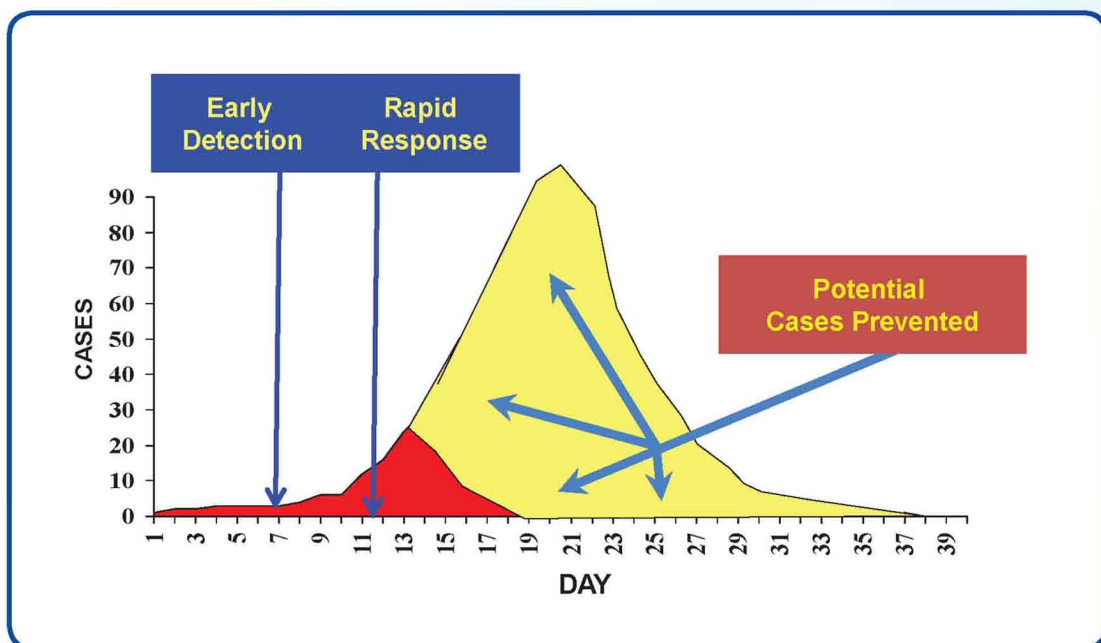


*A guide to*

# EARLY WARNING AND REPORTING SYSTEM (EWARS)



Government of Nepal  
Ministry of Health and Population  
**Department of Health Services**  
Epidemiology and Disease Control Division  
Teku, Kathmandu

(Revised Edition- 2019)

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**PREFACE**

Disease surveillance is the collection of data for action. By collecting information about cases of the disease, and appropriately analyzing the data, we can determine what actions are needed to reduce morbidity, disability and mortality. Decisions on resources allocation and on the definition of priorities and objectives cannot be made without a database in order to identify problems and their pattern of distribution in the population. Following WHO Global and regional call for the implementation of a reliable reporting system capable of early detecting and monitoring new, emerging and/or reemerging diseases, Epidemiology and Disease Control Division of Department of Health Services has established an Early Warning and Reporting System (EWARS).

For the initial phase in 1997, eight sentinel sites were selected and expanded to 24 sites in 1998, 26 sites in 2002, 28 sites in 2003, 40 sites in 2008 and 82 sites in 2016. In May 2019, DoHS decided to incorporate additional 36 sentinel sites. Thus, the total number of current sentinel sites is 118. Sentinel sites include all the central hospitals, provincial hospitals, district hospitals, medical colleges including selected private hospitals. Control room was established under surveillance and research section in order to maintain quality, accuracy, timeliness and completeness of data received from EWARS sentinel sites. EWARS bulletin is produced and shared with all the concerned bodies and stakeholders through email. EDCD has recently initiated the roll out for DHIS2 for EWARS.

Two aspects are knit within this guideline those being technical and operational. The technical aspect is more concerned with the clinicians whereas the operational aspect is more concerned with the medical recorders and laboratory personnel. Though this guidebook is not detailed in itself but can surely render brief information to the clinicians/physicians. I would request you to refer the recently updated national guideline and protocol for reference of particular diseases and their explanation.

I would like to thank the surveillance and research section team and also would like to extend my sincere gratitude to the senior physicians and experts for proactively involving in updating this guideline. Last but not the least, the meticulous suggestions and feedbacks from our contributors are highly appreciated.

  
Dr. Bibek Kumar Lal  
Director  
July, 2019





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**ACKNOWLEDGEMENT**

Public health surveillance is a continuous, systematic collection, analysis and interpretation of health-related data needed for the planning, implementation, and evaluation of public health practice. The main aim of public health surveillance is to timely detect public health emergencies and monitor trends of diseases, health problems and other determinants of health.

The main objective of EWARS is to strengthen the flow of information on outbreak prone infectious diseases and vector borne diseases from the sentinel sites throughout the country and to facilitate prompt outbreak response to be carried out by rapid response teams at federal, provincial and local level government. It is designed to provide timely reports for the early detection of selected diseases with outbreak potential.

The sentinel sites have been identified for the current sentinel surveillance systems. The numbers of sentinel sites have been gradually expanded to all medical colleges and selected private hospitals recently in order to capture the mentioned notifiable diseases. The data from sentinel sites are compiled and analyzed at EDCC and the weekly electronic bulletin is shared to all the relevant stakeholders. This year the reporting from the sentinel sites (mainly timeliness and completeness) is gradually increasing.

This guidebook will assist medical officers, physicians, paramedics and nursing staff who are working in OPD, emergency and indoor departments at the sentinel sites. Similarly, medical recorder and laboratory personnel can also avail from this guidebook for the appropriate reporting of diseases.

I extend my heartfelt gratitude to Dr. Anup Bastola, Chief Consultant Physician, Prof. Dr. Sheetal Adhikari, Dr. Suman Thapa, Save the Children Nepal, Dr. Bimal Sharma Chalise, Senior Consultant Physician, Dr. AK Mishra, Senior Consultant Physician, Dr. Udip Maharjan, Senior Consultant Physician, Dr. Surendra Urawn Asst. Professor BPKIHS for their input in disease part and all the other experts for their hard work and efforts to bring out this guidebook.

I would especially like to thank my colleagues at the surveillance and research section and a WHO consultant working with this section for their contribution, invaluable suggestions and encouragement as well as for compilation of this guide.

**Shambhu Prasad Jnawali**

Chief

Surveillance and Research Section

July, 2019



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## LIST OF ABBREVIATION

|         |                                                   |
|---------|---------------------------------------------------|
| AGE     | Acute Gastroenteritis                             |
| AIDS    | Acquired Immune Deficiency Syndrome               |
| CDC     | Centers for Disease Control and Prevention        |
| CNS     | Central Nervous System                            |
| CSF     | Cerebrospinal fluid                               |
| DHF     | Dengue Hemorrhagic Fever                          |
| DNA     | Deoxyribonucleic acid                             |
| DoHS    | Department of Health Services                     |
| DSS     | Dengue Shock Syndrome                             |
| E. Coli | Escherichia coli                                  |
| EDCD    | Epidemiology and Disease Control Division         |
| ELISA   | Enzyme-linked Immunosorbent Assay                 |
| ETEC    | Enterotoxigenic Escherichia coli                  |
| EWARS   | Early Warning and Reporting System                |
| GI      | Gastrointestinal Infection                        |
| HD      | Health Directorate                                |
| HFs     | Health Facilities                                 |
| HMIS    | Health Management Information System              |
| HO      | Health Office                                     |
| HUS     | Hemolytic Uremic Syndrome                         |
| ICD     | International Classification of Diseases          |
| IFA     | Immuno Fluorescence assay                         |
| ILI     | Influenza Like Illness                            |
| IM      | Intra Muscular                                    |
| IV      | Intra Venous                                      |
| MoHP    | Ministry of Health and Population                 |
| OPD     | Out Patient Department                            |
| ORS     | Oral Rehydration Salts                            |
| PCR     | Polymerase Chain Reaction                         |
| RDTs    | Rapid Diagnostic Tests                            |
| RIA     | Radioimmunoassay                                  |
| RNA     | Ribonucleic acid                                  |
| RRT     | Rapid Response Team                               |
| SARI    | Severe Acute Respiratory Infection                |
| TTP     | Thrombotic Thrombocytopenic Purpura               |
| VBDRTC  | Vector Borne Disease Research and Training Centre |
| VBDs    | Vector Borne Diseases                             |
| VL      | Visceral Leishmaniasis                            |
| VP      | Viral protein                                     |
| WHO     | World Health Organization                         |



# PART I. INTRODUCTION

## Public health surveillance

Public health surveillance is the continuous, systematic collection, analysis and interpretation of health-related data needed for the planning, implementation, and evaluation of public health practice. Main objectives of public health surveillance are:

- Early detection and timely response to outbreaks and other public health emergencies
- To monitor trends of diseases, health problems and determinants of health

## Importance of surveillance

- Early warning and detection of outbreaks
  - ☞ Timely detection and response to outbreaks and other public health emergencies
  - ☞ Surveillance provides alerts on the burden of notifiable diseases
  - ☞ Helps in emergency planning and preparedness
- Assessing the health status and issues of the population
  - ☞ Keeps the record of existing health problems
  - ☞ Helps in the interpretation of mortality and morbidity status
- Detecting change in the trend of diseases
  - ☞ Continuous recording/reporting of data notifies about the disease trend
  - ☞ Keeps the track of disease
- Collection of data for Planning, Monitoring and Evaluation
  - ☞ Helpful for evidence-based planning and policy formation and setting priorities
  - ☞ Useful to monitor the progress and evaluate the effectiveness of health programmes

## Types of public health surveillance

Public health surveillance can be broadly divided into three types, based on how data are collected:

### Active surveillance

- Active surveillance involves proactively collecting or searching data by reviewing the records, contacting /visiting health facilities and applying similar methods
- It is often used for the diseases at the verge of elimination and eradication and also in the time of outbreak investigation

### Passive surveillance

- In passive surveillance, health officials receive data regularly from the reporting sites without having to look for it actively
- Health Information Management System (HMIS) of Department of Health Services (DoHS) is

an example of it (All institutions that provide health services to general people are the part of this surveillance)

- Uniform format of reporting is followed

### **Sentinel surveillance**

- Sentinel surveillance uses data from a few selected sites rather than the data from all sites. It is particularly useful as a compliment to the routine system when routine reports are late, incomplete or inaccurate
- Sentinel surveillance is the collection, reporting and analysis of data by only the designated sites, chosen for their geographic location, medical specialty, and ability to accurately diagnose and report high quality data
- For example, district hospitals may be required to report specific conditions such as AGE in order to quantify the burden of disease
- It is a surveillance system which is used when the need of high-quality data cannot be met through passive surveillance
- Generally, sentinel surveillance is useful for answering specific epidemiologic questions, but, because sentinel sites may not represent the general population or the general incidence of disease, they may have limited usefulness in analysing national disease patterns and trends

### **Sentinel site**

- Specific catchment area is selected for surveillance
- Selection of sentinel surveillance site depends on possibility of high probability of disease and with quality diagnostic facilities
- It deliberately involves limited network of carefully selected reporting sites. Example: a network of large hospitals might be used to collect high-quality data on various diseases
- Sentinel sites are chosen because they are likely to see cases of a certain diseases and their staff have been trained and motivated, and are willing to report timely, regularly and accurately

Sentinel reporting can serve as a useful early warning system. Data from a sentinel hospital are available more quickly than the data from the districts as a whole and can provide an early warning of outbreaks. These health facilities report the number of cases of disease that occur for a specific time period. They will also be asked to report additional information, such as age, location, immunization status, etc., as well as weekly “ZERO” reports (no occurrence of cases).

## **Steps of surveillance**

### **Reporting**

- Data have to be reported by the medical recorder, health worker, and other staff
- Data need to be reported in a pre-specified format

### **Accumulation of data**

- The reported data need to be collected and compiled
- The data are collected in a designated institution
- Data collection follows the certain chain

### **Data analysis and interpretation**

- All the collected data are then analyzed
- The data are converted in terms of rates, ratios, proportion, trends, figures, etc
- Wise judgement needs to be made

### **Dissemination of information**

- The information needs to be disseminated to relevant authorities so that the further action can be taken

### **Early Warning and Response (EWAR)**

Early warning and response (EWAR) is one of the main functions of public health surveillance. WHO, 2014 defines it as a “mechanism to detect as early as possible any abnormal occurrence or any divergence from the usual or normally observed frequency of phenomena”. EWAR is required to increase timeliness and sensitivity of detection of outbreaks or other public health emergencies, improve quality of risk assessment, and carry out prompt and effective response. International Health Regulations (IHR) requires all World Health Organisation’s (WHO) member states to have EWAR capacity.

EWAR can be implemented through indicator-based surveillance (IBS) and event-based surveillance (EBS). IBS is the systematic collection, reporting and of structured information on pre-identified diseases/syndromes/health events on a regular basis whereas EBS is the organized collection, analysis and interpretation of mainly unstructured ad hoc information regarding health events or risks, which may represent an acute risk to human health IBS primarily collects information from health facilities whereas EBS relies on different sources such as media, community people, police, etc.

### **Early Warning and Reporting System (EWARS) in Nepal**

Early Warning and Reporting System (EWARS) is operational in Nepal to perform EWAR function. EWARS is a hospital-based sentinel surveillance system where the selected hospitals send immediate and weekly reports (including zero reports) on six priority diseases and outbreaks of any diseases (see Part II). It is designed to provide timely report of selected epidemic prone, vector-borne, water and food borne diseases for the early detection of outbreaks.

It was established in 1997 first in 8 sentinel sites and expanded to 24 sites in 1998, 26 sites in 2002, 28 sites in 2003, 40 sites in 2008 and 82 sites in 2016. In May 2019, additional 36 sites (private hospitals and medical colleges across Nepal) were declared as sentinel sites by the DOHS. Thus,

the total number of current sentinel sites is 118. Sentinel sites include all the central hospitals, provincial hospitals, district hospitals, medical colleges including selected private hospitals.

The main objective of EWARS is to strengthen the flow of information on outbreak prone infectious diseases and vector borne diseases from the districts and to facilitate prompt outbreak response to be carried out by rapid response teams (RRTs) at federal, provincial and local level. It is designed to provide timely report for the early detection of selected vector-borne, water and food borne diseases with outbreak potential.

## **EWARS and International Health Regulation (IHR)**

One of the most important aspects of IHR 2005 is the establishment of a global surveillance system for public health emergencies of international concern. The IHR requires the rapid detection of public health risks, as well as the prompt risk assessment, notification, and response to these risks. EWARS in Nepal works as an indicator-based surveillance in line with the requirement of IHR 2005.

The structure of EWARS and the roles and responsibilities of the EWARS system is in line with the public health policy and legislation. Furthermore, it used for preparedness and response to any kind of public health emergency. The data received by EWARS are assessed at EDCD by the National Focal point for IHR. The identified public health risks and events are communicated within the country, with WHO and with other countries as needed.

## **Purpose and target audience of this guide**

Purpose of this guide are:

- To provide an overview on disease surveillance activities of the Ministry of Health and Population of Nepal
- To introduce EWARS and its mechanism in Nepal
- To guide health workers and medical recorders on case recording and reporting using provided tool for the EWARS
- To introduce about case definitions of notifiable diseases included in EWARS
- To aid in response activities

This guide is intended for physicians, medical officers, paramedics and nursing staff working in emergency, indoor and outpatients at the hospitals. This will also be beneficial for persons working with EWARS including medical recorders and laboratory personnel or others who are directly or indirectly working with EWARS.

# PART II. MECHANISM OF EWARS

## Reportable diseases/health events

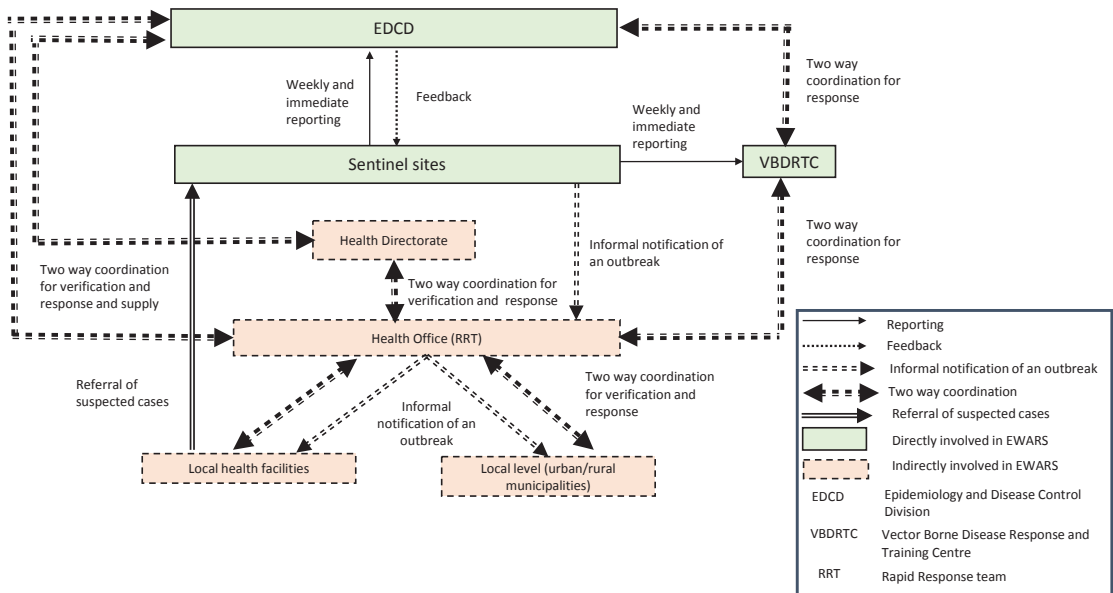
Currently, six diseases are reported in EWARS as shown in the box.

| Epidemic prone diseases                   | Vector borne diseases |
|-------------------------------------------|-----------------------|
| Acute Gastroenteritis (AGE)               | Malaria               |
| Cholera                                   | Dengue                |
| Severe Acute Respiratory Infection (SARI) | Kala-azar             |

Scrub typhus and ILI cases have also been reported since few years. So these diseases have also been included in this guide.

