaccine as an important component of the vaccine introduction activities. The effect of JE vaccine on reducing the number of new laboratory-confirmed JE cases can be measured through a number of study designs. This manual highlights a case-control design. Surveillance of JE, ideally laboratory-confirmed, is recommended for monitoring trends in JE disease burden over time.
2. Measuring JE vaccine effectiveness

Vaccine *efficacy* is defined as the proportionate reduction in disease incidence attributable to a vaccine when given under ideal conditions, such as those found in a controlled vaccine trial. By contrast, we define vaccine *effectiveness* as the proportionate reduction in disease incidence attributable to vaccination under real-world conditions, which includes the effect of programmatic factors, such as injection techniques, reduced vaccine potency following inappropriate storage, pre-existing immunity to the target illness such as that conferred by a previous episode of the target illness, population characteristics such as malnutrition, and any other factors that distinguish a community immunization programme from the controlled setting of a vaccine trial. This definition, which corresponds to what has also been called “field efficacy,” does not capture low population effect of an immunization programme caused by low vaccination coverage, which is an important cause of suboptimal impact of vaccination programmes in many low- and middle-income countries. Effectiveness studies can also capture vaccine performance over a longer period of time than typically done in clinical trials. There are a number of approaches to measuring vaccine effectiveness, including cohort studies, case-control studies, and cluster-randomized studies.

Specific to JE, a vaccine effectiveness study measures the extent by which laboratory-confirmed JE disease is reduced among vaccinated persons compared to similar unvaccinated persons when the vaccine is delivered in the context of a public health programme in a JE-endemic setting. After JE vaccine is introduced into a population, post-licensure, observational studies are needed to evaluate the performance of the vaccine in the field with disease endpoints rather than immunological endpoints, with consideration of possible waning immunity. Observational studies reflect routine use, and the effectiveness estimates that are obtained are influenced by the practical issues, such as vaccine cold chain, delivery, and potential effects that vary between population groups. Vaccine effectiveness studies can also answer specific questions related to the immunization programme, such as coverage, timeliness and an estimation of the relative effectiveness of different dosing schedules.

Because JE is a relatively rare disease, a case-control design is most appropriate to measure vaccine effectiveness; the costs and time required to measure effectiveness using other methods is typically excessive and prohibitory. When carrying out such studies, it is strongly advised that literature and experts be consulted to properly address study design, surveillance protocols, sample size and selection procedures, bias and appropriate adjustment for confounders, all of which may not be recognized in advance. The remainder of this section of the manual will address the case-control study design.
### 2.1. Case-control studies

Case-control studies have become a widely used approach to document JE vaccine effectiveness (13–16, 31–34). In a case-control study, individuals with laboratory-confirmed JE disease (cases) are ascertained through active or passive surveillance, and one or more appropriate controls (individuals without the disease) are selected for each case. Vaccination status is optimally determined independently of recruitment of the cases and controls. Vaccine effectiveness is calculated using the appropriate formula and using the odds ratio (OR) to approximate the relative risk (RR), assuming the disease is rare. In cases where disease is rare, the OR, and its corresponding confidence interval, is very similar to the RR (and its confidence interval) which cannot be directly calculated in case-control studies. Once an OR is measured, there is a straightforward formula to calculate vaccine efficacy. The use of regression-based statistical models to account for factors such as differences in demographic characteristics, economic level or access to or use of health care that may exist between cases and controls may account for confounding and produce adjusted effectiveness estimates that better approximate vaccine protective effect than unadjusted estimates. If controls are appropriately identified concomitantly with the cases, temporal variation in JE disease is expected to be adequately accounted for.

In contrast to cohort studies, case-control studies represent a more feasible methodology for rare events, such as laboratory-confirmed JE, because details like vaccination history are needed only for the cases and a relatively small number of controls from the population under evaluation. (Please refer to the online generic protocol for a more complete discussion of choosing controls.) Compared to other study designs, case-control studies can be cost-effective and time efficient.

Notwithstanding the advantages cited above, case-control studies are susceptible to confounding and bias. Just like cohort studies, case-control studies will not capture reduced vaccine impact due to suboptimal coverage, and cannot provide a picture of overall vaccine programme performance; cluster-randomized trials (including stepped-wedge design) and, to some extent, surveillance programmes that track disease rates over time, can provide that information. In addition, because a number of factors can be related to both receipt of vaccine and disease risk—such as age, access to care and socioeconomic factors—care must be taken to reduce the influence of these potential confounders on vaccine effectiveness estimates by appropriate statistical adjustment.

Case control studies are sufficiently complicated and complex so it is important to work with experts and appropriate personnel to plan for the necessary time, resources, and effort to conduct these studies. Researchers should ensure they are well prepared with sufficient expertise, as these studies should only be carried out if they can be conducted well. Generally, vaccine coverage should be around 20–80% before a case-control study should be conducted; though high vaccine coverage is programmatically desirable, in the context of a vaccine effectiveness study, high vaccine coverage may result in a biased estimate, where those who do not get vaccinated may be different from those who do in ways that could be associated with higher or lower risk of JE disease. A number of preparatory measures to ensure sufficient understanding of the local context must be taken before designing and implementing a case-control study, including those listed in Table 3.
Table 3: Preparatory measures for assessing JE vaccine effectiveness

<table>
<thead>
<tr>
<th>Preparatory Action</th>
<th>Rationale</th>
</tr>
</thead>
</table>
| Understand factors that affect case ascertainment:  
  – Source population for cases  
  – Healthcare seeking behaviour  
  – Barriers to care  
  – Determinants of hospitalisation  
  – Diagnostic capacities  
  – Case definition |  
  Accurate definition and identification of cases is needed in order to minimize bias in selection of cases and to avoid misclassification of those with and without JE disease.  
  Understanding the population from which cases are derived is important for the identification of appropriate controls. |
| Pathogen-specific study endpoints generally preferred | Having a clear and specific case definition aids in avoiding misclassification of those with and without JE disease. |
| Potential sources of controls | Source population for controls should be the same as cases in order to minimize selection bias. |
| Vaccine coverage estimate | Information about the vaccine coverage is useful to ensure inclusion of sufficient numbers of individuals who are and are not vaccinated. |
| Factors affecting vaccination (geography, age, sex, socioeconomic status, etc.) | Information aids in understanding whether those who get vaccinated are different from those who do not, which may bias results.  
  Estimate should account for confounding variables related to both JE disease and vaccination status. |
| Ability to ascertain vaccination status | Accurate ascertainment of vaccination status helps to avoid misclassification of exposure. Procedures for ascertaining vaccination status should be the same for both cases and controls to minimize bias. |
| Identify key confounding factors and how to measure them | Estimate should account for confounding variables related to both JE disease and vaccination status. |
| Pilot test enrolment procedures and data collection tools | Detailed procedures and appropriate tools help to ensure study implementation and data collection are conducted to ensure the highest quality. |

A more detailed description of how to conduct case-control studies to assess JE vaccine effectiveness against JE disease is included in the online generic protocol.

2.2. Case finding and identification

Cases should be defined as clinically diagnosed acute encephalitis syndrome (AES) or meningoencephalitis AND laboratory-confirmation through detection JEV-specific IgM antibody in a single sample of cerebrospinal fluid (CSF). Detection of JE IgM
in CSF is considered the gold standard for diagnosis of JE, and this is required in order to minimize risk of false positive results, or the inclusion of individuals as cases who are not true cases. In the context of a case-control study, detection of JE IgM in serum samples might not be specific enough for JE, and could also indicate 1) simultaneous asymptomatic JEV infection and encephalitis due to another cause; 2) persistent IgM following recent (e.g. <6 months) JE vaccination and encephalitis due to another cause; or 3) false positive test results due to cross-reactivity with another co-circulating flavivirus (e.g. dengue virus or West Nile virus).

As for all case-control studies, a clear case definition is critically important, and only incident (new) cases should be included. In a predefined time period for a case-control study, individuals may serve as both cases and controls. For example, an individual may first be defined as a new case. S/he may then fully recover from the disease and once healthy again for at least 6 months, may then serve as a control. Conversely, an individual may first be selected as a control and later be identified as a case if s/he becomes ill and fulfills the case definition for JE. Not allowing such individuals to be included as controls may bias the measured effect of the vaccine. Defining the population from which controls are drawn to ensure that they are a representative sample of the source population that gave rise to the cases is critically important.

2.3. Choosing the location

Cases identified in a surveillance system should ideally be all of the cases in the population. In most resource-poor countries, identifying cases in hospital settings is often the most feasible strategy, since clinical evaluation and diagnostic testing is more readily available in these than in other settings. Controls should be individuals from the same communities (e.g. villages or neighbourhoods) as cases. Both hospitals and community sites included in the study should have:

- populations that are representative of the target population and large enough to achieve the desired or required case numbers;
- registries, clinical records, or residents with vaccination cards to allow documentation of vaccination;
- capacity to conduct a methodologically strong study.

During hospital site selection, it is important to ensure hospitals have the capacity to support the study, including:

- good surveillance for case finding;
- supporting infrastructure and qualified and trained health care providers able to perform lumbar punctures to obtain CSF specimens;
- supporting infrastructure and qualified and trained laboratory personnel able to conduct ELISA testing to diagnose JE.

If sites do not have all the characteristics listed above, the capacity of sites should be enhanced prior to the start of the study. If resources or time constraints preclude making the necessary improvements to sites, the study should not be conducted or sites
that do not require such improvement should be sought. Conducting a JE case-control study in sites lacking the necessary requirements may expose participants to undue risks and render study findings invalid and uninterpretable.

In addition, the status of JE vaccine documentation and retention of records in the community should be considered when selecting sites for a case-control study. The fact that JE vaccine is often given in mass campaigns where vaccination records are frequently limited or even unavailable presents a particular challenge for JE vaccine exposure ascertainment. Mass campaigns for JE vaccination in a community do not preclude it as a site for a potential case-control study; however, special consideration should be given to assessing the reliability of existing records or maternal/child reports of vaccination status in these settings. A similar challenge is encountered if the aim is to monitor JE vaccine effectiveness for a longer period of time following vaccination to assess whether protection wanes. In this situation, retention of vaccination records may be greatly reduced.

2.4. Choosing the ages for inclusion

The study population should include only those who are eligible to receive JE vaccine through the national immunization programme. All age-eligible individuals (without contraindications for vaccination) identified at one of the surveillance sites during the study period should be eligible for inclusion. When conducting case-control studies, individuals should be included in an assessment only once they have had an opportunity to be vaccinated. The age range of the study population may vary depending on a country’s JE vaccination programme. For example, if the selected country provides JE vaccines in infancy as part of the routine immunization schedule, only those who had an opportunity to be vaccinated when they were infants should be included. The ages selected should also reflect the time since vaccination that is of interest. For example, if vaccine effectiveness five years post-vaccination is the outcome of interest, children at the appropriate age during the study who have been vaccinated or eligible to have been vaccinated five years earlier should be included (if vaccination records are available and reliable).