Besides these prioritized diseases, other infectious diseases also need to be reported in EWARS in case of their outbreaks.

## Mechanism of information flow



## Data collection

Depending upon the nature and severity of diseases, cases originating from the communities may attend various departments of the hospitals like out-patient, inpatient, emergency, pediatric, etc. Medical recorder of the sentinel sites should visit those departments every day and fill up EWARS form (Annex 1).



## Data reporting

EWARS consists of two types of reporting based on magnitude and type of disease occurrence: immediate and weekly.

### Immediate reporting

The sentinel hospitals should immediately report, i.e. within 24 hours of confirmation of diagnosis (clinical and/or laboratory) of EWARS reportable diseases in following cases:

- One confirmed case of Cholera
- One case of confirmed Malaria
- One case of confirmed case of Dengue
- Five or more cases of AGE or SARI from same geographical area within one week
- One case of confirmed Kala-azar

Consolidated immediate reports should be verified and forwarded by medical recorder of the hospital and sent to EDCC and VBDRTC.

### Weekly reporting

The sentinel hospitals should prepare weekly report based on the epidemiological week calendar which starts on the first week of January (Epidemiological Week 1) and ends on last week of December (Epidemiological Week 52). Each week starts on Sunday and ends on Saturday.

For example, for the year 2019, Epidemiological Week 1 is or starts from December 30, 2018 (Epidemiological Week 1) and ends on December 28, 2019 (Epidemiological Week 52).

Consolidated weekly reports should be prepared for the epidemiological week and sent to EDCC and VBDRTC by Friday of the following week.

Based on timeliness of reporting, reports are categorised as:

- **On time:** Report of an epidemiological week received within Friday of the following week.
- **No Report:** Not receiving of Report till Friday

### Completeness

$$\% \text{ Completeness: } \frac{\text{Total number of weeks with report}}{\text{Epidemiological Week No.}} \times 100$$

*Note: Disease reported to EWARS should also be reported to HMIS in aggregate form.*

## Data analysis, feedback and dissemination

EDCC analyses the reported data and develops weekly bulletin and provides feedback to the sites as needed. Feedback is provided mainly to improve the data quality. Weekly electronic EWARS bulletin is disseminated via email to all the key personnel of MoHP and DoHS, provinces, all sentinel sites and concerned organizations working in the health sector. The bulletin is also uploaded to the EDCC's website.

## **PART III. ROLES AND RESPONSIBILITIES**

### **Sentinel site**

- Weekly review of registers in different wards (in-patient, out-patient, and emergency) of the health facility
- Daily/ weekly coordinate with OPD, IPD and laboratory departments in hospitals for data collection
- Daily consolidate records of cases and deaths of notifiable diseases and report to EWARS
- Review all death and cases of reportable diseases weekly basis
- Follow feedback from EDCD
- Get updated with EWARS weekly bulletin
- Inform to various levels of RRTs within the catchment area of sentinel sites

### **Epidemiology and Disease Control Division**

- Compile and analyse the data
- Prepare and disseminate the weekly report as a feedback to the all sites by preparing an EWARS Bulletin
- Provide feedback to the sentinel sites when needed
- Assists to all levels of RRTs for disease verification and response activities
- Maintain regular supply system of rapid diagnostic kits and drugs
- Facilitate in resource mobilization for smooth functioning of EWARS-related activities

### **Vector Borne Disease Research and Training Center**

- Investigation of the reported cases
- Provide feedback to the sentinel sites
- Support in response activities
- Coordinate with MoHP, EDCD and provinces

### **Health Directorate**

- Supervision and monitoring of sentinel sites
- Regular feedback to sentinel sites
- Resource allocation
- Regularly conduct orientation, review and training to sentinel sites
- Coordinate with MoHP, DoHS and provinces for strengthening of sentinel sites
- Recommend DoHS for expansion of sentinel site

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- International Health Regulations (2005). Second edition. World Health Organization; 2008.



## Instructions to fill up the EWARS form

| Instructions for filling the form |                                                                |
|-----------------------------------|----------------------------------------------------------------|
| Sentinel Site Name                | List of Sentinel site is provided, select your site.           |
| Email                             | Contacts where this report is to be sent periodically (weekly) |

| Form Fields to be filled           |                                                                                               |                                                                                                    |
|------------------------------------|-----------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------|
| SN                                 | Enter the serial number                                                                       |                                                                                                    |
| Nepali Date                        | Nepali date (BS) of the patient registration, please type Year-month-day (eg: 2076-03-27)     |                                                                                                    |
| Week No                            | The epidemiological week number which the patient is registered. Week will be auto generated. |                                                                                                    |
| Reg. No                            | Enter the hospital registration number of the patient.                                        |                                                                                                    |
| OPD/Eme/IPD                        | Please select type of patient registration (OPD/IPD/Emergency).                               |                                                                                                    |
| Name of Patient                    | Enter full name of the patient                                                                |                                                                                                    |
| Age                                | Age of the patient, please type whole number                                                  |                                                                                                    |
|                                    | Select Year or month or day for patient age.                                                  |                                                                                                    |
| Sex                                | Select sex of the patient.                                                                    |                                                                                                    |
| District                           | Address of the patient                                                                        | District, Select from the list.                                                                    |
| Municipality(urban/rural)          |                                                                                               | Municipality, select from the list.                                                                |
| Ward No.                           |                                                                                               | Ward number, please type                                                                           |
| Village/Tole                       |                                                                                               | Type the name of village or tole                                                                   |
| Contact No                         |                                                                                               | Type the contact number of the patient                                                             |
| Disease Name                       | Disease which the patient was diagnosed                                                       | Name of the disease, select from the list.                                                         |
| ICD Code                           |                                                                                               | ICD code associated with the disease, automatically populated.                                     |
| If Other, specify                  |                                                                                               | Type the disease name if others is selected in previous cell.                                      |
| Diagnosis                          | Type of diagnosis, select among probable, confirmed and suspect.                              |                                                                                                    |
| Method                             | Lab report                                                                                    | Method of the diagnosis, select from the list.                                                     |
| Result                             |                                                                                               | Result of the lab test, select from the list.                                                      |
| Place                              |                                                                                               | Place/Lab name where the test was performed.                                                       |
| Outcome                            | Outcome                                                                                       | Select the outcome.                                                                                |
| If Referred, Location/ Institution |                                                                                               | If the outcome is 'referred', type the name of the health facility where the patient was referred. |

## ANNEX 2: DISEASE DESCRIPTION

### Malaria (ICD-10: B50-54)

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#### Identification

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Malaria is an infection that is due to parasite of the genus plasmodium. Infection with the malaria species can present sufficiently similar symptoms to make species differentiation generally impossible without laboratory studies. Furthermore, the fever pattern of the first few days of infection resembles that seen in early stages of many other illnesses (bacterial, viral and parasitic).

Severe malaria is usually due to *Plasmodium falciparum* infections and may present with variable clinical features, including fever, chills, sweats, cough, diarrhoea, respiratory distress and headache, and may progress to icterus, coagulation defects, shock, renal and liver failure, acute encephalopathy, pulmonary and cerebral edema, coma and death. Severe malaria may be the cause of coma and other CNS symptoms, such as disorientation and delirium, in any non-immune person recently returned from a tropical area. Prompt treatment is essential, even in mild cases, since delay in treatment may lead to complications and even death, Case-fatality rates among children and non - immune adults on treatment may be 10% - 40% or even higher.

Although other human malaria, vivax (benign tertian), malariae (quartan) and ovale generally are not life threatening yet severe malaria may be seen with *P. vivax* infection. Illness may begin, with malaise and a slowly rising fever of several days' duration, followed by a shaking chill and rapidly rising temperature, usually accompanied by headache and nausea, and ending with profuse sweating. After an interval free of fever, the cycle of chills, fever and sweating is repeated, daily, every other day or every third day. Duration of an untreated primary attack varies from a week to a month or longer. Recurrence of asexual parasitaemia in *P. vivax* or *P. ovale* infections arise from hypnozoites in liver and usually occurs after 6 weeks of treatment but may be seen up to 5 years. Malariae infections may persist for life with or without recurrent febrile episodes. Persons who are partially immune or who have been taking prophylactic drugs may show an atypical clinical picture and a prolonged incubation period.

Demonstration of the parasites in the peripheral blood smear is the gold standard for malaria diagnosis. If microscopy is not feasible in the facility, then quality assured RDTs should be used for the diagnosis. All positive cases and 10 % of negative cases should be sent to the nearest microscopy quality check center.

Blood smear (10-20 mm diameter) is taken onto a clean glass slide. When blood smear is dried, wrap the blood smear slide into a wrapping paper and sent to the laboratory as soon as possible for laboratory examination. If delay is anticipated for staining, fix the smear by adding 2-3 drop of pure methanol and dry at room temperature before rapping by paper. Alternatively, blood sample can be collected onto what man No. 3 filter paper and dry at room temperature.

Repeated microscopic examinations every 12-24 hours may be necessary because the density of *Plasmodium falciparum* parasites in the peripheral blood varies and parasites are often not demonstrable in films from patients recently or actively under treatment. The most promising diagnostic tool is the Rapid Diagnostic Tests (RDTs), which are point of care test that detect circulating antigens in patient blood. Quality assured RDTs is a valuable component to microscopy because it complements microscopy and ensures increase access to diagnosis at the point of care and will contribute significantly to minimizing treatment based on clinical features.

---

### **Infectious agents**

---

*Plasmodium vivax*, *P. falciparum*, *P. malariae*, *P. ovale*, and *P. knowlesi* sporozoan parasites. Mixed infections are not infrequent in endemic areas.

---

### **Reservoir**

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Humans are the only important reservoir of human malaria. Nonhuman primates are naturally infected by many malaria species, including *p. knowlesi*, *p. cynomolgi*, *P. brazilianum*, *P. inui*, *p. schwezi* and *P. simium*, which can infect humans experimentally, but natural transmission to humans is rare.

---

### **Mode of transmission**

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By the bite of an infective female *Anopheles* mosquito. Most species feed at dusk and during early night hours; some important vectors have biting peaks around midnight or the early hours of the morning. When female *Anopheles* mosquito ingests blood from people infected with the parasite, the sexual stages of the parasite (gametocytes), male and female gametes unite to form the ookinete in the mosquito stomach which then penetrates the stomach wall to form oocyst on the outer surface in which thousands of sporozoites develop; this requires 8-35 days, depending on the species of parasite and the temperature. These sporozoites migrate to various organs of the infected mosquito, and some that reach the salivary glands mature and are infective when injected into a person as the insect takes the next blood meal.

In the susceptible host, the sporozoites enter liver hepatocytes and develop into exoerythrocytic schizonts. The hepatocytes rupture and asexual parasites (tissue merozoites) reach the bloodstream through the hepatic sinusoids and invade the erythrocytes to grow and multiply cyclically. Most will develop into asexual forms, from trophozoites to mature blood schizonts that rupture the erythrocyte within 48-72 hours, to release 8-30 (depending on the species) free erythrocytic merozoites that invade other erythrocytes. Clinical symptoms are produced at the time of each cycle, by the rupture of large numbers of erythrocytic schizonts. Within infected erythrocytes, some of the merozoites may develop into the male (microgametocyte) or the female (macrogametocyte), the sexual forms.

The period between the infective bite and the detection of the parasite in a thick blood smear is

the "prepatent period," which is generally 6–12 days with *p. falciparum*, 8-12 days with *p. vivax* and *p. ovale*, and 12-16 days with *p. malariae*(but may be shorter or longer). Delayed primary attacks of some *p. vivax* strains may occur 6-12 months after exposure. Gametocytes usually appear in the blood stream within 3 days of parasitemia with *p. vivax* and *p. ovale*, and after 10-14 days with *p. falciparum*. Some exoerythrocytic forms of *p. vivax* and *p. ovale* exist as dormant forms (hypnozoites) that remain in hepatocytes to mature months or years later and produce relapses. This phenomenon does not occur in *falciparum* or *malariae* malaria, and reappearance of these forms of the disease is the result of inadequate treatment, treatment failure or new infection. Malaria may also be transmitted by injection or transfusion of blood from infected persons or by use of contaminated needles and syringes, as by injecting drug users. Congenital transmission occurs rarely, but stillbirth from infected mothers is more frequent.

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### **Incubation period**

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The time between the infective bite and the appearance of clinical symptoms is approximately 7-14 days for *P. falciparum*, 8-14 days for *P. vivax* and *P. ovale*, and 7-30 days for *P. malariae*. Some strains of *P. vivax*, mostly from temperate areas may have a protracted incubation period of 8-10 months. The incubation period depend on the number of parasites infused when infection is by blood transfusion, but it is usually short and may range up to about 2 months.

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### **Period of communicability**

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For infectivity of mosquitoes, if infective gametocytes are present in the blood of patients; this varies, with species and strain of parasite and with response to therapy. Untreated or insufficiently treated patients may be a source of mosquito infection for more than 3 years in *malariae*, 1-2 years in *vivax*, and generally not more than 1 year in *falciparum* malaria; the mosquito remains infective for life. Transmission by transfusion may occur if asexual forms remain in the circulating blood; with *p. malariae* this can continue for 40 years or longer. Stored blood can remain infective for at least a month.

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### **Susceptibility and resistance**

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Susceptibility is universal except in humans with specific genetic traits. Tolerance or refractoriness to clinical disease is present in adults in highly endemic communities where exposure to infective anophelines is continuous over many years with the development of immunity. But immunity may wane on return to an endemic area after some time of residence in non- endemic area. Persons with sickle cell trait have relatively low parasitemia when infected with *p. falciparum*, and therefore are relatively protected from severe disease.

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### **Rationale for surveillance**

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Malaria continues to be one of the priority public health problems in Nepal, especially for those living in forested, forest fringe and foothills of southern Terai and inner Terai districts and Upper



Hilly River Valleys, where the risk of contracting the disease is far greater than the rest of the country.

Malaria transmission is evident in 69 of the 77 districts in Nepal. The recent micro stratification study, 2018 concluded that 43.3 % of the total population is residing in areas at risk (high, moderate and low) of malaria. There are 202 wards identified as high and moderate risk of malaria in 20 districts (as per new federal structure). Approximately 3.96% of total population is living in malaria endemic (high & moderate risk) areas. Among them, 0.22 million live-in high-risk areas (49 wards), 0.93 million in moderate risk areas (253 wards) and 11.34 million in low risk areas (2543 wards). The high and moderate risk is attributed to the receptivity and vulnerability characteristics of the area as evident from :abundance of vector - mosquitoes, suitable environment, mobile & migrant and vulnerable population, , and socio-economic factors. Receptivity and vulnerability are critical elements in malaria transmission and areas that were formerly classified as “No Malaria”; are in fact areas that have substantial receptive potential and high vulnerability characteristics as seen in upper hilly river valleys such as Baitadi, Bajura, and Mugu. High vulnerability due to heavy seasonal migration to malaria endemic Indian States leading exposure to infection and carrying the parasites back to their villages in Nepal, and receptivity due to favorable eco-environmental conditions and presence of vectors; thereby leading to conducive environment for transmission of malaria in the areas. The epidemic potential is a real concern as evident from periodic outbreaks in the past including outbreak in Banke district in September/October 2006. Epidemics have occurred at regular intervals in 1985, 1991, 1996-97, 2002 and 2006.

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## **Recommended Case Definition**

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### **Laboratory criteria for diagnosis**

- Demonstration of malaria parasite in the peripheral blood films by quality-controlled microscopy
- Detection of malarial antigen by quality assured rapid diagnostic test kit, where microscope is not available.
- Detection of antibodies against malaria in the serum by indirect immunofluorescence (IFA) or enzyme linked immunosorbent assay (ELISA)
- Detection of malaria parasite by polymerase chain reaction (PCR)

### **Case classification**

*Probable severe malaria:* A person requiring hospitalization for symptoms and/or signs of severe malaria, who receives antimalarial treatment.

*Confirmed severe malaria:* A patient requiring hospitalization for signs of severe illness and/or evidence of vital organ dysfunction confirmed by microscopy or RDT diagnosis.

*Confirmed uncomplicated malaria:* Confirmed uncomplicated malaria is defined as a symptomatic

case of malaria without signs of severity or evidence of vital organ dysfunction which is confirmed by microscopy or rapid diagnostic test.