2.5. Informed consent

At the time of enrolment, the study staff should provide potential participants or parents/guardians of participating children with information about the study and review with them an informed consent document. Study staff should answer any questions the potential participants or the parents/guardians may have about the study. Participants should be notified that all information collected as part of this study should be kept confidential. Private details should be kept in locked cabinets or offices, and study collection tools should include only study identification numbers and not names. Study staff should explain that participation is entirely voluntary and can be withdrawn at any time without any repercussions. Potential participants should be informed of all benefits and risks to participating. Since laboratory confirmation of JEV-specific IgM antibody in a single sample of cerebrospinal fluid (CSF) is the preferred method of diagnosis, the risks involved with a lumbar puncture (LP) should be communicated clearly to potential participants. However, in most settings, an LP to
obtain a CSF sample is the standard of care and therefore, the study should not pose more than minimal added risks compared to care that would be received outside of the study. Further details regarding consent procedures and forms are provided in the online generic protocol.

2.6. Vaccination status ascertainment

“Vaccinated” is typically defined as two weeks following receipt of 1 dose of JE vaccine. Ascertaining whether a child has been vaccinated can be extremely difficult. In study designs with cases and controls, vaccination status must be gathered from cases and controls in a non-differential way (i.e. at the same time point and using the same method). To reduce recall bias in the study, it is necessary to obtain accurate vaccination records for all study participants.

Vaccination histories that are given verbally should ideally be confirmed with written records:

- vaccination cards (e.g. Expanded Programme on Immunization or EPI cards);
- provider records (hospitals, health clinics), although it can be more difficult to obtain vaccination records from private medical facilities.

Confirmation with written records may be especially challenging in settings where mass campaigns have been conducted or in case-control studies conducted five years or longer after vaccination to evaluate whether protection wanes. If a history of receiving vaccine cannot be confirmed and the caregiver cannot confirm that the child was ever/never vaccinated, the participant should typically be excluded from the study. However, unvaccinated children are more likely to give only verbal history of no vaccination; if these children are excluded, this can bias the vaccine effectiveness estimates. All cases and controls should be retained, but replacement cases and controls should be obtained for those who say they have been vaccinated but do not have documentation. This allows calculation of effectiveness with both the original set of cases as well as with the set with replaced cases, and this can help clarify if there would be bias in excluding cases.

2.7. Minimizing bias and limitations

Potential sources of bias include issues in the design and execution of case-control studies related to case definition and case ascertainment, ascertaining vaccination status, comparability of cases and controls, and selection of controls. Consistent case definitions and accurate verification of vaccination history are critical to obtaining valid results from case-control studies. A lack of specificity in case ascertainment may lead to bias. Sensitivity is not as critical, though lower sensitivity may lead to a loss of power. Case ascertainment should include either all cases in the defined location (hospital or community) and time window, or else a random subset of all cases. If the study is hospital-based, the catchment area should be well defined, and cases falling outside the catchment area should be excluded. Ascertainment of vaccination status can be a challenging aspect in many low-income and middle-income countries, where vaccination records may be limited or of poor quality. Ideally vaccination status should be
linked for both cases and controls to a vaccination register. In general, both guardian and child recall are not sufficiently reliable for a vaccine effectiveness study. Ideally, those identifying cases and controls should be blinded to vaccination status to ensure that ascertainment of case status does not affect ascertainment of vaccination status and to minimize information bias.

A possible threat to the validity of a case-control study is the risk of selection bias that can result from differences in the source population from which cases and controls are drawn. The appropriate methods to select controls depend on the methods used to select cases. Data should always be collected on factors likely to confound the vaccine effectiveness estimate (e.g. those associated with disease risk and likelihood to be vaccinated, such as socio-economic status). In selecting cases and controls, it should always be ensured that the inclusion and exclusion criteria are the same, except for confirmed JE diagnosis (only for cases). For population-based case-control studies, selection bias is less likely because the population from which the cases come is clearly defined. For hospital-based case-control studies, selection bias is more likely because the population from which the cases come is more difficult to define. For hospital-based studies, options for the control group include patients admitted to the same hospital for other diseases or neighbors of cases. A challenge with hospital-based controls is that individuals hospitalized due to illness from vaccine-preventable diseases need to be excluded so as not to introduce bias from a control population that might be less likely to receive vaccines, including JE vaccine. Specific to JE, because laboratory confirmation of JEV-specific IgM antibody in a single sample of CSF is the preferred, yet resource intensive, method for case identification, cases would likely be identified in a hospital (rather than an outpatient facility or in the community). To ensure controls are not precluded from receiving JE vaccination due to underlying chronic illness, community-based selection of controls for a JE case-control study is recommended. In order to mitigate the risk of recruiting different source populations of hospital-based cases and community-based controls, matching cases and controls on location of residence (village or neighborhood) and age is important. Matching cases and controls is discussed in further detail in the online generic protocol. In addition, efforts to gather individual and population-level demographic information to provide information on non-participation are useful to assess the risk of potential non-response bias because individuals who participated may be different from those who did not participate.

2.8. Data collection and management

After consent has been obtained from individuals or parents/guardians of children, data should be collected by interviewing study participants using a study questionnaire, medical record review and vaccine history review. An accurate, detailed vaccination history including dates of vaccination is critical, and should ideally be obtained from written records. Data-collection forms should not include any identifiable information (e.g. name or home address) but instead use unique identifiers. A separate form should be maintained that links the identifiers with participant names and this should be kept in a locked cabinet or otherwise protected to ensure confidentiality.
Once completed, originals of the data-collection forms should be kept in a main study office or at the sentinel hospital, where cases were originally diagnosed, with a copy sent to the main study office. To maintain confidentiality, all data-collection forms should be kept in secure, locked cabinets, accessed only by the necessary study personnel. A central electronic database should be developed for all sites and should be maintained at the main study office. Data from each site should be entered into the database and reviewed for completeness and any data entry errors. Means of capturing data directly on hand-held computers or mobile phones may, over the next few years, become the preferred choice for data capture. For electronic data capture, it is important to ensure that all procedures related to confidentiality, data security and maintaining data quality apply.

Once data collection and analysis have been completed, the linking form should be destroyed.

2.9. Data analysis

While randomized clinical trials (RCTs) and cohort studies permit direct estimation of RRs or incidence rate ratios (IRRs), case-control studies estimate ORs. Multivariable regression analysis allows adjustment for confounding variables, such as gender and age. Regression modelling can also detect and quantify effect modification. Subgroup-specific effect measures with confidence intervals as well as statistical significance levels of interactions can thereby be identified and reported.

For the primary vaccine effectiveness analysis, vaccinated study subjects should be compared with unvaccinated subjects. A sensitivity analysis should be conducted in which subjects for whom vaccination status could not be obtained are considered vaccinated or unvaccinated to check whether these assumptions change result estimates (35). If estimates change meaningfully, this may point to the presence of bias as, for example, in the case in which vaccination status may have been more likely to be obtained for cases than controls. In these situations, results must be interpreted with an awareness of the study’s limitations. Further guidance for analysis in case-control studies is provided in the online generic protocol.

2.10. Interpretation and extrapolation of results from vaccine effectiveness studies

Findings of any new JE vaccine effectiveness study should be interpreted in the light of earlier results from previous effectiveness studies. If vaccine effectiveness is found to be different than expected, it is particularly important that further investigation be conducted, including an examination of the vaccine management and vaccine administration practices. The results can then be used to take corrective action, if necessary. The study methods should also be examined to ensure that case definitions were applied consistently, that case ascertainment was appropriate, vaccination status was appropriately determined, confounding was controlled for and biases do not adversely affect results.

Policy-makers are an important audience for the results of effectiveness studies. For example, if results of a vaccine effectiveness study shows that protection is low at five years following vaccination, policy-makers may want to consider the possibility
of introducing a booster dose to the JE vaccination schedule. If results show that JE protection remains high after five years, then policy-makers have evidence to support that there is no need for an additional booster dose.

2.11. Summary and key points

1) Because JE disease is relatively rare, a case-control study design is the generally the most feasible method for assessing JE vaccine effectiveness; the costs and time required to measure effectiveness using other methods are typically excessive and prohibitory.

2) Laboratory confirmation of JE by detecting IgM in CSF samples is required in order to minimize the risk of inclusion of false positive cases in case-control studies.

3) Hospitals are likely the only feasible locations for the identification of JE cases, and should be carefully selected based on their capacity to do LPs as part of routine diagnosis of etiology of encephalitis.

4) Controls should be selected from the same communities (e.g. villages or neighbourhoods) as cases. Ideally, cases and controls should be matched on location of residence and age.

5) Case-control studies are complex and should only be conducted if selected sites have the capacity, infrastructure and time to support high-quality research and investigators have the experience and skills needed to do them well.
3. Assessing vaccine impact by monitoring trends in disease surveillance data

Surveillance is defined as the ongoing and systematic collection, consolidation, analysis and dissemination of data to monitor disease and to identify and describe patterns of disease. JE disease surveillance has the following main objectives:

1) Demonstrate the burden of confirmed JE disease.

2) Provide data for evidence-based decision-making regarding the introduction and sustained use of JE vaccine.

3) Monitor for problems within vaccination programmes (e.g. an increase in disease incidence could be due to a breakdown in the cold chain leading to reduced activity of vaccines, suboptimal coverage or lack of vaccines).

4) Establish epidemiologic patterns of JE disease after vaccine introduction, including changes in age distribution and seasonality.

Surveillance may be active or passive. Active case finding – in which efforts are made to proactively capture all cases in a population – should provide more complete case ascertainment than passive reporting where public health officials rely on clinicians or laboratories to report cases without providing regular reminders. Regardless of whether surveillance is active or passive, changes in surveillance practices may occur around the time of vaccine introduction, as a clinician’s awareness may be raised about the diseases prevented by the vaccine, and this factor should be considered when interpreting surveillance data. Additionally, vaccine impact on JE disease in a population is affected by many factors, including vaccine efficacy, vaccine coverage, time elapsed since vaccine introduction and/or the presence of a vaccination catch-up campaign. A high level of immunization coverage may be needed to show an impact on less specific disease outcomes (e.g. AES), and year-to-year variation of JE disease, and diseases with similar clinical manifestations (e.g. other causes of encephalitis) can make it difficult to discern the actual effects of a vaccination programme if clinical outcomes are used. Despite these known limitations of using trends to monitor vaccine impact, surveillance is an essential part of any immunization and public health programme because it can provide data to meet the desired objectives described above.
The WHO JE surveillance standards document lists multiple approaches to surveillance (8). Case-based active surveillance with laboratory confirmation (Section 3.6.1) should be used in countries where a high level of JE control has been achieved. Sentinel hospital site case-based surveillance with laboratory confirmation (Section 3.6.2) is recommended in endemic countries where there is not yet a high level of control of the disease. For countries in the latter group, utilization of a combination of syndromic surveillance for AES and sentinel surveillance for laboratory-confirmed JE cases may allow for a large enough geographical representation for tracking AES cases while limiting the burden of laboratory confirmation to only sites with sufficient capacity confirm cases. For all surveillance designs, the quality of the surveillance system should be monitored over time by standard surveillance performance indicators. Proposed performance indicators are available online.