*Treatment failure:*Inability to clear malarial parasitemia or prevent recrudescence after administration of an antimalarial medicine, regardless of whether clinical symptoms are resolved

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### **Recommended Types of Surveillance for Sentinel Sites**

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- Patient records should be maintained at Hospital level in each EWARS sentinel sites.
- Medical Recorders of EWARS sentinel sites should be maintained EWARS-1 register by recording of all confirmed malaria after consulting the Emergency register, Inpatient/OPD register, Laboratory register and other concerns registers.
- Medical Recorders of EWARS sentinel sites must report all cases of probable and/or confirmed severe & complicated malaria including within 24 hours on immediate reporting forms (EWARS-2).
- Medical Recorders of EWARS sentinel sites should reporting on all confirmed cases of Malaria in the weekly EWARS reporting form including zero reporting.
- Nursing In charge should be informed to Medical Recorder about all cases (probable/confirmed) of Severe Malaria admitted in any wards.
- Timely recognition of malaria epidemic and notification at all times; all **outbreaks** (clinical cases) should be reported **immediately** to the respective Health Directorates and the EDCD/DoHS and/or VBDRTC, Hetauda for immediate investigation and laboratory confirmation.

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### **Recommended Minimum Data**

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As per EWARS reporting forms and guide.

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### **Principles uses for data for action**

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- Identify high-risk groups and problem areas (e.g. districts where therapeutic efficacy of anti-malarial drugs studies must urgently be carried out) and micro stratification should be done by district in order to identify high-risk low risk and no risk areas/villages/ clusters.
- Evaluate impact of control measures
- Adjust and target control measures
- Guide allocation of resources and training efforts.
- Institutionalization of drug resistance monitoring.

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### **Specific treatment for all malaria**

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#### **Severe Malaria**

##### **Clinical assessment**

Severe malaria is generally due to *P. falciparum* infection but not all *P.falciparum* malaria cases are severe. Severe malaria may be due to *P. vivax* and *P. knowlesi* infections also. Severe malaria is

a medical emergency. The airway should be secured in an unconscious patient and breathing and circulation assessed. An intravenous cannula should be inserted and immediate measurements of blood glucose (stick test), haematocrit / haemoglobin, and parasitaemia and, in adults, renal function should be taken. Blood should be taken for cross-match, and (if possible) full blood count, platelet count, clotting studies, blood culture and full biochemistry should be conducted

The assessment of fluid balance is critical in severe malaria. Respiratory distress, with acidotic breathing in severely anaemic children, often indicates hypovolaemia and requires prompt rehydration and, where indicated, blood transfusion. Symptoms in children may deteriorate suddenly. Mortality amongst pregnant women and children who develop severe malaria is particularly high. Hypoglycemia may be seen frequently especially in children and pregnant women.

### Diagnosis of severe malaria

The signs of severe malaria are nonspecific and they can occur in other febrile diseases such as meningitis, encephalitis, septicemia, typhoid fever, leptospirosis and viral infections that are common in malaria endemic area. Therefore, the clinical diagnosis of severe malaria must be confirmed by microscopy and if not available or feasible then diagnosis must be done by RDTs.

### Specific treatment in severe malaria

- Treatment should be started immediately after the diagnosis is suspected but blood must be taken immediately before starting treatment to confirm the diagnosis by microscopy if available and if not available or feasible then by RDTs.
- A drug regimen as recommended in the National Malaria Treatment Protocol should be used. It is essential that antimalarial treatment in full doses is given as soon as possible in severe malaria.
- The antimalarial drug should be given parenterally preferably iv.
- Once a patient has received at least 24 hrs of parenteral therapy and can tolerate oral therapy, treatment must be given orally.

**Dose of Artesunate:** Severe malaria is a medical emergency. Parenteral (IV) Artesunate is the drug of choice for severe malaria (table 1). After rapid clinical assessment of the patient, a full dose of parenteral antimalarial treatment should be started without delay.

**Table 1: Dose of Artesunate in severe malaria**

| Groups                                                                                     | Drug            | Dose                                                                               | Remarks                                                                                                      |
|--------------------------------------------------------------------------------------------|-----------------|------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------|
| Children weighing < 20 kg should receive a higher dose of artesunate (3 mg/kg bw per dose) | Artesunate I.V. | 3 mg/kg bw* i.v. on admission (time = 0h), then at 12 h and 24 h, then once a day. | After 24 hours and when patient is able to take oral medication then switch to oral ACT(6 doses over 3 days) |

| Groups                               | Drug            | Dose                                                                                 | Remarks                                                                                                      |
|--------------------------------------|-----------------|--------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------|
| Children weighing > 20 kg and Adults | Artesunate I.V. | 2.4 mg/kg bwi.v. on admission<br>(time = 0h), then at 12 h and 24 h, then once a day | After 24 hours and when patient is able to take oral medication then switch to oral ACT(6 doses over 3 days) |
| Pregnancy all trimester              | Artesunate I.V. | as for adults                                                                        | as for adults                                                                                                |

bw\* = body weight

Artesunate is soluble in water but has poor stability in aqueous solutions at neutral or acid pH. In the injectable form, artesunic acid is drawn up in sodium bicarbonate to form sodium artesunate immediately before injection.

### Oral Medication:

- If severe malaria is due to Pf: After 24 hours and when patient is able to take oral medication then switch to oral ACT(6 doses over 3 days)
- If severe malaria is due to Pv: After 24 hours and when patient is able to take oral medication then switch to oral ACT 6 doses over 3 days.

### Reducing the transmissibility of treated *P. falciparum* infections

To reduce transmission – Primaquine single dose of 0.25 mg/kg bw – (except in pregnant women, infants aged < 6 months and women breastfeeding infants aged < 6 months). Testing for glucose-6-phosphate dehydrogenase (G6PD) is not required.

### Preventing relapse in *P. vivax* or *P. ovale* malaria

- 14-day course of primaquine - (except pregnant women, infants aged < 6 months, and women breastfeeding infants aged < 6 months).
- G6PD testing is encouraged prior to 14 days PQ therapy but in case testing is not available closely supervised 14 days PQ therapy will be given.
- Counselling should be done to patient and followed up on days 3, 7 and 14 to monitor for adverse effects and compliance with primaquine.
- In women who are pregnant or breastfeeding - weekly chemoprophylaxis with chloroquine until delivery and breastfeeding are completed, then, treat with primaquine to prevent future relapse.

All age groups and in all trimester of pregnancy: **Artesunate is the drug of choice for severe malaria.**

## Other Drugs:

The use of following drugs in the management of severe malaria is of no beneficial effect and may indeed be harmful and should be avoided:

- Corticosteroids
- Other anti-inflammatory agents
- Agents given for cerebral oedema such as urea, mannitol.
- Low molecular weight dextran
- Epinephrine
- Heparin.

### a. Treatment of uncomplicated confirmed malaria

Microscopy is the basis of diagnosis of malaria in hospitals. The use of RDTs in these facilities is justified only during off hours when microscopy is not feasible.

#### i. Treatment of vivax malaria

Chloroquine is the drug of choice in the treatment of *P. vivax* malaria. In addition, Primaquine is added for radical cure as *P. vivax* tends to relapse frequently. Primaquine is effective for the prevention of relapses. Therefore, chloroquine and primaquine should be administered to the patient according to the dosages given in table 2.

The first line treatment for vivax malaria is chloroquine (CQ). Chloroquine is given at an initial dose of 10 mg base/kg body weight, followed by 10 mg/kg body weight on the second day and 5 mg/kg body weight on the third day. Treatment should be encouraged based on weight of the patient as above, in case weight of the patient is not feasible then it may be based on age groups as detailed below.

**Table 2. Dosage of Chloroquine and primaquine by age group**

| Days    | Drug                         | Age in years |       |       |         |      |
|---------|------------------------------|--------------|-------|-------|---------|------|
|         |                              | < 1          | 1 - 4 | 5 - 9 | 10 - 14 | > 14 |
| 1       | Chloroquine tablet (150mg.)  | ½            | 1     | 2     | 3       | 4    |
|         | Primaquine tablet (7.5 mg.)  | Nil          | ½     | 1     | 1 ½     | 2    |
| 2       | Chloroquine tablet (150 mg.) | ½            | 1     | 2     | 3       | 4    |
|         | Primaquine tablet (7.5 mg.)  | Nil          | ½     | 1     | 1 ½     | 2    |
| 3       | Chloroquine tablet (150 mg.) | ½            | ½     | 1     | 1 ½     | 2    |
|         | Primaquine tablet (7.5 mg)   | Nil          | ½     | 1     | 1 ½     | 2    |
| 4 - 14* | Primaquine tablet (7.5 mg.)  | Nil          | ½     | 1     | 1 ½     | 2    |

Note : \* = Standard 14 days Primaquine treatment is recommended if adequate monitoring and follow up can be ensured.

Table 2. Dosage of Chloroquine by age group. (Each tablet of Chloroquine contains 150mg base)

### Anti-relapse treatment

To prevent relapse, *P. vivax* malaria should be treated in children and adults (except pregnant women, infants aged <6 months, and women breastfeeding infants <6 months) with a 14-day course of primaquine at 0.25 mg/kg body weight per day. (Table 3.3). G6PD deficiency should be done prior to treatment. To achieve the goal of malaria elimination and in the light of the public health benefit and significance of achieving radical cure, it is recommended to use the 14 day regimen of primaquine in all cases even where G6PD status or testing is not available. However, all patient receiving primaquine should be properly counselled and closely supervised for detection and management of primaquine-induced hemolysis. The patient should be followed up on Day 3, 7 and 14, both to monitor for adverse effect and to encourage adherence to the 14 days treatment schedule.

| Days          | Medicine           | Age in years |     |     |       |     | Follow-up schedule |
|---------------|--------------------|--------------|-----|-----|-------|-----|--------------------|
|               |                    | < 6 months   | 1-4 | 5-9 | 10-14 | >14 |                    |
| 1             | Primaquine (7.5mg) | Nil          | ½   | 1   | 1 ½   | 2   |                    |
| 2             | Primaquine (7.5mg) | Nil          | ½   | 1   | 1 ½   | 2   |                    |
| 3             | Primaquine (7.5mg) | Nil          | ½   | 1   | 1 ½   | 2   | Y                  |
| 4-6           | Primaquine (7.5mg) | Nil          | ½   | 1   | 1 ½   | 2   |                    |
| 7             | Primaquine (7.5mg) | Nil          | ½   | 1   | 1 ½   | 2   | Y                  |
| 8-13          | Primaquine (7.5mg) | Nil          | ½   | 1   | 1 ½   | 2   |                    |
| 14            | Primaquine (7.5mg) | Nil          | ½   | 1   | 1 ½   | 2   | Y                  |
| TOTAL TABLETS |                    | Nil          | 3½  | 7   | 10½   | 14  |                    |

Table 3. Dosage and follow up schedule for primaquine by age group

(7.5mg tablet of primaquine dosed at 0.25mg/kg bw daily for 14 days.).

*Note: = Standard 14 days Primaquine treatment is recommended ensuring close monitoring of the patients. PQ should be taken with food to minimize GIT adverse events.*

### ii. Treatment of uncomplicated falciparum malaria

Attached is the A-L table.

| Weight | Age (yrs) | Artemether – Lumefantrine* |                    |                    | Primaquine<br>(0.25mg/kg) |
|--------|-----------|----------------------------|--------------------|--------------------|---------------------------|
|        |           | Day 1                      | Day 2              | Day 3              |                           |
|        |           | 1st dose<br>After 8 hours  | morning<br>evening | morning<br>evening |                           |

| Weight          | Age (yrs)    | Artemether – Lumefantrine* |               |               | Primaquine (0.25mg/kg)                                               |
|-----------------|--------------|----------------------------|---------------|---------------|----------------------------------------------------------------------|
|                 |              | Day 1                      | Day 2         | Day 3         |                                                                      |
| < 15 kg         | < 3          | 1 tab 1 tab                | 1tab 1 tab    | 1tab 1 tab    | ½ tablet (excluding breastfeeding infants less than 6 months of age) |
| 15 -< 25 kg     | 3- 9         | 2 tabs 2 tabs              | 2 tabs 2 tabs | 2 tabs 2 tabs | 1 tab                                                                |
| 25 – <35 kg     | 10 - < 14    | 3 tabs 3 tabs              | 3tabs 3 tabs  | 3 tabs 3 tabs | 1.5 tab                                                              |
| 35 kg and above | 14 and above | 4 tabs 4 tabs              | 4tabs 4 tabs  | 4tabs 4 tabs  | 2 tab                                                                |

\*(each tablet of AL contains 20mg/120mg artemether and lumefantrine respectively)

**iii. Target dose range of artemether + lumefantrine (AL): Total dose of 5-24 mg/kg - bw of artemether and 29-144 mg /kg- bw of lumefantrine**

1. Oral Artemether and Lumefantrine (AL as Coartem R) fixed dose combination) in 6 doses over 3 days is the recommended first line treatment of uncomplicated confirmed falciparum malaria in all age groups and in all trimester of pregnancy (as detailed in table3 below).

|         |           | Artemether + Lumefantrine* |            |         |       |         |       | Primaquine (0.25mg/kg)                                               |
|---------|-----------|----------------------------|------------|---------|-------|---------|-------|----------------------------------------------------------------------|
| Weight  | Age (yrs) | Day 1                      |            | Day 2   |       | Day 3   |       |                                                                      |
|         |           | First Dose                 | After 8hrs | Morning | Night | Morning | Night |                                                                      |
| < 15 kg | < 3       | 1 tab                      | 1 tab      | 1 tab   | 1 tab | 1 tab   | 1 tab | ½ tablet (excluding breastfeeding infants less than 6 months of age) |

Table 4. Dosage of artemether + lumefantrine by age and weight group

(each tablet of AL contains 20mg/120mg artemether and lumefantrine respectively.

**Reducing the transmissibility of treated P. falciparum infections**

- To reduce transmission – Primaquine single dose of 0.25 mg/kg bw – (except in pregnant women, infants aged < 6 months and women breastfeeding infants aged < 6 months). Testing for glucose-6-phosphate dehydrogenase (G6PD) is not required.
- For ease of monitoring and to ensure compliance, primaquine should be given on day 1, single dose of 0.25 mg/kg bw along with the first dose of AL as directly observed treatment

## Second Line Treatment:

- **Second line treatment:**The recommended 2<sup>nd</sup> line option in Nepal is dihydroartemisinin + piperazine (DHA/PPQ). The longer half-life of piperazine gives it an advantage over lumefantrine in the treatment of vivax malaria. DHAP is given over 3 days (dihydroartemisinin at a dose of 4 mg/kg bw per day and 18 mg/kg bw per day piperazine once a day for 3 days) (Table 5). DHA-PPQ is the second line drug for both vivax and falciparum malaria.

### A second line antimalarial should be used in the following situations:

- Where a patient does not tolerate or has adverse reactions to the first line medicine
- Recrudescence (treatment failure) - reappearance of symptoms and parasites within 28 days following initial antimalarial treatment of the 1st line drug
- Suspected chloroquine resistant vivax infection – all cases imported from areas with chloroquine-resistant infections (Mekong Region, Countries in South America and Africa, Indonesia, Timor Leste and PNG) should be considered as potentially CQ resistant and treated with 2nd line medicine.

| Weight (Kg) | Age (Years) | Dihydroartemisinin(DHA)/Piperazine (PPQ)<br>40 mg/320 mg base tablets |        |        |
|-------------|-------------|-----------------------------------------------------------------------|--------|--------|
|             |             | Day 1                                                                 | Day 2  | Day 3  |
| <10         | Under 1     | ¼ tab                                                                 | ¼ tab  | ¼ tab  |
| 11-24       | 1-6         | 1 tab                                                                 | 1 tab  | 1 tab  |
| 24-50       | 7– 13       | 1½ tab                                                                | 1½ tab | 1½ tab |
| 50-70       | 14-18       | 2 tabs                                                                | 2 tabs | 2 tabs |
| ≥70         | ≥18         | 3 tabs                                                                | 3 tabs | 3 tabs |

Table 5. Dihydroartemisinin Piperazine (DHAP) Dosing Regimen for the 40mg/320mg formulation

The recommended 2<sup>nd</sup> line option is dihydroartemisinin + piperazine (DHA/PPQ). This is given over 3 days at a dose of dihydroartemisinin 4 mg/kg bw per day and 18 mg/kg bw per day piperazine once a day for 3 days (Table 3.4)



## Kala-azar (ICD-10: B55.0)

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### Introduction

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Kala-azar is a major public health problem in Nepal. The first case of kala-azar was reported in Nepal as early as 1960s. The programme initially identified 12 districts as an endemic from central and eastern Terai region. However, six new districts were added to that list in endemicity in 2016, including hilly districts, because sporadic cases have been consistently reported from other parts of the country including hilly and Kathmandu valley districts and local transmission was verified and documented by epidemiological and entomological studies. Cases have been also reported from other 27 districts which are hitherto considered as non-endemic districts and disease transmission verification in these districts is in progress. Irrespective of the endemicity status, new kala-azar cases have been reported from 50 (out of 77) districts in the country in 2072. Despite this geographical expansion of the disease, the programme has seen a steady decline in the incident cases and mortality since 2003. Over 8.6 million people living in these 18 endemic districts are at risk of Kala-azar.

Kala-azar (the most severe form) caused by intracellular protozoa of the genus *leishmania*. The disease is characterized by prolonged irregular fever, splenomegaly, anemia, and progressive weight loss and sometimes darkening of the skin. Fever is of gradual or sudden onset, persistent and irregular, often with two daily peaks, with alternating periods of a pyrexia and low-grade fever. Post-kala-azar dermal lesion may occur after apparent cure of Kala-azar disease.

In endemic areas, children and young adults are mainly affected. The disease is fatal if not treated or delay treatment. It affects the poorest and most marginalized people of the community and is commonly associated with malnutrition, poor housing conditions and a weak immune system.

The rapid dipstick “rK39” test is the mainstay in the serological diagnosis of kala-azar. The rapid dipstick “rK39” test is a specific test available for the diagnosis of kala-azar for the first episode. This RDT is a simple test which can be used at all levels of the health care services. Results can be read easily and within 10 minutes. It does not need highly skilled laboratory staff and test results expedite the initiation of treatment provided standard case definitions are followed.

Demonstration of *Leishmania Donovanii* is the most specific test for the diagnosis of kala-azar. This can be done by examination of bone marrow or splenic aspirate. Examination of aspirates from these sites is recommended since the concentration of the parasites is high at these sites. Since the specificity and the sensitivity of these tests are very high, these tests are considered as the “gold standard” for the diagnosis of kala-azar. However, the procedures are invasive with risks to the patient, and therefore not recommended for routine use in the programme. Only trained personnel should carry out these tests in well-equipped hospitals, to minimize the risk of complications.

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**Infectious agents**

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Leishmania donovani

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**Reservoir**

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Humans are the only known reservoir in India, Nepal and Bangladesh.

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**Mode of transmission**

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Through bite of infected phlebotomine (Phlebotomus argentipes) sand flies

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**Incubation period**

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The average incubation period ranges 2-6 months.

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**Period of communicability**

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Infection is transmitted with the bite of an infected female sand-fly into a susceptible host. The transmission is 'anthroponotic' – human to human transmission by the vector without other animals in between.

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**Susceptibility and resistance**

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Susceptibility is general. Kala-azar apparently includes lasting homologous immunity. Considerable evidence indicates that in apparent and subclinical infections are common and that malnutrition predisposes to clinical disease and activation of in apparent infections. Manifest disease occurs among AIDS patients, presumably as reactivation of latent infections.

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**Rationale for surveillance**

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Kala-azar is endemic in 18 districts of central and eastern Terai region including hilly districts. Over 8.6 million people living in these 18 endemic districts are at risk of Kala-azar. Kala-azar is a re-emerging disease of chronic in nature and mainly clustered. It is also expected and hypothesized that there is under reporting of Kala-azar cases in the endemic areas. A good surveillance along with other strategies is very important to contribute on ongoing Kala-azar elimination. Therefore, epidemiological surveillance systems including both disease and vector surveillance need to be strengthened further at the district level.

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**Recommended case definition**

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**Case definitions:****Probable VL (KA) case:**

A person living in or having travelled to Kala-azar endemic areas showing clinical signs and symptoms of Kala-azar (mainly irregular fever lasting more than two weeks and splenomegaly and/or weight loss), after ruling out malaria in endemic areas

### **Confirmed VL case:**

- **Laboratory-confirmed VL case:**

A probable VL case with laboratory confirmation, either serological (RDT, DAT, ELISA, IFAT) and/or parasitological (smear, culture) and/or positive by PCR or related techniques.

OR

- **Clinically-confirmed VL case:**

A probable VL case that has not been confirmed by any laboratory test (i.e. test(s) not done or negative) but is assessed by a clinician to be a confirmed VL case based on clinical grounds.

All confirmed VL cases, either clinically or laboratory; should be treated according to the protocol and reported.

### **Laboratory criteria for diagnosis –**

- Demonstration of LD bodies in the smear prepared from bone marrow, spleen and peripheral blood samples
- Detection of parasite specific antigen by rapid diagnostic test kit eg. rK-39 test
- Detection of parasite by immune-fluorescence assay (IFA) or enzyme linked immunosorbent assay (ELISA)
- Detection of parasite DNA by polymerase chain reaction (PCR)

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### **Recommended types of surveillance for sentinel sites**

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- Patient records should be maintained at Hospital level in each EWARS sentinel sites.
- Medical Recorders of EWARS sentinel sites should be maintained EWARS-1 forms by recording of all clinical case/s (probable/confirmed) of Kala-azar after consulting the case investigation forms, Emergency register, Inpatient/OPD register, Laboratory register and other concerns registers.
- Medical Recorders of EWARS sentinel sites should reporting on all clinical case/s (probable/confirmed) of Kala-azar in the weekly EWARS reporting form (EWARS-3) including zero reporting.
- Nursing In charge should be informed to Medical Recorder about all clinical case/s (probable/confirmed) of Kala-azar admitted in any wards.

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### **Recommended minimum data**

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As per EWARS reporting forms and guidelines.

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### **Principal uses of data for action**

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- Evaluate the real extent of the problem and the main populations at risk
- Improve and focus the control activities

- Identify technical and operational difficulties
- Evaluate impact of control interventions
- Anticipate epidemics, apply epidemic preparedness, epidemic containment

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## **Specific treatment**

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### **Primary Kala-azar**

- First line regimen- Liposomal Amphotericin B
- WHO Expert Committee on Leishmaniasis in 2010 and Regional Technical Advisory Group (RTAG) for the Kala-azar elimination programme meeting in 2011 recommended Liposomal Amphotericin B (L-AmB) as the first option regimen, during the attack phase, for the Indian sub- continent (ISC).
- Liposomal amphotericin B at the dose of 10mg/kg single dose over 2 hours. Single dose treatment ensures 100% treatment compliance.
- Liposomal amphotericin B is safe in pregnant women, severely ill patients, children less than 2 years old and old aged patients and HIV co-infected patients.
- Successful therapy improves the general condition, resolves fever in most of the cases by end of week and causes regression of splenomegaly in most of the cases and recovery of blood counts towards normal in most of the cases by end of weeks. Complete regression of splenomegaly may take several months however most cases it completely regresses by 6 months. A good indicator of definitive cure is the absence of clinical relapse at 6 months.
- Most clinical trials have been conducted with a reference liposomal Amphotericin B formulation. Therefore, all other lipid formulations should be evaluated for toxicity, bioequivalence and efficacy before they are used clinically. Currently the national programme is receiving AmBisome (Liposomal Amphotericin B) donation through WHO. Therefore, details about the indications, preparations, storage and other aspects of L-AmB in this guideline has been made with reference to as AmBisome.

### **Things to remember for L-AmB treatment**

- Do not use underweight dose
- Give test dose before starting L-AmB infusion
- Do not freeze
- Always prepare in Dextrose solutions
- L-AmB is not compatible with saline and other fluids
- Concern to prevent foam formation while constituting drug

*Preparations, mode of administration, dose calculations are given in the annexure III*

## Second line treatment

Other than liposomal amphotericin B, mono drug therapy is not recommended. Combined regime reduces the dose requirement of individual drugs and its consequences without compromising the cure rate. Ministry of Health, Nepal has endorsed following treatments for kala-azar ranked in order of preference as per WHO recommendations<sup>1</sup>

## Combination regimens

Three separate combinations showed 95.06–99.78% cure rates. These include co-administration of

1. Liposomal amphotericin B (5 mg/kg, single infusion) plus 7 days Miltefosine 50 mg BID in adult or 2.5mg/kg/day  
OR
2. Liposomal amphotericin B (5 mg/kg, single infusion) plus 10 days' Paromomycin (11 mg/kg base),  
OR
3. Miltefosine plus Paromomycin for 10 days

No safety issues were recorded with above regimens. Combination regimens have the potential advantages of reducing the probability of selection of drug-resistant parasites, thereby prolonging the effective life of the available medicines. Regional Technical Advisory Group (RTAG) recommends use of combination regimen once the attack phase is over.

The implementation of combination regimens will be used in patients where the first line treatment is either not indicated or not available. It will be made available as a second line regimen for patients who cannot be given Liposomal Amphotericin B monotherapy.

## Third line treatment

In case of lack of first and second line drugs third line can be accepted however national guideline strongly recommends first line treatment. Amphotericin B deoxycholate: 0.75–1.0 mg/kg per day by infusion, daily or on alternate days for 15–20 doses.

## Fourth line treatment

In very uncommon instances when first, second and third line treatment are not available, the fourth line can be considered.

## Miltefosine

Miltefosine is the only available oral anti kala-azar drug. It is available in two doses: as 10mg and

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1 *Control of the leishmaniasis, Report of a meeting of the WHO Expert Committee on the Control of Leishmaniasis, Geneva, 22–26 March 2010, [http://apps.who.int/iris/bitstream/handle/10665/44412/WHO\\_TRS\\_949\\_eng.pdf?jsessionid=E636D979AE734A8800D17380232A6304?sequence=1](http://apps.who.int/iris/bitstream/handle/10665/44412/WHO_TRS_949_eng.pdf?jsessionid=E636D979AE734A8800D17380232A6304?sequence=1)*

50mg capsule. It is to be noted that Miltefosine monotherapy has observed higher relapse rates in Nepal therefore it is preferred as part of the combination therapy. However, the monotherapy course for the treatment of kala-azar is 28 days if at all used as fourth line in absence of first, second and third line treatment as already mentioned under treatment section.

### Recommended doses of Miltefosine according to body weight

| Drug category                                                                              | Morning | Evening | Duration |
|--------------------------------------------------------------------------------------------|---------|---------|----------|
| More than 12 years of age and more than 50 kg body weight): 150mg/day                      | 100mg   | 50mg    | 28 days  |
| More than 12 years of age and more than 25-50 Kg body weight) at a dose of 100mg/day       | 50mg    | 50mg    | 28 days  |
| ≥12 years of age and less than 25 Kg body weight) at a dose of 50mg /day.                  | 50 mg   | 0       | 28 days  |
| Children aged (2-11 years age) at (2.5mg/kg body weight 10mg formulation in divided doses) |         |         | 28 days  |

Source: WHO TRS [http://apps.who.int/iris/bitstream/10665/44412/1/WHO\\_TRS\\_949\\_eng.pdf](http://apps.who.int/iris/bitstream/10665/44412/1/WHO_TRS_949_eng.pdf).

### Contraindications of Miltefosine and methods of verification

| Contraindication                   | Method of verification                                    |
|------------------------------------|-----------------------------------------------------------|
| Pregnancy                          | History of last menstrual period (LMP) and Pregnancy test |
| Pregnancy                          | History of last menstrual period (LMP) and Pregnancy test |
| MWRA not using contraceptives      | History                                                   |
| Lactating mother                   | History                                                   |
| Less than 2 years                  | History                                                   |
| Severe illness, bed bound          | History and Physical examination                          |
| Malnutrition                       | < 10 percentile weight for age                            |
| Severe anemia (Hb% < 5 gm)         | Level of Hb                                               |
| Patients with known kidney disease | Edema, decreased urine output, Proteinuria                |
| Patients with known liver disease  | Jaundice                                                  |
| Chronic alcoholism                 | History                                                   |

### Side effects and its management

- The common side effects of Miltefosine are vomiting, diarrhoea and abdominal pain. Rarely, there may be liver or kidney related side effects.
- Usually the drug may produce vomiting and diarrhoea during the first week of treatment in some patients. The symptoms are generally mild, of short duration and reversible.

- Patients having diarrhoea should be advised to take oral re-hydration solution frequently and they should be reassured that the diarrhoea and vomiting will stop after a few days.
- If vomiting is severe and does not stop, the patient should be referred to level III health institution for further treatment.
- Puffiness of face, jaundice, or decreased urine output may be liver or kidney related side effects. The patients, family members, FCHVs should be advised to monitor these symptoms. If these symptoms are reported, the patient should be referred to level III health institution for further investigation and treatment.
- If fever persists in spite of taking Miltefosine for two weeks, then the patient may have other infections along with Kala-azar. Such patients should be referred to level III health institution for further investigation and treatment.
- Do pregnancy test/rule out pregnancy

### **Indications for stopping Miltefosine treatment**

If any of the following conditions is observed, stop the Miltefosine and immediately refer the patient to level III health institution.

- Pregnancy during the treatment
- Development of any of the following signs and symptoms:
  - Jaundice
  - Puffiness of face
  - Decreased urine output
  - Breathlessness
  - Severe vomiting
  - Severe diarrhoea

### **Paromomycin: 15 mg (11 mg base) per kg body weight per day intramuscularly for 21 days.**

Paromomycin is an aminoglycoside antibiotic and promising new effective drug for the treatment of Kala-azar. The recommended dose is 15mg/kg/day to be given by intramuscular (IM) injections for 21 days. Paromomycin is absorbed quickly after intramuscular injection, reaching peak plasma levels within 1 hour.

### **Paromomycin dosage and administration**

- The recommended dose is 15 mg/kg sulfate (equivalent to 11 mg/kg base); no maximum dose
- Patients must remain well hydrated. Tell patients to drink enough
- If patients have severe vomiting and diarrhoea, do not give the injections.
- This medicine **cannot** be given intravenously
- Weigh the patient weekly and recalculate the dose.
- Not recommended during pregnancy.

## **Common side-effects**

The medicine is safe with minimal ototoxicity or nephrotoxicity. In the recommended dose, the ototoxicity is reversible. Pain in injection site is common. Paromomycin can be administered intramuscularly according to body weight to patients with visceral leishmaniasis who have normal renal function including children without the need for therapeutic monitoring or dose adjustment. These effects are usually mild to moderate and transient or reversible at the end of treatment. There is increase in liver enzymes aspartate aminotransferase (AST) and alanine aminotransferase (ALT), pyrexia, abnormal audiogram, and vomiting.

The drug is particularly useful for child bearing age women and children since safety and efficacy are not affected by gender and age. Monitoring of aspartate amino-transferase or alanine aminotransferase levels, or both, will be important for patients with pre-existing liver disease.

In pregnant women, Paromomycin crosses the placenta and can cause renal and auditory damage in the fetus. Therefore, it is not recommended in pregnancy. Paromomycin is excreted in breast milk and adverse effects in the breastfed infant cannot be excluded.

## **Things to be remembered for treatment**

- Paromomycin is administered intramuscularly (IM) only
- Do not use during pregnancy
- Paromomycin should be avoided in patients with severe anaemia with hemoglobin <5g/dl
- Do not use in patients with hypersensitivity to paromomycin or to other aminoglycoside antibiotics. Discontinue use if an allergic reaction occurs.
- Paromomycin is contraindicated in patients with renal insufficiency
- In cases where Paromomycin or the combination therapy using Paromomycin do not lead to a VL cure at or before 6 months, do not repeat therapy. Instead, switch to another anti-leishmanial drug
- The medicine may have minimal ototoxicity or nephrotoxicity. Other factors that may increase patient risk of toxicity are dehydration and advanced age.
- It should be stored below 30°C but do not freeze. It should also be protected from light.

## **Fifth line treatment**

Rescue treatment in case of non-response and relapse:

Non-responder or relapses are recommended for liposomal amphotericin B at higher cumulative doses up to 30mg/kg

OR

Conventional Amphotericin B deoxycholate

OR

Combination regime of two drugs.



## **Amphotericin B deoxycholate**

Amphotericin B deoxycholate has been used in the past for treatment of visceral leishmaniasis. However, due to its side-effects, it has been replaced by safer liposomal formulations, however, it is still a rescue medicine in non-responsive patients to anti-leishmanial medicines.

**Dosage:** The drug is given at 0.75-1mg/kg daily as IV infusion in 5% dextrose over 4 hours for 14days. If there is poor response to the treatment, the drug has to be continued for a period of 21-28 days. A test dose of 1 mg, given by infusion is recommended followed by a full dose 4-6 hours later.

The cure rate of this drug is very high, exceeding 90%. The patient must be admitted at level III health institution or special referral centers for administering Amphotericin B as it requires monitoring of renal parameters.

**Indications:** Amphotericin B is generally recommended in the following conditions:

- This is the third line regimen used when first and second line treatment regimen are not available
- Kala-azar treatment failure i.e. unresponsive to first and second line regimen or in cases of relapse.
- Kala-azar patients whose first and second line therapy is discontinued due to severe side effects.

## **Adverse events due to Liposomal amphotericin B (in order of frequency of occurrence)**

Reported side effects of AmBisome in order of frequency of occurrence include infusion related fever and rigor, chills, nausea/vomiting, headache, backache, chest pain, hypokalemia, dyspnoea, bronchospasm, tachycardia, hypotension, nephrotoxicity, and hepatobiliary disorders. Side effects like feverish feeling, nausea, backache are more common. Life threatening ADR (adverse drug reaction) are very rare. In case of infusion related reactions, infusion can be slowed down and/or physician may give medicines to prevent or treat infusion related reactions, such as diphenhydramine (antihistamine), paracetamol and or hydrocortisone to reduce immune system response.

## **Indications for stopping L-AmB treatment**

Patients who develop hypersensitivity reactions require cessation of L-AmB and switching to an alternative treatment. If a severe anaphylactic reaction occurs, the infusion should be immediately discontinued, and the patient should not receive any further infusions.

## **Storage conditions**

Before use, medicine should be stored at 2–25 °C and should not be frozen. It should also be protected from exposure to light. Once reconstituted, the product must be used immediately

## **Complete Treatment**

Cure from Kala-azar can be achieved only after completion of treatment regimen. The following measures are recommended to complete the treatment:

### **Counseling**

After confirming the diagnosis of kala-azar the following needs to be explained to the patient and family:

- Explain the importance of the need to treat kala-azar, and inform that early diagnosis and treatment is crucial.
- Inform that the drug is provided free of cost.
- Explain the need to complete the full course of the treatment.
- In case of treatment with L-AmB, patients should be counselled that the current symptoms will decrease in severity, frequency and then gradually disappear in next few days.
- Patient should be informed to report back to the health facility if symptoms persist beyond two weeks or recur during any period after discharge/cure
- Explain the need to start and continue treatment under supervision/observation.
- Inform that the patient will begin to start feeling better after a few days of treatment, but this does not mean cure. The symptoms will reappear if the treatment is not taken as advised and cure would occur only when full treatment has been taken.
- Explain the side effects of the treatment and advised them to contact the health worker if such events occur.