### 3.1. Choosing the outcome

Different outcomes can be used to measure the disease impact of JE vaccine. First and foremost, a consistent and accurate case definition must be developed that can be used to identify cases and distinguish persons with the disease from those without the disease. When choosing a case definition, there is an art to balancing sensitivity and specificity. Outcomes will vary in their sensitivity and specificity depending on whether they are confirmed JE (such as laboratory-confirmed JE, which has a high specificity but low sensitivity) or based on clinical signs and symptoms (such as AES, which has a high sensitivity but low specificity). Using case definitions and outcomes that are very specific, measuring the impact of JE vaccine on laboratory-confirmed JE is the most direct way to assess impact of the vaccine. However, more specific outcomes will limit the number of cases that are identified, and larger surveillance populations may be needed. By contrast, case definitions with higher sensitivity, such as clinical case definitions, will capture more JE disease, and may promote representativeness, but they will be less specific and thus a lower proportion of cases will be due to JEV. Using less specific outcomes, such as AES, may be considered because of the difficulty of laboratory confirmation of JE in some settings. If suspected JE cases cannot be further verified through laboratory-confirmation, there is a high risk of a biased impact assessment due to the likely inclusion of many non-JE cases.

Demonstrating an impact of JE vaccination on JE disease can be compelling to decision-makers. The challenge lies in identifying hospitals that have sufficient capacity for specimen collection and diagnostic testing because identifying and confirming cases are resource intensive. Furthermore, it can be difficult to demonstrate the impact of the vaccine on non-specific outcomes, such as AES, and a small vaccine impact may be misinterpreted as lack of overall vaccine effect.

Using case definitions for JE-related outcomes that were developed by WHO is recommended (2). Although there may be local reasons for using other case definitions, using common case definitions allows comparison across surveillance sites and countries. It is recommended that case definitions for the primary outcome of interest that are based solely on clinical diagnoses, which can be due to a variety of etiologies that may not be affected by JE vaccination, be avoided. However, AES would be an appropriate secondary outcome.
3.2. Recommended case definition

The case definitions for JE-related disease outcomes are described in this subsection. The clinical case definition for JE is a case of AES, which 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\(^1\)). Other early clinical findings may include an increase in irritability, somnolence or abnormal behaviour greater than that seen with usual febrile illness.

The following describes the JE case classification terms:

- **Suspected case:** A case that meets the clinical case definition for AES (see above). Suspected cases should be classified in one of the following four ways.
  - Laboratory-confirmed JE: A suspected case that has been laboratory-confirmed as JE.
  - Probable JE: A suspected case that occurs in close geographic and temporal relationship to a laboratory-confirmed case of JE, in the context of an outbreak.
  - “Acute encephalitis syndrome” – other agent: A suspected case in which diagnostic testing is performed and an etiological agent other than JE virus is identified.
  - “Acute encephalitis syndrome” – unknown: A suspected case in which no diagnostic testing is performed or in which testing was performed but no etiological 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.

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\(^1\) 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 convolution lasting less than 15 minutes, and who recovers consciousness within 60 minutes of the seizure.
Laboratory confirmation of a JEV infection includes:

1) presence of JE virus-specific IgM antibody in a single sample of cerebrospinal fluid (CSF) or serum, as detected by an IgM-capture ELISA specifically for JE virus;

or any of the following:

2) detection of JE virus antigens in tissue by immunohistochemistry; OR

3) detection of JE virus genome in serum, plasma, blood, CSF, or 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 serum, plasma, blood, CSF, or tissue; OR

5) detection of a four-fold or greater rise in JE virus-specific antibody as measured by haemagglutination 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. The IgG test should be performed in parallel with other confirmatory tests to eliminate the possibility of cross-reactivity, as indicated in footnote 2.

Note:

- 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 are recommended when feasible.

- Only the first 5–10 JE cases of an outbreak typically need be confirmed by laboratory testing. During periods of epidemic transmission of JE virus, laboratory confirmation of every case may not be necessary.

2 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 or at the time of death and tested for presence of JE virus specific IgM.

3 Further confirmatory tests (e.g. looking for cross-reactivity with other flaviviruses circulating in the geographical area) should be carried out: (a) when there is an ongoing dengue or other flavivirus outbreak; (b) when vaccination coverage is very high; or (c) in cases in areas where there are no epidemiological and entomological data supportive of JE transmission.

4 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 a clinically ill JE case. 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.
3.3. Choosing the location for an impact study

Cases identified in a surveillance system should ideally be representative of the cases in the population. In most low resource countries, identifying cases in hospital settings is often the most feasible strategy, since clinical evaluation and diagnostic testing is more readily available in these than in other settings. However, identifying cases at referral facilities will select for more severe and complicated cases. Limiting case identification to hospitalized cases will probably not identify less severe cases, however. When choosing a site for case identification, one should carefully consider the practical aspects of identifying cases and performing appropriate diagnostic and laboratory tests.

Given that JE is typically a rural disease, participation of a number of sentinel sites in a variety of settings may be required in surveillance systems in order to ensure accurate geographical representation of the disease. For JE surveillance, the number of sites with sufficient capacity may be a limitation. Selection of the location should involve careful consideration of the geographic coverage that is needed to avoid underestimating the burden of JE disease in the community. Depending on existing surveillance activities, integration of surveillance systems at sentinel sites for encephalitis and meningitis may be feasible in some contexts. Some caveats include the fact that JE surveillance typically requires more geographical representation and meningitis surveillance is typically confined to children aged 1–59 months.

3.4. Choosing the ages for inclusion

When conducting hospital-based sentinel surveillance, WHO recommends that all individuals under the age of fifteen years who are admitted with JE disease should be included in the surveillance reporting. Depending on the age distribution of JE cases in countries and regions, a shift in the burden of disease toward older populations may warrant the inclusion of older age groups in the surveillance programme. The case report form should capture the specific ages of individuals with JE. The impact of the vaccination programme is likely to be highest in individuals who fall in the age range for which disease incidence, disease prevalence and vaccination coverage rates are highest.

3.5. Primary data sources

Primary data sources for JE disease include prospectively-gathered data from active population-based surveillance, sentinel site surveillance, periodic surveys, and nationally notifiable disease surveillance. Some examples of primary sources are listed below.

3.5.1. Active population-based surveillance

When available, active population-based surveillance for JE disease is the most accurate method of monitoring trends in JE disease. Active population-based surveillance ideally takes place in all hospitals and clinics within a geographically well-defined area with good access to health facilities, little inward or outward migration and few changes in health-seeking behaviour. It is essential to ensure that everyone from the at-risk population will be captured in the hospitals or health-care centres selected.
If these criteria are not met, a survey of health-care utilization practices can help define the health-seeking behaviour of the population. The most accurate active population-based surveillance is prospective and involves actively finding cases, either in the community or at a hospital. The catchment area of patients utilizing the hospitals and clinics should be known, and every effort should be made to include all hospitals and clinics in the area where individuals could seek care for JE disease.

Because active population-based surveillance results in a complete enumeration of cases among a defined at-risk population, this method of surveillance can be truly representative of the area (or population under surveillance) and allows incidence rates (i.e. the number of cases divided by the person-time at risk) to be calculated. An accurate estimate of the size of the population under surveillance is needed for this calculation (36, 37). It is important to ensure the population under surveillance is large enough to generate a sufficient number of cases, particularly as the number of JE cases will decline following vaccine introduction. A significant disadvantage of active population-based surveillance is that tracking the population at risk is highly resource-intensive. Hospital-based surveillance may not provide an accurate measure of disease burden in a population when subjects do not seek care at participating facilities, appropriate testing is not reliably performed and/or appropriate case definitions are not utilized.

### 3.5.2. Hospital-based sentinel site surveillance

Hospital-based sentinel site surveillance is the most common method used for describing JE disease trends in resource-poor settings because it is less resource-intensive than active population-based surveillance and can be restricted to a limited number of hospitals that have adequate laboratory capacity. In contrast to population-based surveillance, sentinel site surveillance typically takes place in one or more, but not all, hospitals or clinics in a country or region. This type of surveillance system does not allow calculation of incidence rates, as the true catchment population is usually unknown, but with an estimated catchment area, disease trends may be measured over time if hospital admission rates, health-seeking behaviour and surveillance methods remain stable (36, 37). The generalizability of surveillance data is limited if the sentinel site or population is not representative of the national population, particularly if vaccine coverage varies sub-nationally. In general, it is best to choose hospitals that serve areas with the highest incidence of JE as sentinel hospitals in order to identify the largest possible number of cases for surveillance analyses. However, the relatively small number of patients with JE at a single sentinel hospital, even a large referral facility, may limit the ability to use sentinel hospital surveillance to demonstrate direct vaccine impact on disease occurrence. There are approaches to describe the primary catchment area of a hospital, which allows incidence estimates to be generated for the catchment population (36).

### 3.5.3. Nationally-notifiable disease surveillance

Nationally-notifiable diseases are legally mandated to be reported to public health officials to help monitor, prevent and control disease. Notifiable disease surveillance is a passive system in which cases are reported by medical or laboratory professionals.
The list of notifiable diseases in some countries may include JE disease. If reporting of notifiable diseases has been consistent, the surveillance system can be used to monitor trends in disease. However, it is important to recognize that because this type of surveillance is passive, underreporting of disease will be common and so this method is likely to underestimate its true occurrence. There may also be other biases in reporting that are difficult to measure and account for.

3.6. Secondary data sources

In contrast to primary data sources that are collected on health outcomes, secondary data sources are existing data collected for another purpose, such as routine hospital clinical and administrative data. Such secondary data sources are a potential source of information to describe trends and can be analysed retrospectively. Secondary data have been successfully used to monitor the impact of vaccines, such as rotavirus vaccines, on diarrhoeal disease (38), and in places where active surveillance is not available. It is attractive to consider using existing data to monitor JE vaccine impact since the data are routinely gathered and limited effort is needed. However, the disadvantage to routine data is that there is no measure of consistency over time. For JE, any reduction in mortality might be too small to detect using routine statistical methods since the burden is comparatively low. In general, secondary data sources are not recommended for use as the main method of measuring JE vaccine impact.

3.7. Data collection, analysis and reporting

Appropriate, timely, accurate and complete recording of surveillance data is essential to facilitate meaningful data analysis. Data should be compiled regularly in an electronic database or paper-tracking logbook that allows for easy updating and checking of records, both at surveillance sites and at a central unit in the country. Missing information should be obtained and entered into the surveillance database. External supplemental data, such as that from a reference laboratory, should be entered upon receipt. In addition, simple data checks should be in place to help maintain quality of the data. For example, where surveillance is among children less than five years of age, only an age between 0 and 59 months should be allowed in the database. One adequately-resourced unit or institution per country should be responsible for overall data management, and one person in that unit should routinely perform quality-control assessments, such as measuring rates of LPs among suspected cases, and ensuring completion of missing data.

Preliminary analysis of surveillance data should be done periodically by persons experienced in interpretation of data to look for trends, as well as for additional checks of data problems. Data analysis for a vaccine impact assessment should only occur after the data have been cleaned (i.e. when data are as accurate and complete as possible). When available, incidence rates are preferable to case counts because incidence rates account for the population at risk and, over time, they account for population denominator variations. The incidence of all disease syndromes can be crudely adjusted for access to care by dividing the measured incidence by the estimated proportion of children with disease syndromes that go to a health-care facility, a figure typically obtained from health-care utilization surveys in actual or comparable settings.
The simplest method to measure the impact of JE vaccine on disease when only sentinel site data are available is to observe the change in the absolute number of cases of the outcome of interest using the pre-vaccine year(s) as the baseline. In addition, one can measure the change in the percentage of JE among all AES cases. Table 4 presents strategies that can be used to analyse population-based or sentinel surveillance systems. A statistician or epidemiologist familiar with measuring vaccine impact should be consulted for vaccine impact calculations. Recommendations for analysis of surveillance data are included in WHO's VPD surveillance manual (8).