*Note: Please refer to the national guideline of Kala-azar 2019 for update.*

## Dengue fever (ICD-10: A 90)

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### Identification

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Dengue is the most rapidly spreading mosquito-borne viral disease in the world. Dengue Fever is an acute febrile viral disease characterized by sudden onset of fever, intense headache, myalgia, arthralgia, retro-orbital pain, GI disturbances and rash. Early generalized erythema occurs in some cases. A generalized maculopapular rash usually appears about the time of defervescence. Minor bleeding phenomena, such as petechiae, epistaxis or gum bleeding may occur at any time during the febrile phase. Sometime patient may have major bleeding phenomena. Lymphadenopathy and leukopenia with relative lymphocytosis; thrombocytopenia (less than  $100 \times 10^9/L$ ) and elevated transaminases are the usual presentation in our clinical practice. Recovery may be associated with prolonged fatigue and depression. Epidemics are explosive, but fatalities in the absence of severe dengue are rare.

Differential diagnosis includes influenza, measles, Chikungunya, infectious mononucleosis, HIV seroconversion, scarlet fever, meningococcal infection, drug reactions, yellow fever, measles, rubella, malaria, leptospirosis and other systemic febrile illnesses, especially those accompanied by rash.

HI, CF, IgG and IgM ELISA, and neutralization tests are diagnostic aids. IgM antibody, indicating current or recent infection, is usually detectable by day 6–7 after onset of illness. Virus is isolated from blood by inoculation of mosquitoes, or into mosquito or vertebrate cell cultures, and then identified with serotype specific monoclonal antibodies.

Illness is biphasic; it begins abruptly with fever and, in children, with mild upper respiratory complaints, often anorexia, and facial flush and mild GI disturbances. Coincident with defervescence and decreasing platelet count, the patient's condition suddenly worsens, with marked weakness, severe restlessness, facial pallor and often diaphoresis, severe abdominal pain and cyanosis. The liver may be enlarged, usually 2 or more days after defervescence. Hemorrhagic phenomena are seen frequently and include scattered petechiae, a positive tourniquet test, easy bruisability, and less frequently, epistaxis, bleeding at venipuncture sites and gum bleeding. GI haemorrhage is an ominous prognostic sign that usually follows a prolonged period of shock. In severe cases, findings include accumulation of fluids in serosal cavities, low serum albumin, elevated transaminases, a prolonged prothrombin time and low levels of C3 complement protein. Case-fatality rates in untreated or mistreated shock have been as high as 40%-50%; with good physiologic fluid replacement therapy, rates should be 1%-2%.

Serological tests show a rise in antibody titre against dengue viruses. IgM antibody, indicating a current or recent flavivirus infection, is usually detectable by day 6-7 after onset of illness. Virus can be isolated from blood during the acute febrile stage of illness by inoculation of mosquitoes or cell cultures. Isolation from organs at autopsy is difficult, but chances are improved by mosquito inoculation. Virus specific nucleic acid sequences may be detected by PCR.

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## **Infectious agent**

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Dengue virus (DEN) is a small single-stranded RNA virus comprising four distinct serotypes (DEN-1 to -4). These closely related serotypes of the dengue virus belong to the genus *Flavivirus*, family *Flaviviridae*.

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## **Reservoir**

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The viruses are maintained in a human *Aedes aegypti* mosquito cycle in tropical urban centres; a monkey mosquito cycle serves as a reservoir in Southeast Asia and West Africa. Dengue outbreaks have also been attributed to *Aedes albopictus*, *Aedes polynesiensis* and several species of the *Aedes scutellaris* complex.

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## **Mode of transmission**

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This disease is transmitted by the bite of infective mosquitoes, principally *Ae. aegypti*. This is a day biting species, with increased biting activity for 2 hours after sunrise and several hours before sunset. In Malaysia, *Aeniveus* complex and in West Africa *Ae. furcifer-taylori* complex mosquitoes are involved in enzootic monkey mosquito transmission.

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## **Incubation period**

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From 3 to 14 days, commonly 4-10 days.

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## **Period of communicability**

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Not directly transmitted from person-to-person. Patients are infective for mosquitoes from shortly before to the end of the febrile period, usually a period of 3-5 days. The mosquito becomes infective 8-12 days after the viremic blood meal and remains so for life.

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## **Susceptibility and resistance**

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Susceptibility in humans is apparently universal, but children usually have a milder disease than adults. Recovery from infection with one serotype provides lifelong homologous immunity but does not provide protection against other serotypes and may exacerbate subsequent infections.

In DHF/DSS the risk factor described best is the circulation of heterologous dengue antibody, acquired passively in infants or actively from an earlier infection. Such antibodies may enhance infection of mononuclear phagocytes through the formation of infectious immune complexes. Geographic origin of dengue strain, age, gender and human genetic susceptibility are also important risk factors.

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## **Rationale for surveillance**

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Dengue fever is the most significant arthropod borne viral disease worldwide. It occurs in over

100 countries and territories and threatens the health of over 2500 million people in tropical and subtropical regions. Dengue fever is a severe disease with high epidemic potential.

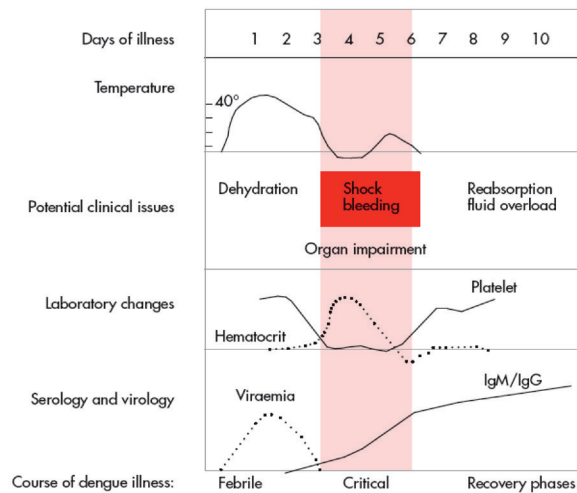
## Recommended case definition

## clinical management and delivery of clinical services

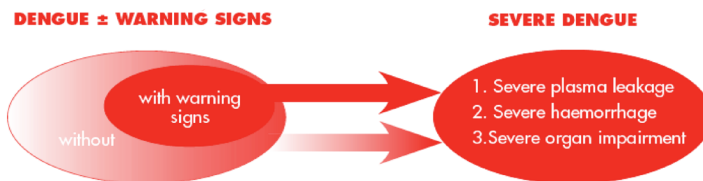
### OVERVIEW

Dengue infection is a systemic and dynamic disease. It has a wide clinical spectrum that includes both severe and non-severe clinical manifestations. After the incubation period, the illness begins abruptly and is followed by the three phases -- febrile, critical and recovery

### The course of dengue illness



### Suggested dengue case classification and levels of severity



#### CRITERIA FOR DENGUE ± WARNING SIGNS

##### Probable dengue

- live in /travel to dengue endemic area.
- Fever and 2 of the following criteria:
  - Nausea, vomiting
  - Rash
  - Aches and pains
  - Tourniquet test positive
  - Leukopenia
  - Any warning sign

**Laboratory-confirmed dengue**  
(important when no sign of plasma leakage)

##### Warning signs\*

- Abdominal pain or tenderness
- Persistent vomiting
- Clinical fluid accumulation
- Mucosal bleed
- Lethargy, restlessness
- Liver enlargement >2 cm
- laboratory: increase in HCT concurrent with rapid decrease in platelet count

\*[requiring strict observation and medical intervention]

#### CRITERIA FOR SEVERE DENGUE

##### Severe plasma leakage

- leading to:
- Shock (DSS)
  - Fluid accumulation with respiratory distress

##### Severe bleeding

as evaluated by clinician

##### Severe organ involvement

- Liver: AST or ALT  $\geq$  1000
- CNS: Impaired consciousness
- Heart and other organs

## **Febrile phase**

Patients typically develop high-grade fever with flu like syndrome and usually lasts 2–7. Monitoring for warning signs is crucial to recognizing progression to the critical phase.

Mild haemorrhagic manifestations like petechiae and mucosal membrane bleeding (e.g. nose and gums) may be seen. Massive vaginal bleeding (in women of childbearing age) and gastrointestinal bleeding may occur during this phase but is not common.

## **Critical phase**

Around the time of defervescence, usually on days 3–7 of illness, an increase in capillary permeability with increasing haematocrit levels may occur.

Progressive leukopenia and thrombocytopenia may occur. Patients with increased capillary permeability may develop Pleural effusion and ascites depending on the degree of plasma leakage and the volume of fluid therapy. Shock occurs when a critical volume of plasma is lost through leakage.

Some cases will deteriorate to severe dengue.

## **Recovery phase**

If the patient survives the 24–48-hour critical phase, a gradual reabsorption of extravascular compartment fluid takes place in the following 48–72 hours.

The various clinical problems during the different phases of dengue can be summarized as in table

## **Febrile, critical and recovery phases in dengue**

|                                                                                                                                     |
|-------------------------------------------------------------------------------------------------------------------------------------|
| <b>1. Febrile phase Dehydration, high fever may cause neurological disturbances and febrile seizures in young children</b>          |
| <b>2. Critical phase Shock from plasma leakage; severe haemorrhage; organ impairment</b>                                            |
| <b>3. Recovery phase Hypervolaemia (only if intravenous fluid therapy has been excessive and/ or has extended into this period)</b> |

## **Severe dengue**

Severe dengue is defined by one or more of the following:

- plasma leakage that may lead to shock (dengue shock) and/or fluid accumulation, with or without respiratory distress, and/or
- severe bleeding, and/or
- severe organ impairment

Severe dengue should be considered if the patient is from an area of dengue risk presenting with fever of 2–7 days plus any of the following features:

- plasma leakage, with circulatory compromise or shock.
- Significant bleeding.
- Altered level of consciousness
- Severe gastrointestinal involvement.
- Severe organ impairment or other unusual manifestations.

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### **Recommended types of surveillance for sentinel sites**

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- Patient records should be maintained at Hospital level in each EWARS sentinel sites.
- Medical Records of EWARS sentinel sites should be maintained EWARS-1 register by recording of all clinical case/s (suspected/probable/confirmed) of Dengue Fever including DHF & DSS after consulting the case investigation forms, Emergency register, Inpatient/OPD register and other concerns registers.
- Medical Records of EWARS sentinel sites must report of each clinical case (suspected/probable/confirmed) of Dengue Fever including DHF & DSS within 24 hours on immediate reporting forms (EWARS-2).
- Medical Records of EWARS sentinel sites should reporting on all clinical case/s (suspected/probable/confirmed) of Dengue Fever including DHF & DSS in the weekly EWARS reporting form (EWARS-3) including zero reporting.
- Nursing In charge should be informed to Medical Recorder about all clinical case/s (suspected/probable/confirmed) of Dengue Fever including DHF & DSS admitted in any wards.
- All clinical case/s (suspected/probable/confirmed) of Dengue Fever including DHF & DSS should be reported immediately to the respective DHO/DPHO, Regional Health Services Directorate, and the EDCC/DHS for immediate investigation and, if possible, laboratory confirmation.

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### **Recommended minimum data elements**

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As per EWARS reporting forms and guidelines

- Evaluate the real magnitude of problems
- Target high risk areas for intervention – i.e. risk approach for interventives
- Monitor changes in serotype and rate of DHF / DSS.
- Monitor trends in endemic disease or re-emergence of disease

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## Specific treatment

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### Stepwise approach to the management of dengue

#### *Step I*

##### Overall assessment

- History, including information on symptoms, past medical and family history
- Physical examination, including full physical and mental assessment
- Investigation, including routine laboratory and dengue-specific laboratory

#### *Step II*

- Diagnosis, assessment of disease phase and severity

#### *Step III*

##### Management

III.1 Disease notification

III.2 Management decisions.

Depending on the clinical manifestations and other circumstances, patients may:

- be sent home;
- be referred for in-hospital management;
- require emergency treatment and urgent referral.

A number of criteria may be used to decide when to transfer a patient to a high dependency unit. These include:

- early presentation with shock (on days 2 or 3 of illness);
- severe plasma leakage and/or shock;
- undetectable pulse and blood pressure;
- severe bleeding;
- fluid overload;
- organ impairment (such as hepatic damage, cardiomyopathy, encephalopathy, encephalitis and other unusual complications).

### Recommendations for treatment

#### *Step I*

- Overall assessment
- History
- Physical examination
- Investigation



### **Step II**

- Diagnosis, assessment of disease phase and severity

### **Step III**

- Management
- Disease notification
- In dengue-endemic countries, cases of suspected, probable and confirmed dengue should be notified.
- Management decisions

Depending on the clinical manifestations and other circumstances, patients may

- send home,
- be referred for in-hospital management)
- or require emergency treatment and urgent referral

### **Treatment according to groups**

Group A – patients who may be sent home

These are patients who are able to tolerate adequate volumes of oral fluids and pass urine at least once every six hours, and do not have any of the warning signs, particularly when fever subsides.

Group B – patients who should be referred for in-hospital management

Patients may need to be admitted to a secondary health care centre for close observation, particularly as they approach the critical phase. These include patients with warning signs, those with co-existing conditions that may make dengue or its management more complicated (such as pregnancy, infancy, old age, obesity, diabetes mellitus, renal failure, chronic haemolytic diseases), and those with certain social circumstances (such as living alone, or living far from a health facility without reliable means of transport).

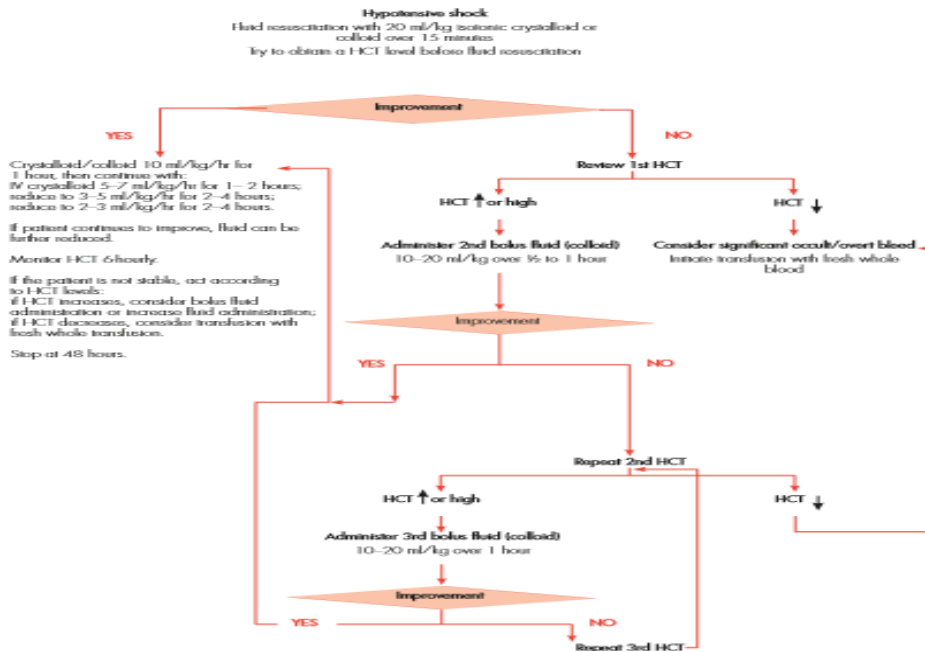
Group C – patients who require emergency treatment and urgent referral when they have severe dengue

Patients require emergency treatment and urgent referral when they are in the critical phase of disease, i.e. when they have:

- severe plasma leakage leading to dengue shock and/or fluid accumulation with respiratory distress;
- severe haemorrhages;
- severe organ impairment (hepatic damage, renal impairment, cardiomyopathy, encephalopathy or encephalitis).

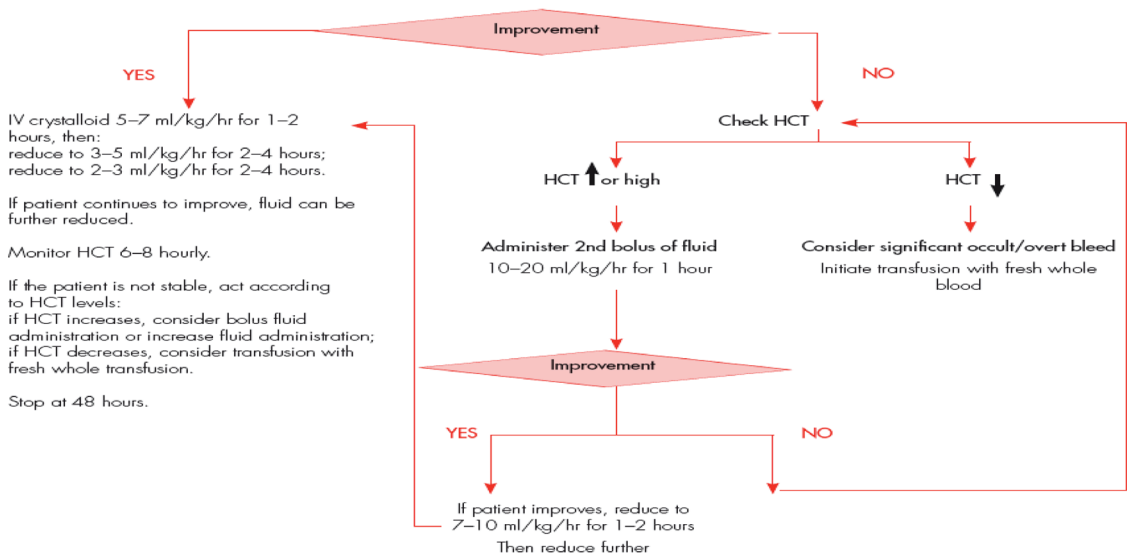
# Treatment of shock

## Algorithm for fluid management in compensated shock



## Algorithm for fluid management in hypotensive shock

Compensated shock (systolic pressure maintained but has signs of reduced perfusion)  
Fluid resuscitation with isotonic crystalloid  
5-10 ml/kg/hr over 1 hour



### For fever

- Paracetamol.
- No NSAIDs

| Age               | Dose (syrup 125 mg/5ml) | ml/dose/d |
|-------------------|-------------------------|-----------|
| <1 year           | 1/2 teaspoonful         | 2.5ml     |
| 1-4 years         | 1 teaspoonful           | 5ml       |
| 5 years and above | 2 teaspoonful           | 10ml      |

- Do not give antibiotics as these do not help unless there are other indications
- Oral Rehydration Therapy is recommended for patients with moderate dehydration caused by vomiting and high temperature.