Several important points should be considered when analysing surveillance data to measure vaccine impact.

1) Seasonal and natural year-to-year variation in JE disease rates can occur independent of vaccination. This variation can cause large changes in disease rates, and these can be especially pronounced in surveillance conducted in a single community or a small number of hospitals. To account for this variation, at least two years of data prior to vaccine introduction should be analysed to estimate baseline rates (although one year of pre-vaccination data may be sufficient in some settings and in others two years may be inadequate). Two years of post-vaccine introduction data are recommended to show impact. Maximum impact may take longer to assess if vaccine uptake is slow and if a catch-up campaign of older children is not included in vaccine introduction.

2) Over time, substantial changes in the surveillance system will make it difficult to interpret changes in disease burden, so it is useful to measure surveillance performance indicators. For example, when surveillance moves from a passive to an active system, the number of cases identified will increase, even if there is not a true increase in incidence of disease. Changes in disease rates may be artifacts of measurement if case-identification methods are enhanced or reporting of cases increases at the time of or following vaccine introduction. A change in laboratory practices or specimen testing may also affect the data, as the addition of testing could lead to more case finding and a lack of supplies could result in less case finding. Similarly, changes in the catchment area of sentinel hospitals or large inward or outward migration from the catchment area will also affect the data collected.

3.8. Interpretation and extrapolation of results from vaccine impact studies

The interpretation of an impact assessment will be determined by the outcome studied. An impact assessment can show a change in the outcome at the population-level that can be attributed to a vaccination programme, and this can be used to inform vaccine policy decisions, demonstrate the benefits of vaccination, and enhance understanding of vaccine impact under field conditions. Vaccine impact can be lower than efficacy if coverage is not high (more likely) or if the vaccine had lower potency or was more likely to be administered at suboptimal ages or injected inappropriately in the field setting (less likely). For example, when population-based surveillance data, including pre-vaccination incidence of JE disease, are available, the disease burden prevented by JE vaccine can be estimated by calculating the product of:

\[ a \times b \times c \times d \]
where \( a \) is the incidence of a particular disease outcome from pre-vaccine surveillance; \( b \) the population under surveillance; \( c \) vaccine coverage; and \( d \) effectiveness estimated in a case-control study.

Surveillance system characteristics, including quality, are key issues, and results of impact assessments cannot be considered outside of a good understanding of the surveillance system, quality of data collected, and changes over time, including changes in reporting and changes in detection of disease. Impact measurements require consistent and reliable surveillance data. The surveillance methods used reflect the surveillance capacity in countries. One challenge in comparability of results from vaccine impact studies is that different countries may use different surveillance methods. In addition, in just one country, several different JE surveillance systems may be utilized. These variations must be considered when interpreting and comparing results of JE vaccine impact studies across countries and over time.

Surveillance systems should be set up so they are ongoing and not simply temporary systems designed to conduct an impact assessment. The system should be sustainable and should continue to focus on outcomes that help to inform policymakers and public health officials’ decision-making over time in the context of changing disease epidemiology, interventions, and strategies.

3.9. Case study

In Nepal, an impact analysis was carried out following mass immunization campaigns conducted in 23 districts (12). Post-campaign JE incidence was 72% lower than would have been expected had a JE campaign not been implemented, with 891 JE cases prevented, and post-campaign AES incidence was 58% lower than expected, with 2,787 AES cases prevented. The change in AES incidence suggests that more than three times as many cases were prevented than would have been predicted when just assessing changes in laboratory-confirmed JE cases. However, post-campaign JE incidence and AES incidence only declined significantly in less than half of districts. There are multiple potential reasons for the difference in impact in each of the districts, including limited post-campaign data, low case numbers in some districts, and true differences related to programmatic factors.

This study offers a number of lessons. Monitoring AES trends is generally a good indicator of JE trends, but in some instances, AES trends might not accurately reflect JE disease burden. It does underscore the fact that while AES is less specific than laboratory confirmation for measuring JE disease, it is substantially more sensitive. In addition, the effects of any temporal differences in reporting practices are difficult to determine. Finally, taking into account the effect of any changes in JEV transmission over time is difficult in the absence of surveillance data spanning several years.

3.10. Summary and key points

1) High-quality JE disease surveillance in a large population can measure and monitor the impact of JE vaccine, and data collected can contribute to evidence-based decisions regarding JE vaccine use.
2) Vaccine impact on laboratory-confirmed JE is the preferred outcome to measure, although impact on AES may be a valuable secondary outcome.

3) All countries with endemic JE transmission should consider conducting hospital-based sentinel site surveillance for JE disease as this can be an important platform for measuring JE vaccine impact on disease occurrence in settings where either population-based surveillance is either not possible or not feasible. Monitoring both AES and laboratory-confirmed JE utilizing hospital-based sentinel site surveillance may be a viable option for countries that do not yet have the capacity for population-based surveillance.

4) A minimum of 2 years pre-vaccination and 2 years post-vaccination surveillance data are required to assess vaccine impact.

Table 4: Suggested metrics and data sources to demonstrate vaccine impact from surveillance data

<table>
<thead>
<tr>
<th>Metric/data source</th>
<th>Calculation/method</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Percent reduction in incidence of JE disease (which may include clinical syndromes like AES).</td>
<td>Incidence rates: incidence of JE disease is calculated by dividing the number of individuals with the disease from the hospital catchment area by the total number of individuals from the hospital catchment area. Percent reduction: compare each post-introduction year incidence rate to the baseline pre-vaccination incidence rates.</td>
<td>• Data obtained by conducting active population-based surveillance; passive population-based surveillance may be used but the data must be cautiously interpreted as cases of the disease are likely to be missed. • Recommend data collection for at least two years pre-vaccine introduction and two years post-vaccine introduction. • A decline in incidence or case counts may be observed in the first year following vaccine introduction.</td>
</tr>
<tr>
<td>Percent reduction in the number of cases of JE disease.</td>
<td>Percent reduction: compare each post-introduction year case count to the baseline pre-vaccination rate.</td>
<td>• Data obtained by conducting sentinel surveillance or active population-based surveillance. • It is important to note that a decrease in JE cases resulting from vaccine use will necessarily cause an increase in the proportion of other etiologies for clinical syndromes like AES.</td>
</tr>
<tr>
<td>Percent reduction in the proportion of meningoencephalitis cases that are JE.</td>
<td>Percent reduction: compare the percentage of JE cases among all meningoencephalitis cases in the pre- and post-vaccine years.</td>
<td>• Data obtained by conducting sentinel surveillance or active population-based surveillance. • It is important to note that a decrease in JE resulting from vaccine use will necessarily cause an increase in the proportion of other etiologies for clinical syndromes like AES.</td>
</tr>
</tbody>
</table>
### Metric/data source

- Review ongoing cases of JE disease following introduction of JE vaccine.

### Calculation/method

- Review case notes/vaccination history for cases of JE disease. The following are possible reasons for cases continuing to occur.

  1) Individual not eligible for vaccination (due to age).
  2) Individual eligible but not vaccinated or incompletely vaccinated.
  3) Individual fully vaccinated but has waning immunity.
  4) Individual fully vaccinated but has an underlying condition, which may reduce vaccine effectiveness.
  5) Individual fully vaccinated but vaccine failed.

### Comment

- Data usually obtained from surveillance system to identify cases followed by in-depth investigation to describe the characteristics of the cases. To obtain high-quality data on the vaccination status of cases, public health professionals should usually collect additional data (i.e. review of vaccination cards) to complement the information provided by the sentinel hospitals.

- Data on the vaccination status of cases are essential to interpret and respond to ongoing cases of JE disease.
4. Conclusion

This manual discusses methods for measuring the effectiveness and impact of JE vaccination and describes both case-control studies and surveillance options. Case-control studies are the recommended study design to evaluate JE vaccine effectiveness due to the relatively rare occurrence of the disease. Before conducting a case-control study, an assessment of the capacity of sites is necessary in order to ensure that data collected are of high quality. If sufficient capacity to conduct a case-control study is lacking, efforts should be made to train personnel and improve infrastructure so that sufficient capacity is developed. In the absence of sufficient capacity, a JE case-control study should not be conducted.

The choice of a method to monitor the impact of JE vaccine will depend on whether a surveillance system is in place, how long it has been in place and the quality of the surveillance data. Measuring impact using sentinel site surveillance data may be less rigorous than using population-based surveillance data, but sentinel surveillance is a practical and frequently used strategy for assessing vaccine impact in settings that lack population-based surveillance systems.

Depending on the needs, resources and capacities in particular countries and areas, public health officials may choose both to use surveillance in order to assess the impact of vaccine on disease and to conduct vaccine effectiveness studies. Obtaining high-quality data from either or both of these options will provide important information for decision-makers at national, regional and global levels.
References


## Annex 1.
### Glossary of terms

<table>
<thead>
<tr>
<th>Term</th>
<th>Definition</th>
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<tbody>
<tr>
<td><strong>Case-control study</strong></td>
<td>Observational study design that compares vaccination status of cases of people with a disease of interest to vaccination status of a control group of people without a disease in order to evaluate vaccine effectiveness.</td>
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<tr>
<td><strong>Impact</strong></td>
<td>The overall programme effect on morbidity and/or mortality from disease, brought about by an intervention under study.</td>
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<tr>
<td><strong>Incidence</strong></td>
<td>The number of new cases in a given population at risk over a specific period of time.</td>
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<tr>
<td><strong>Incidence rate</strong></td>
<td>The rate at which new cases occur in a population calculated by dividing the number of cases in specified time period by the number of persons exposed to the risk.</td>
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<tr>
<td><strong>Incidence rate ratio</strong></td>
<td>Incidence rate in the exposed group divided by the incidence rate in the unexposed group.</td>
</tr>
<tr>
<td><strong>Odds ratio</strong></td>
<td>Ratio of the odds of getting disease if vaccinated compared with the odds of getting disease if not vaccinated; generated by case-control study designs.</td>
</tr>
<tr>
<td><strong>Relative risk</strong></td>
<td>Ratio of the risk (probability) of getting disease if vaccinated compared with the risk of getting disease if not vaccinated; generated by cohort study designs. This is also known as risk ratio.</td>
</tr>
<tr>
<td><strong>Vaccine effectiveness</strong></td>
<td>The proportionate reduction in disease incidence attributable to vaccination under real-world conditions, including the effect of programmatic factors such as: injection techniques; reduced vaccine potency following inappropriate storage; indirect (herd) protection against the target illness; pre-existing immunity to the target illness, such as that conferred by a previous episode of the target illness; population characteristics such as malnutrition; and any other factors that distinguish a community immunization programme from the controlled setting of a vaccine trial. A measure usually found in observational studies.</td>
</tr>
<tr>
<td><strong>Vaccine efficacy</strong></td>
<td>Proportionate reduction in disease incidence attributable to a vaccine when given under ideal conditions; a measure typically generated by clinical trials.</td>
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</table>