Food should be given according to appetite..

Discharge criteria (all of the following conditions must be present)

### Clinical

- No fever for 48 hours.
- Improvement in clinical status (general well-being, appetite, haemodynamic status, urine output, no respiratory distress).

### Laboratory

- Increasing trend of platelet count.
- Stable haematocrit without intravenous fluid

## Scrub Typhus (ICD- A75.3)

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### Introduction

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Also known as tsutsugamushi disease, this acute febrile disease is caused by *orientiatsutsugamushi* [Japanese word *tsutsuga* (“dangerous”), *mushi* (“bug”)], previously called *Rickettsia tsutsugamushi*. *O. tsutsugamushi* is transmitted to humans by the bite of the larva of trombiculid mites (chiggers) which are almost microscopic, often brilliantly colored (red). Infected chiggers are found particularly in areas of heavy scrub vegetation during the wet season, (therefore this disease has also been called river/flood fever) when mites lay eggs usually June through November.

It causes a disseminated vasculitic and perivascular inflammatory lesions resulting in significant vascular leakage and end-organ injury. It affects people of all ages and even though scrub typhus in pregnancy is uncommon, it is associated with increased foetal loss, preterm delivery, and small for gestational age infants. After an incubation period of 6-21 days, onset is characterized by fever, headache, myalgia, cough, and gastrointestinal symptoms. A primary papular lesion which later crusts to form a flat black eschar, may be present. If untreated, serious complications may occur involving various organs. Laboratory studies usually reveal leukopenia, thrombocytopenia, deranged hepatic and renal function, proteinuria and reticulonodular infiltrate. Owing to the potential for severe complications, diagnosis, and decision to initiate treatment should be based on clinical suspicion and confirmed by serologic tests.

### Infectious agents

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*O. tsutsugamushi* is a gram-negative coccobacillus that is antigenically distinct from the typhus group rickettsiae. This organism has features that are common to and distinct from other rickettsiae. There are three variants or strains of *O. tsutsugamushi* (Karp, Gilliam, and Kato). Infection with one strain does not preclude reinfection with a different strain.

### Reservoir

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The reservoir and vector of scrub typhus are larval trombiculid mites of the genus *Leptotrombidium*. These larval mites (also known as chiggers) maintain the infection in successive generations via transovarial transmission. At least 8 of the known 60 species of trombiculid mites are capable of transmitting scrub typhus. The disease typically occurs 7 to 10 days after the bite of an infected chigger (range 6 to 19 days).

### Mode of transmission

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Scrub typhus is characteristically a geographically focal disease. Transmission of *O. tsutsugamushi* may occur in sharply delineated "mite islands" that consist of focal locations of scrub vegetation as small as a few square meters. Mites live on the vegetation, and moisture and temperature

conditions are ideal for propagation of chiggers and their small rodent hosts. The risk of disease transmission from chigger bites may be extremely high when humans enter these mite islands.

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### **Incubation Period**

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Infection commonly presents as an acute febrile illness 7 to 10 days after the bite of an infected larval trombiculid mite (chigger).

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### **Period of Communicability**

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Not directly transmitted from person to person. Humans acquire the disease from the bite of an infected chigger. The bite of the mite leaves a characteristic black eschar. The adult mites have a four-stage lifecycle: egg, larva, nymph and adult. The larva is the only stage (chigger) that can transmit the disease to humans and other vertebrates, since the other life stages (nymph and adult) do not feed on vertebrate animals. Both the nymph and the adult are free-living in the soil. The chiggers after getting infected exhibit high degree of potential for the transmission of *Orientia tsutsugamushi*. This happens because of the transfer of the causative agent, *O. tsutsugamushi* in-between different stages of the vector (transstadial transmission) as well as transmission of the agent from adult to the offspring (transovarial transmission). In this way, the vector is able to maintain the infectivity for a prolonged time period. Therefore, it is now believed that mites, apart from being vectors may behave as reservoirs as much as the rodents do.

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### **Susceptibility and surveillance**

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Susceptibility in humans is apparently universal, but children may have a milder disease than adults. Scrub typhus may cause spontaneous abortions or stillbirths in pregnant women.

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### **Rationale for surveillance**

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Scrub typhus is an emerging disease. Following the devastating earthquake in 2015, outbreaks of scrub typhus have been reported in Nepal. If untreated the disease can be fatal. Thus, for timely detection and proper and adequate treatment of scrub typhus cases is essential.

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### **Recommended case definition**

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Scrub typhus may begin insidiously with headache, anorexia, and malaise, or start abruptly with chills and fever. Approximately one-half of all patients develop a characteristically nonpruritic, macular or maculopapular rash. The rash typically begins on the abdomen and spreads to the extremities. The face is also often involved. Rarely, petechiae may develop. A painless papule often appears at the site of the infecting chigger bite. Subsequent central necrosis then occurs, which in turn leads to the formation of a characteristic eschar with a black crust. One or multiple eschars may develop before the onset of systemic symptoms. Occasionally, eschars can be atypical and lack a typical black crust.

As the illness evolves, most patients develop the following symptoms:

- Fever, which typically lasts for long periods in untreated patients (median 14.4 days; range 9-19)
- Intense generalized headache
- Diffuse myalgias
- Localized and subsequent generalized lymphadenopathy occurs in the majority of patients and may be accompanied by inflammation of the lymphatic sinuses, splenomegaly, and portal triaditis.
- Acute kidney injury
- Acalculus cholecystitis
- Meningitis
- Respiratory complaints are often present; rarely acute respiratory distress syndrome may occur.

### **Laboratory criteria for diagnosis**

As with all rickettsial diseases, no laboratory test is diagnostically reliable in the early phases of scrub typhus. The disease is usually recognized when clinicians correlate the presence of compatible clinical signs, symptoms, and laboratory features. Patients with scrub typhus may develop the following laboratory abnormalities:

- Leukopenia and thrombocytopenia with subsequent increase of white blood cell counts to normal levels. In children, leukocyte and platelet counts are usually within normal ranges, although thrombocytopenia and leukocytosis may also occur
- Coagulopathy
- Elevation of liver enzymes and bilirubin - indicating hepatocellular damage
- Proteinuria
- Elevation of creatinine
- Reticulonodular infiltrates (most common finding on chest radiograph). Chest X-rays also reveal transient perihilar or peribronchial interstitial infiltrates
- Cerebrospinal fluid (CSF) examinations show a mild mononuclear pleocytosis with normal glucose levels.

### **Enzyme-linkage Immunosorbent assay**

The “scrub typhus detect IgM rapid test” is a rapid immunochromatographic immunoassay for the qualitative detection of IgM antibodies to members of *O.tsutsugamushi* species in human serum, plasma or blood. After the onset of symptoms, the IgM titers increased gradually over 2-3 weeks, peaked at about 4 weeks and started to decrease rapidly between 4 and 5 weeks.

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## **Recommended types of surveillance for sentinel sites**

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- Patient records should be maintained at Hospital level in each EWARS sentinel sites.
- Medical Recorders of EWARS sentinel sites should be maintained EWARS-1 forms by recording of all clinical case/s (probable/confirmed) of scrub typhus after consulting the case investigation forms, Emergency register, Inpatient/OPD register, Laboratory register and other concerns registers.
- Medical Recorders of EWARS sentinel sites should reporting on all clinical case/s (probable/confirmed) of scrub typhus in the weekly EWARS reporting form including zero reporting.
- Nursing In charge should be informed to Medical Recorder about all clinical case/s (probable/confirmed) of scrub typhus admitted in any wards.

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## **Recommended minimum data elements**

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As per EWARS reporting forms and guidelines.

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## **Principle uses for data for action**

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- Evaluate the real extent of the problem and the main populations at risk
- Improve and focus the control activities
- Identify technical and operational difficulties
- Evaluate impact of control interventions
- Anticipate epidemics, apply epidemic preparedness, epidemic containment

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## **Specific treatment**

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- Doxycycline (100 mg orally or intravenously twice daily) is the drug of choice for this illness. Azithromycin has been advocated as an alternative agent.
- Chloramphenicol was the first drug shown to be effective in the treatment of scrub typhus, and is still commonly used in endemic regions. Doses of 250 to 500 mg orally or intravenously every six hours are effective. Chloramphenicol is specially used if the patients has meningitis. The adverse reactions of chloramphenicol are aplastic anemia, bone marrow depression, granulocytopenia, hypoplastic anemia, pancytopenia, thrombocytopenia (frequency not defined).

## Gastroenteritis

viruses (rotaviruses, enteric adenoviruses, astroviruses and caliciviruses including Norwalk-like viruses) infect children in their first years of life and cause a diarrheal illness that may be severe enough to produce dehydration requiring hospitalization for rehydration. Viral agents such as Norwalk-like viruses are also common causes of epidemics of gastroenteritis among children and adults. The epidemiology, natural history and clinical expression of enteric viral infections are best understood for type A rotavirus in infants and Norwalk agent in adults.

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### IDENTIFICATION

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#### I. ROTAVIRAL ENTERITIS (ICD-10: A08.0)

(Sporadic viral gastroenteritis, Severe viral gastroenteritis of infants and children)

Rotavirus infections are a leading cause of severe, dehydrating gastroenteritis in children <5 years of age. A sporadic, seasonal, often severe gastroenteritis of infants and young children. Rotavirus disease is characterized by vomiting and watery diarrhea for 3 to 8 days. Fever and abdominal pain also frequently occur. Additional symptoms include loss of appetite and dehydration. It is occasionally associated with severe dehydration and death in young children. The primary mode of transmission is the fecal-oral route, usually through direct contact between people. Because the virus is stable in the environment, transmission also can occur through ingestion of contaminated water or food and contact with contaminated surfaces or objects. Secondary symptomatic cases among adult family contacts can occur, although subclinical infections are more common. Rotavirus infection has occasionally been found in pediatric patients with a variety of clinical manifestation, but the virus is probably coincidental rather than causative in these conditions. Rotavirus is a major cause of nosocomial diarrhea of newborns and infants. Although rotavirus diarrhea is generally more severe than acute diarrhea due to other agents, illness caused by rotavirus is not distinguishable from that caused by other enteric viruses for any individual patient.

Diagnosis may be made by rapid detection of rotavirus antigen in stool specimens. Strains may be further characterized by enzyme immunoassay or reverse transcriptase polymerase chain reaction. False-positive ELISA reactions are common in newborns; positive reactions require confirmation by an alternative test.

In both developed and developing countries, rotavirus is associated with about one third of the hospitalized cases of diarrheal illness in infants and young children under 5 years of age. Neonatal rotaviral infections are frequent in certain settings but are usually asymptomatic. Essentially all children are infected by rotavirus in their first 2-3 years of life, with peak incidence of clinical disease in the 6 to 24 month age group. Outbreaks occur among children in day care settings. Rotavirus is more frequently associated with severe diarrhea than other enteric pathogens; in developing countries.

In temperate climates, rotavirus diarrhea occurs in seasonal peaks during cooler months;



in tropical climates, cases occur throughout the year, often with a less pronounced peak in the cooler dry months. Infection of adults is usually subclinical, but outbreaks of clinical disease occur in geriatric units. Rotavirus occasionally causes travellers' diarrhea in adults and diarrhea in immunocompromised (including AIDS) patients, parents of children with rotavirus diarrhea and the elderly.

Four oral, live, attenuated rotavirus vaccines, Rotarix™, RotaTeq™, Rotavac™ and RotaSiil™ are available internationally and WHO prequalified. All four vaccines are considered highly effective in preventing severe gastrointestinal disease.

## II. EPIDEMIC VIRAL GASTROENTEROPATHY (ICD-10: A08.1)

(Norwalk agent disease, Norwalk-like disease, Viral gastroenteritis in adults, Epidemic Viral gastroenteritis, Acute infectious nonbacterial gastroenteritis, Viral diarrhea, Epidemic diarrhea and vomiting, Winter vomiting disease, Epidemic nausea and vomiting).

Usually a self-limited, mild to moderate disease that often occurs in outbreaks, with clinical symptoms of nausea, vomiting, diarrhea, abdominal pain, myalgia, headache, malaise and low grade fever. GI symptoms characteristically last 24 -48 hours.

The virus may be identified in stool by direct or immune EM or, for the Norwalk virus, by RIA or by reverse transcription polymerase chain reaction (RT-PCR). Serological evidence of infection may be demonstrated by IEM or, for the Norwalk virus, by RIA. Diagnosis requires collection of a large volume of stool, with aliquots stored at 4°C (39°F) for EM, and at -20°C (-4°F) for antigen assays. Acute and convalescent sera (3-4 week interval) are essential to link particles observed by EM with disease etiology. RT-PCR is more sensitive than IEM and can be used to examine links among widely scattered clusters of disease.

Worldwide and common; most often in outbreaks but also sporadically; all age groups are affected. In most developing countries, antibodies are acquired much earlier. Sero-response to Norwalk virus was detected in infants and young children in Bangladesh and Finland.

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## INFECTIOUS AGENT

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- I. rotaviral enteritis: Rotavirus is a member of the family reoviridae and the genus rotavirus. by electron microscopy, the virus is observed to have a 70 nm, non-enveloped, icosahedral structure that surrounds a double-stranded RNA genome. Group A is common, group B is uncommon in infants but has caused large epidemics in adults while group C appears to be uncommon in humans. Groups A, B, C, D, E and F occur in animals. There are 4 major, and at least 10 minor, serotypes of group A human rotavirus, based on antigenic differences in the viral protein 7 (VP7) outer capsid surface protein, the major neutralization antigen. Another outer capsid protein, designated VP4, is associated with virulence and also plays a role in virus neutralization.

- II. Epidemic viral gastroenteropathy: Norwalk-like viruses are small, 27-to 32-nm, structured RNA viruses classified as caliciviruses; it has been implicated as the most common etiological agent of the nonbacterial gastroenteritis outbreaks. Several morphologically similar but antigenically distinct viruses have been associated with gastroenteritis outbreaks.

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## **RESERVOIR**

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- I. ROTAVIRAL ENTERITIS: The reservoir of rotavirus is the gastrointestinal tract and stool of infected humans. Although rotavirus infection occurs in many nonhuman mammals, transmission of animal rotaviruses to humans is believed to be rare and probably does not lead to clinical illness. Although immunodeficient persons may shed rotavirus for a prolonged period, a true carrier state has not been described.
- II. EPIDEMIC VIRAL GASTROENTEROPATHY: Humans are the only known reservoir.

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## **MODE OF TRANSMISSION**

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- I. ROTAVIRAL ENTERITIS: Probably fecal-oral with possible contact or respiratory spread. Although rotaviruses do not effectively multiply in the respiratory tract, they may be encountered in respiratory secretions. There is some evidence that rotavirus may be present in contaminated water.
- II. EPIDEMIC VIRAL GASTROENTEROPATHY: Probably by the fecal-oral route, although contact or airborne transmission from fomites has been suggested to explain the rapid spread in hospital settings. Several outbreaks have strongly suggested primary community foodborne, waterborne and shellfish transmission.

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## **INCUBATION PERIOD**

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- I. ROTAVIRAL ENTERITIS: Approximately 24-72 hours.
- II. EPIDEMIC VIRAL GASTROENTEROPATHY: Usually 24-48 hours; in volunteer studies with Norwalk agent, the range was 10 - 50 hours.

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## **PERIOD OF COMMUNICABILITY**

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- I. ROTAVIRAL ENTERITIS: During the acute stage of disease, and later while virus shedding continues. Rotavirus is not usually detectable after about the eighth day of infection, although excretion of virus for 30 days or more has been reported in immunocompromised patients. Symptoms last for an average of 4-6 days.
- II. EPIDEMIC VIRAL GASTROENTEROPATHY: During acute stage of disease and up to 48 hours after Norwalk diarrhea stops.

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## **SUSCEPTIBILITY AND RESISTANCE**

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- I. ROTAVIRAL ENTERITIS: Susceptibility is greatest between 6 and 24 month of age. By age 3 years, most individuals have acquired rotavirus antibody. Immunocompromised individuals are at particular risk for prolonged rotavirus antigen excretion and intermittent rotavirus diarrhea. Diarrhea is uncommon in infected infants less than 3 months of age.
- II. EPIDEMIC VIRAL GASTROENTEROPATHY: Susceptibility is widespread. Short-term immunity lasting up to 14 weeks has been demonstrated in volunteers after induced Norwalk illness, but long-term immunity was variable; some individuals became ill on rechallenge 27-42 months later. Levels of preexisting serum antibody to Norwalk virus did not correlate with susceptibility/resistance.

## Acute Diarrhoea

Diarrhea is often accompanied by other clinical signs and symptoms including vomiting, fever, dehydration and electrolyte disturbances. It is a symptom of infection by many different bacterial, viral and parasitic enteric agents. Diarrhea can also occur in association with other infectious diseases such as malaria and measles, as well as chemical agents. Change in the enteric flora induced by antibiotics may produce acute diarrhea by overgrowth and toxin production by *Clostridium difficile*.

Approximately 70%-80% of the vast number of sporadic diarrheal episodes in people visiting treatment facilities in less developed countries could be diagnosed etiologically if the complete battery of newer laboratory tests were available and utilized.

### **From a practical clinical standpoint, diarrheal illnesses can be divided into six clinical presentations:**

1. Simple diarrhea, managed by oral rehydration with solutions containing water, glucose and electrolytes, with its specific etiology not important in management;
2. Bloody diarrhea (dysentery), caused by organisms such as *Shigella*, *E. coli O157:H7* and certain other organisms;
3. Persistent diarrhea that lasts at least 14 days;
4. Severe purging as seen in cholera;
5. Minimal diarrhea, associated with vomiting, typical of some viral gastroenteritides; and illness from the toxins, such as those of *Staphylococcus aureus*, *Bacillus cereus* or *Cl.perfringens*; and
6. Hemorrhagic colitis, with watery diarrhea containing gross blood but without fever or fecal leukocytes.

### **Diarrhea caused by Escherichia coli**

Strains of *Escherichia coli* that cause diarrhea are of six major categories:

1. Enterohemorrhagic;
2. enterotoxigenic;
3. enteroinvasive;
4. enteropathogenic;
5. enteroaggregative; and
6. diffuse-adherent.

Each category has a different pathogenesis, possesses distinct virulence properties, and comprises a separate set of O:H serotypes. Differing clinical syndromes and epidemiological patterns may also be seen.

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## IDENTIFICATION

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### I. DIARRHEA CAUSED BY ENTEROHEMORRHAGIC STRAINS (ICD-10: A04.3)

(EHEC, Shiga toxin producing *E. coli* [STEC], *E. coli* O157:H7, Verotoxin production *E. coli* [VTEC])

The diarrhea may range from mild and nonbloody to stools that are virtually all blood but contain no fecal leukocytes. The most feared clinical manifestations of EHEC infection are the hemolytic uremic syndrome (HUS) and thrombotic thrombocytopenic purpura (TTP). Approximately 2–7% of subjects who manifest EHEC diarrhea progress to develop hemolytic uremic syndrome (HUS).

EHEC elaborate potent cytotoxins called Shiga toxins 1 and 2. Shiga toxin 1 is identical to Shiga toxin elaborated by *Shigella dysenteriae* 1; notably, HUS is also a well-recognized severe complication of *S. dysenteriae* 1 disease. Previously, these toxins were called verotoxins 1 and 2 or Shiga-like toxins 1 and 2. Elaboration of these toxins depends on the presence of certain phages carried by the bacteria. In addition, EHEC strains harbor a virulence plasmid that is involved in attachment of the bacteria to intestinal mucosa. Most EHEC strains have within their chromosome a pathogenicity island that contains multiple virulence genes encoding proteins that cause attaching and effacing lesions of the human intestinal mucosa. Lack of fever in most patients can help to differentiate this from shigellosis and dysentery caused by enteroinvasive strains of *E. coli* or by *Campylobacter*.

These infections are now recognized to be an important problem in North America, Europe, South Africa, Japan, the southern cone of South America and Australia. Their relative importance in the rest of the world is less well established. Serious outbreaks, including cases of hemorrhagic colitis, HUS and some deaths, have occurred from inadequately cooked hamburgers, unpasteurized milk, apple cider (made from apples that were probably contaminated by cow manure).

### II. DIARRHEA CAUSED BY ENTEROTOXIGENIC STRAINS (ETEC), (ICD-10:A04.1)

A major cause of travelers' diarrhea in people from industrialized countries who visit less developed countries. This bacterial disease is also an important cause of dehydrating diarrhea in infants and children in less developed countries. Enterotoxigenic strains may behave like *Vibrio cholerae* in producing profuse watery diarrhea without blood or mucus. Abdominal cramping, vomiting, acidosis, prostration and dehydration can occur, and low-grade fever may or may not be present; the symptoms usually last fewer than 5 days.

ETEC can be identified by demonstrating enterotoxin production, by immunoassays, bioassays or by DNA probe techniques that identify LT and ST genes (for heat labile and heat stable toxins) in colony blots.

It is an infection primarily of developing countries. During the first 3 years of life, children in developing countries experience multiple ETEC infections, which leads to the acquisition of immunity; consequently, illness in older children and adults occurs less frequently. Infection occurs among travelers from industrialized countries that visit less-developed countries.

### **III DIARRHEA CAUSED BY ENTEROINVASIVE STRAINS (EIEC) (ICD-10: A04.2)**

This inflammatory disease of the gut mucosa and submucosa caused by EIEC strains of *E.coli* closely resembles that produced by *Shigella*. The organisms possess the same plasmid dependent ability to invade and multiply within epithelial cells. However, clinically, the syndrome of watery diarrhea due to EIEC is much more common than dysentery. The O antigens of EIEC may cross-react with *Shigella* O antigens. Illness begins with severe abdominal cramps, malaise, watery stools, tenesmus and fever; in less than 10% of patients, it progresses to the passage of multiple, scanty, fluid stools containing blood and mucus.

EIEC may be suspected by the presence of many fecal leukocytes visible in a stained smear of mucus, a finding also in shigellosis. An immunoassay test that detects the plasmid encoded specific outer membrane proteins that are associated with epithelial cell invasiveness; a bioassay (the guinea pig-keratoconjunctivitis test) detects epithelial cell invasiveness; DNA probes detect the enteroinvasiveness plasmid.

EIEC infections are endemic in less developed countries, and cause about 1-5% of diarrheal episodes among people visiting treatment centres. Occasional infections and outbreaks of EIEC diarrhea have been reported in industrialized countries.

### **IV DIARRHEA Caused by Enteropathogenic Strains (ICD-10: A04.0)**

(EPEC, Enteropathogenic *E. coli* enteritis)

This is the oldest recognized category of diarrhea producing *E. coli*. implicated in 1940s and 1950s studies in which certain O:H serotypes were found to be associated with infant summer diarrhea, outbreaks of diarrhea in infant nurseries, and community epidemics of infant diarrhea. Diarrheal disease in this category is virtually confined to infants less than 1 year of age in whom it causes watery diarrhea with mucus, fever and dehydration. EPEC cause dissolution of the microvilli of enterocytes and initiate attachment of the bacteria to enterocytes. The diarrhea in infants can be both severe and prolonged, and in developing countries may be associated with high case-fatality.

EPEC can be tentatively identified by agglutination with antisera that detect EPEC O serogroups, but confirmation requires both O and H typing with high quality reagents. EPEC organisms exhibit HEp-2 cells in cell cultures, a property that requires the presence of an EPEC virulence plasmid. The EPEC adherence factor (EAF) DNA probe detects the EPEC virulence plasmid; there is a 98% correlation between the detection of localized adherence and EAF probe positivity.

Since the late 1960s, EPEC has largely disappeared as an important cause of infant diarrhea in North America and Europe. However, it remains a major agent of infant diarrhea in many developing areas, including Asia.

#### **V. Diarrhea Caused by enteroaggregative E.Coli (EAggEC) (ICD-10: A04.4)**

This category of diarrhea producing *E. coli* is an important cause of infant diarrhea in less developed countries where it is the single most common cause of persistent diarrhea in infants. In animal models, these *E. coli* organisms evoke a characteristic histopathology in which EAggEC adhere to enterocytes in thick biofilm of aggregating bacteria and mucus. At present, the most widely available method to identify EAggEC is by the HEp-2 assay.

This category of diarrhea producing *E. coli* was first associated with infant diarrhea in a study in Chile in the late 1980s. It was subsequently recognized in developing countries as being particularly associated with persistent diarrhea (diarrhea that continues unabated for at least 14 days), an observation that has since been confirmed by reports from Brazil, Mexico and Bangladesh.

Reports associating EAggEC with infant diarrhea, and particularly persistent diarrhea, has come from multiple countries in Latin America, Asia and Africa. Reports suggest that EAggEC may be responsible for a small proportion of diarrheal disease in industrialized countries as well.

#### **VI. Diarrhea Caused by Diffuse - Adherence E.Coli (DAEC) (ICD-10: A04.4)**

A sixth category of diarrhea producing *E. coli* now recognized is diffuse adherence *E. coli* (DAEC). The name derives from the characteristic pattern of adherence of these bacteria to HEP-2 cells in tissue culture. DAEC is the least well-defined category of diarrhea causing *E. coli*. Nevertheless, data from several epidemiological field studies of pediatric diarrhea in less developed countries have found DAEC to be significantly more common in children with diarrhea than in matched controls; other studies have failed to find such a difference. Notably, preliminary evidence suggests that DAEC may be more pathogenic in children of preschool age rather than in infants and toddlers. Two DAEC strains failed to cause diarrhea when fed to volunteers and no outbreaks due to this category have yet been recognized. At present little is known about the reservoir, modes of transmission, and host risk factors or period of communicability of DAEC.

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### **INFECTIOUS AGENT**

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#### **I. Diarrhea caused by Enterohemorrhagic Strains (EHEC)**

While the main EHEC serotype is *E. coli* O157:H7, other serotypes such as O26:H11, O111:H8, O103:H2, O113:H21, and O104:H21 have been implicated.

## II. DIARRHEA CAUSED BY ENTEROTOXIGENIC STRAINS (ETEC)

ETEC elaborate a heat labile enterotoxin (LT), a heat stable toxin (ST) or both toxins (LT/ST). The most common O serogroups include O6, O8, O15, O20, O25, O27, O63, O78, O80, O114, O115, O128ac, O148, O153, O159 and O167.

## III. DIARRHEA CAUSED BY ENTEROINVASIVE STRAINS (EIEC)

Strains of *E. coli* shown to possess enteroinvasiveness dependent on the presence of a larger virulence plasmid encoding invasion plasmid antigens. The main O serogroups in which EIEC fall includes O28ac, O29, O112, O124, O136, O143, O144, O152, O164 and O167.

## IV. DIARRHEA Caused by Enteropathogenic Strains

(EPEC, Enteropathogenic *E. coli* enteritis)

The major EPEC O serogroups include O55, O86, O111, O119, O125, O126, O127, O128ab and O142.

## V. Diarrhea Caused by enteroaggregative E.Coli (EAggEC)

EAggEC harbour a virulence plasmid required for expression of the unique fimbriae that encode aggregative adherence and many strains express a cytotoxin/enterotoxin. Among the most common EAggEC O serotypes and O3:H2 are O44:H18. Many EAggEC strains initially appear as rough strains lacking O antigens.

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## RESERVOIR

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Cattle are the most important reservoir of EHEC (Diarrhea caused by Enterohemorrhagic strains); humans may also serve as a reservoir for person-to-person transmission.

Humans are the reservoir of etec (diarrhea caused by enterotoxigenic strains). etec infections are largely species specific; people constitute the reservoir for strains causing diarrhea in humans.

Humans are the reservoir of EIEC (Diarrhea caused by Enteroinvasive strains) and EPEC (Diarrhea caused by Enteropathogenic strains).

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## MODE OF TRANSMISSION

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### I. Diarrhea caused by Enterohemorrhagic Strains

Transmission occurs mainly by ingestion of contaminated food; as with *Salmonella*, it is most often due to inadequately cooked beef (especially ground beef) and also raw milk and fruit or vegetables contaminated with ruminant feces. As with *Shigella*, transmission also occurs directly from person-to-person, in families, childcare centres and custodial institutions. Waterborne transmission has also been documented; one outbreak was associated with swimming in a crowded lake and one was caused by drinking contaminated unchlorinated municipal water.



## **II. DIARRHEA CAUSED BY ENTEROTOXIGENIC STRAINS (ETEC)**

Contaminated food and, less often, contaminated water. Transmission via contaminated weaning foods may be particularly important in infection of infants. Direct contact transmission by fecally contaminated hands is believed to be rare.

## **III DIARRHEA CAUSED BY ENTEROINVASIVE STRAINS (EIEC)**

Scant available evidence suggests that EIEC is transmitted by contaminated food.

## **IV DIARRHEA Caused by Enteropathogenic Strains (EPEC)**

By contaminated infant formula and weaning foods. In infant nurseries, transmission by fomites and by contaminated hands can occur if handwashing techniques are compromised.

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## **INCUBATION PERIOD**

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- I. DIARRHEA CAUSED BY ENTEROHEMORRHAGIC STRAINS (EHEC): Typically relatively long, ranging from 2 to 8 days, with a median of 3 - 4 days.
- II. DIARRHEA CAUSED BY ENTEROTOXIGENIC STRAINS (ETEC): Incubations as short as 10 - 12 hours have been observed in outbreaks and in volunteer studies with certain LT-only and ST-only strains. The incubation of LT/ST diarrhea in volunteer studies has usually been 24-72 hours.
- III DIARRHEA CAUSED BY ENTEROINVASIVE STRAINS (EIEC): Incubations as short as 10 and 18 hours have been observed in volunteer studies and outbreaks, respectively.
- IV DIARRHEA CAUSED BY ENTEROPATHOGENIC STRAINS (EPEC): As short as 9 -12 hours in adult volunteer studies. It is not known whether the same incubation applies to infants who acquire infection by natural transmission.
- V. DIARRHEA CAUSED BY ENTEROAGGREGATIVE *E.COLI* (EAggEC): The incubation period is estimated to be 20 -48 hours.

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## **PERIOD OF COMMUNICABILITY**

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- I. DIARRHEA CAUSED BY ENTEROHEMORRHAGIC STRAINS (EHEC): The duration of excretion of the pathogen, which is typically for a week or less in adults but 3 weeks in one third of children. Prolonged carriage is uncommon.
- II. DIARRHEA CAUSED BY ENTEROTOXIGENIC STRAINS (ETEC): For the duration of excretion of the pathogenic ETEC, which may be prolonged.
- III DIARRHEA CAUSED BY ENTEROINVASIVE STRAINS (EIEC): Duration of excretion of EIEC strains
- IV DIARRHEA CAUSED BY ENTEROPATHOGENIC STRAINS (EPEC): Limited to the duration of excretion of EPEC, which may be prolonged.

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## SUSCEPTIBILITY AND RESISTANCE

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- I. DIARRHEA CAUSED BY ENTEROHEMORRHAGIC STRAINS (EHEC): The infectious dose is very low. Little is known about difference in susceptibility and immunity. Old age appears to be a risk factor, so hypochlorhydria may be a factor contributing to susceptibility. Children less than 5 years of age are at greatest risk of developing HUS.
- II. DIARRHEA CAUSED BY ENTEROTOXIGENIC STRAINS (ETEC): Epidemiological studies and rechallenge studies in volunteers clearly demonstrate that serotype specific immunity is acquired following ETEC infection. Multiple infections with different serotypes are required to develop broad-spectrum immunity against ETEC.
- III. DIARRHEA CAUSED BY ENTEROINVASIVE STRAINS (EIEC): Little is known about susceptibility and immunity to EIEC.
- IV. DIARRHEA CAUSED BY ENTEROPATHOGENIC STRAINS (EPEC): Although susceptibility to clinical infection appears to be confined virtually to young infants in nature, diarrhea can be induced experimentally in some adult volunteers, specific immunity may be important in determining susceptibility. EPEC infection is uncommon in breast fed infants.

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## RATIONALE FOR SURVEILLANCE

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In Nepal diarrhoeal diseases are one of the major causes of deaths and malnutrition. Within first 60 months of her/his life he/she experiences 2.3 episodes per year resulting in about 30,000 deaths annually. In addition to that these repeated attacks of diarrhoea are a major cause of malnutrition and faltering height and weight and malnourished children also suffer more severe attack of diarrhoea and hence higher mortality in this country.

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## RECOMMENDED CASE DEFINITION

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### Clinical case definition

Acute watery diarrhoea (passage of 3 or more loose or watery stools in the past 24 hours) with or without dehydration.

### Laboratory criteria for diagnosis

Laboratory culture of stools may be used to confirm possible outbreaks of specific agents, but is not necessary for case definition.

- Demonstration of specific antigen of possible pathogen by rapid diagnostic test kit
- Isolation, identification and characterization of causative agent
- Detection of possible pathogen by IFA, ELISA
- Detection of pathogen by PCR assay

### Case classification

Not applicable

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## **RECOMMENDED TYPES OF SURVEILLANCE FOR SENTINEL SITES**

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- Patient records should be maintained at Hospital level in each EWARS sentinel sites.
- Medical Recorders of EWARS sentinel sites should be maintained EWARS-1 register by recording of all clinical cases of Acute Diarrhoeal Diseases (including Gastroenteritis) after consulting the case investigation forms, Emergency register, Inpatient/OPD register and other concerns registers.
- Medical Recorders of EWARS sentinel sites should reporting on all clinical cases including zero reports of Acute Diarrhoeal Diseases (including Gastroenteritis) in the weekly EWARS reporting from (EWARS-3).
- Medical Recorders of EWARS sentinel sites must reporting on immediate reporting forms (EWARS-2), when the observed number of cases exceeds the expected number of cases or more than 5 cases from a same geographical area are admitted.
- Nursing In charge should be informed to Medical Recorder about the acute diarrhoeal cases admitted in any wards.
- Lab personnel should be informed to Medical recorder about the laboratory confirmation of the pathogen.
- All outbreaks (clinical cases) should be reported immediately to the respective DHO/DPHO, Regional Health Services Directorate and the EDCCD/DHS for immediate investigation and, if possible, laboratory confirmation.

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## **RECOMMENDED MINIMUM DATA ELEMENTS**

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As per EWARS reporting forms and guidelines.

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## **PRINCIPAL USES OF DATA FOR ACTION**

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- Monitor trends in diseases incidence.
- Detect possible outbreak and rapid response at the local level.
- Identify high-risk areas for further targeting of intervention.
- Estimate incidence rate and case-fatality rate.
- Estimate the incidence, attack, and case-fatality rate during outbreak situation.
- Undertake appropriately timed investigations and assess the spread and progress of the disease
- Support plan for the distribution of medical supplies/logistics (diagnostic test, antibiotics etc.) and allocation of control teams.
- Determine the effectiveness of control measures.

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## **SPECIFIC TREATMENT**

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Aggressive rehydration by oral and intravenous routes to repair fluid and electrolyte deficits and to replace the prodigious ongoing diarrhoeal losses is the cornerstone of diarrhoea therapy.

As rehydration therapy becomes increasingly effective, patients who survive from hypovolemic shock and severe dehydration manifest certain complications such as hypoglycemia that must be recognized and treated promptly.

In initiating prompt aggressive fluid therapy with volumes of electrolyte solution adequate to correct dehydration, acidosis and hypokalemia most patients with mild or moderate fluid loss can be treated entirely with oral rehydration using solutions that contain glucose 20 g/L (or sucrose 40 g/L or cooked rice powder 50 g/L); NaCl (3.5g/L); KCl (1.5 g/L) and trisodium citrate dihydrate (2.9 g/L) or  $\text{NaHCO}_3$  (2.5 g/L). Mild and moderate volume depletion should be corrected with oral solutions by replacing, over 4-6 hours, a volume matching the estimated fluid loss (approximately 5% of body weight for mild and 7% for moderate dehydration). Continuing losses are replaced by giving, over 4 hours, a volume of oral solution 1.5 times the stool volume lost in the previous 4 hours.

Patients in shock should be given rapid IV rehydration with a balanced multielectrolyte solution containing approximately 130 mEq/L of  $\text{Na}^+$ , 25-48 mEq/L of bicarbonate, acetate or lactate ions, and 10-15 mEq/L of  $\text{K}^+$ . Useful solutions include Ringer's lactate or WHO "diarrhea treatment solution" (4 g NaCl, 1 g KCl, 6.5 g sodium acetate and 8 g glucose/L), and "Dacca solution" (5 g NaCl, 4 g  $\text{NaHCO}_3$  and 1 g KCl/L), which can be prepared locally in an emergency. The initial fluid replacement should be 30 ml/kg in the first hour for infants and in the first 30 minutes for persons over 1 year of age, after which the patient should be reassessed. After circulatory collapse has been effectively reversed, most patients can be switched to oral rehydration to complete the 10% initial fluid deficit replacement and to match continuing fluid loss.

- I. DIARRHEA CAUSED BY ENTEROHEMORRHAGIC STRAINS (EHEC): Fluid and electrolyte replacement is important when diarrhea is watery or there are signs of dehydration. The role of antibacterial treatment of infections with *E. coli* O157:H7 and other EHEC is uncertain. Some evidence suggests that treatment with TMP+SMX fluoroquinolones and certain other antimicrobials may precipitate complications such as HUS.
- II. DIARRHEA CAUSED BY ENTEROTOXIGENIC STRAINS (ETEC): Electrolyte-fluid therapy to prevent or treat dehydration is the most important measure (see Cholera, section 9B7). Most cases do not require any other therapy. For severe travelers' diarrhea in adults, early treatment with loperamide (not for children) and an antibiotic such as a fluoroquinolone (ciprofloxacin PO 500 mg twice daily) or norfloxacin (PO 400 mg daily) is given for 5 days. Fluoroquinolones are used as initial therapy because many ETEC strains worldwide are resistant to a variety of other antimicrobials. However, if local strains are known to be sensitive, TMP-SMX (PO) (160 mg- 800 mg) twice daily or doxycycline (PO) (100 mg) once daily, for 5 days are useful. Feeding should be continued, according to the patient's appetite.
- III. DIARRHEA CAUSED BY ENTEROPATHOGENIC STRAINS: Electrolyte-fluid therapy (oral or IV) is the most important measure. Most cases do not require any other therapy. For severe enteropathogenic infant diarrhea, oral TMP-SMX (10-50 mg/kg/day) has been shown to

ameliorate the severity and duration of diarrheal illness; it should be administered in 3 - 4 divided doses for 5 days. However, since many EPEC strains are resistant to a variety of antibiotics, selection should be based on the sensitivity of local isolated strains. Feeding, including breast-feeding, should be continued.

- IV. ROTAVIRAL ENTERITIS: None. Oral rehydration therapy with oral glucose–electrolyte solution is adequate in most cases. Parenteral fluids are needed in cases with vascular collapse or uncontrolled vomiting (see cholera). Antibiotics and antimotility drugs are contraindicated.
- V. EPIDEMIC VIRAL GASTROENTEROPATHY: Fluid and electrolyte replacement in severe cases.

# CHOLERA

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## Introduction

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Cholera is an acute diarrhoeal infection caused by ingestion of food or water contaminated with the gram negative bacterium *Vibrio cholerae*, which can result in profound, rapidly progressive dehydration and death in untreated patients.

Primarily linked to insufficient access to safe water and proper sanitation, its impact can be even more

dramatic in areas where basic environmental infrastructures are disrupted or have been destroyed.

Cholera gravis (the severe form) is a much-feared disease, particularly in its epidemic presentation.

Individuals with lower immunity, such as malnourished children or people living with HIV, are at greater risk of death if infected by cholera. Cholera remains a global threat to public health and an indicator of inequity and lack of social development. Researchers have estimated that every year, there are roughly 1.3 to 4.0 million cases, and 21,000 to 1,43,000 deaths worldwide due to cholera.

## Epidemiology

Cholera can be endemic or epidemic. A cholera-endemic area is an area where confirmed cholera cases were detected during the last 3 years with evidence of local transmission (meaning the cases are not

imported from elsewhere). In cholera endemic countries an outbreak can be seasonal or sporadic and represents a greater than expected number of cases. In a country where cholera does not regularly occur, an outbreak is defined by the occurrence of at least 1 confirmed case of cholera with evidence of local transmission in an area where there is not usually cholera.

Cholera transmission is closely linked to inadequate access to clean water and sanitation facilities.

Ingestion of water contaminated by human faeces is the most common means of acquisition of *V. cholerae*. Consumption of contaminated food also can contribute to spread. There is no known animal reservoir. Cholera is predominantly a pediatric disease in endemic areas, but it affects adults and children equally when newly introduced into a population. In endemic areas, the burden of disease is often greatest during "cholera seasons" associated with high temperatures, heavy rainfall, and flooding, but cholera can occur year-round. A humanitarian crisis in a country or region can result in cholera outbreaks. For unexplained reasons, susceptibility to cholera is significantly influenced by ABO blood group status; persons with type O blood are at greatest risk of severe disease if infected, whereas those with type AB are at least risk.

## **Microbiology**

The species *V. cholerae* is classified into more than 200 serogroups based on the carbohydrate determinants of their lipopolysaccharide (LPS) O antigens, but only two – O1 and O139 – cause outbreaks (the serogroups with epidemic potential). *V. cholerae* O1 has caused all recent outbreaks. There is no difference in the illness caused by the two serogroups. Two biotypes of *V. cholerae* O1, classical and El Tor, are distinguished. Each biotype is further subdivided into two serotypes, termed Inaba and Ogawa.

The other serogroups are known collectively as Non-O1/O139 (Noncholera) *V. cholerae*. These serogroups can cause a diarrhoeal disease which is less severe than cholera and does not have epidemic potential.

## **Pathogenesis**

The major virulence factor for *V. cholerae* O1 and O139 is cholera toxin, a multimeric protein composed of one A subunit and five B subunits. Toxin binding to enterocytes leads to an elevation in cyclic AMP within the intestinal mucosa, causing an increase in chloride secretion and a reduction in sodium absorption. This leads to massive loss of fluid and electrolytes, and produces the signs and symptoms of cholera gravis, or severe disease.

## **Clinical manifestations**

Some individuals are asymptomatic or have only mild diarrhoea; others present with the sudden onset of explosive and life-threatening diarrhoea (cholera gravis). Among people developing symptoms, 80% of episodes are of mild or moderate severity. The remaining 10%-20% of cases develop severe watery diarrhoea with signs of dehydration. It takes between 12 hours and 5 days for a person to show symptoms after ingesting contaminated food or water.

Patients often vomit. If fluids and electrolytes are not replaced, hypovolemic shock and death may ensue. Fever is usually absent. The stool has a characteristic appearance: a nonbilious, gray, slightly cloudy fluid with flecks of mucus, no blood, and a somewhat fishy, inoffensive odor. It has been called "rice-water" stool because of its resemblance to the water in which rice has been washed.

## **Clinical symptoms parallel volume contraction**

At losses of <5% of normal body weight, thirst develops; At 5—10%, postural hypotension, weakness, tachycardia, and decreased skin turgor are documented; At > 10%, oliguria, weak or absent pulses, sunken eyes (and, in infants, sunken fontanelles), wrinkled ("washerwoman") skin, somnolence, and coma are characteristic.

Muscle cramps and tetany due to electrolyte disturbances are common.

Complications derive exclusively from the effects of volume and electrolyte depletion and include renal failure due to acute tubular necrosis.

Thus, if the patient is adequately treated with fluid and electrolytes, complications are averted and the process is self-limited, resolving in a few days.

## Diagnosis

WHO recommends the following clinical definition be used for cholera cases.

**Suspected cholera case:** In areas where a cholera outbreak has not been declared: Any patient 2 years old or older presenting with acute watery diarrhoea and severe dehydration or dying from acute watery diarrhoea. In areas where a cholera outbreak is declared: any person presenting with or dying from acute watery diarrhoea.

## Confirmed cholera case

A suspected case with *Vibrio cholerae* O1 or O139 confirmed by culture or PCR and, in countries where cholera is not present or has been eliminated, the *Vibrio cholerae* O1 or O139 strain is demonstrated to be toxigenic. Clinical diagnostic tools include Gram stain/culture (augmented with methods for detection of toxinogenic strains) and dark field microscopy. Gram stain of stools may show sheets of curved gram-negative rods. Isolation and identification of *Vibrio cholerae* serogroup O1 or O139 by culture of a stool specimen remains the gold standard for the laboratory diagnosis of cholera. Cary Blair media is ideal for transport, and the selective thiosulfate–citrate–bile salts agar (TCBS) is ideal for isolation and identification. It can be detected directly by dark-field microscopy on a wet mount of fresh stool (The organisms are motile and resemble "shooting stars") and its serotype can be discerned by immobilization with specific antiserum.

## Treatment

Death from cholera is due to hypovolemic shock; thus treatment of individuals with cholera first and foremost requires fluid resuscitation and management.

Treatment includes:

1. Rehydration therapy: meaning prompt restoration of lost fluids and salts through rehydration therapy is the primary goal of treatment.
2. Antibiotic treatment: which reduces fluid requirements and duration of illness, is indicated for severe cases of cholera.
3. Zinc treatment: has also been shown to help improve cholera symptoms in children.

## Rehydration Therapy

Rehydration is the cornerstone of treatment for cholera. Up to 80% of cases can be successfully treated

with oral rehydration solution (ORS). Severe cases will need rapid treatment with intravenous fluids and antibiotics. Oral rehydration salts and, when necessary, intravenous fluids and electrolytes, if administered in a timely manner and in adequate volumes, will reduce fatalities



to well under 1% of all patients. Breastfed infants should continue to breastfeed.

Other types of fluids, such as juice, soft drinks, and sports drinks should be avoided.

WHO guidelines for assessment of dehydration:

| Clinical features       | Predicted degree of dehydration |                                 |                                  |
|-------------------------|---------------------------------|---------------------------------|----------------------------------|
|                         | None (<5 percent)               | Some dehydration (5-10 percent) | Severe dehydration (>10 percent) |
| General appearance      | Well, alert                     | Restless, irritable             | Lethargic or unconscious         |
| Eyes                    | Normal                          | Sunken                          | Sunken                           |
| Thirst                  | Drinks normally, not thirsty    | Thirsty, drinks eagerly         | Drinks poorly or unable to drink |
| Skin pinch              | Goes back quickly               | Goes back slowly                | Goes back very slowly            |
| Estimated fluid deficit | <50 mL/kg                       | 50-100 mL/kg                    | >100 mL/kg                       |

| WHO Fluid Replacement or Treatment Recommendations |     |                              |                                      |               |
|----------------------------------------------------|-----|------------------------------|--------------------------------------|---------------|
| No dehydration                                     | ORS | Administer after each stool: |                                      |               |
|                                                    |     | Age                          | Volume of ORS                        |               |
|                                                    |     | <2 years                     | 50–100 ml, up to 500 mL/day          |               |
|                                                    |     | 2–9 years                    | 100–200 ml, up to 1000 mL/day        |               |
|                                                    |     | ≥10 years                    | As much as wanted, up to 2000 mL/day |               |
| Some dehydration                                   | ORS | Administer in first 4 hours: |                                      |               |
|                                                    |     | Age                          | Weight                               | Volume of ORS |
|                                                    |     | <4 months                    | <5 kg                                | 200–400 mL    |
|                                                    |     | 4–11 months                  | 5–7.9 kg                             | 400–600 mL    |
|                                                    |     | 1–2 years                    | 8–10.9 kg                            | 600–800 mL    |
|                                                    |     | 2–4 years                    | 11–15.9 kg                           | 800–1200 mL   |
|                                                    |     | 5–14 years                   | 16–29.9 kg                           | 1200–2200 mL  |
|                                                    |     | ≥15 years                    | 30 kg or more                        | 2200–4000 mL  |

| WHO Fluid Replacement or Treatment Recommendations |                                                                                                                                             |                                                                                     |              |
|----------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------|--------------|
| No dehydration                                     | ORS                                                                                                                                         | Administer after each stool:                                                        |              |
| Severe dehydration                                 | Intravenous Ringer's Lactate or, if not available, normal saline and ORS as outlined above. Do not give plain glucose or dextrose solution. | Administer up to 200 ml/kg IV fluids in first 24 hours                              |              |
|                                                    |                                                                                                                                             | Age < 12 months                                                                     |              |
|                                                    |                                                                                                                                             | Timeframe                                                                           | Total volume |
|                                                    |                                                                                                                                             | 0–30 min                                                                            | 30 ml/kg*    |
|                                                    |                                                                                                                                             | 30 min–6 h                                                                          | 70 ml/kg     |
|                                                    |                                                                                                                                             | 6 h–24 h                                                                            | 100 ml/kg    |
|                                                    |                                                                                                                                             | Age ≥ 1 year                                                                        |              |
|                                                    |                                                                                                                                             | Timeframe                                                                           | Total volume |
|                                                    |                                                                                                                                             | 0–30 min                                                                            | 30 ml/kg*    |
|                                                    |                                                                                                                                             | 30 min–3 h                                                                          | 70 ml/kg     |
|                                                    |                                                                                                                                             | 3 h–24 h                                                                            | 100 ml/kg    |
|                                                    |                                                                                                                                             | Start rapidly then slow down                                                        |              |
|                                                    |                                                                                                                                             | Continue until the patient is awake , can ingest ORS and no longer has weak pulse . |              |

### Signs of Adequate Rehydration:

- \* Skin goes back normally when pinched.
- \* Thirst has subsided.
- \* Urine has been passed.
- \* Pulse is strong.

### Recommendations for the Use of Antibiotics for the Treatment of Cholera

Findings from randomized controlled trials evaluated the effectiveness of selected antibiotics on three

Main outcomes: stool output, duration of diarrhoea, and bacterial shedding.

Findings indicate that antibiotics reduced volume of stool output by 8-92%, duration of diarrhoea by 50

56%, and duration of positive bacterial culture by 26-83%.

In many areas, macrolides such as erythromycin (adults, 250 mg orally four times a day for 3 days; children, 12.5 mg/kg per dose four times a day for 3 days) or azithromycin (adults, a single 1-g dose; children, a single 20-mg/kg dose) are the agents of choice. Increasing resistance to tetracyclines is widespread; however, in areas with confirmed susceptibility, tetracycline (nonpregnant adults, 500 mg orally four times a day for 3 days; children >8 years old, 12.5 mg/kg per dose four times a day for 3 days) or doxycycline (nonpregnant adults, a 300-mg single dose; children >8 years old, a single dose of 4-6 mg/kg) may be used. In most countries, Doxycycline (single 300mg dose) is recommended as first-line treatment for adults, while azithromycin (1 g single dose) is recommended as first-line treatment for children and pregnant women.

### **Zinc Treatment**

Zinc is an important adjunctive therapy for children under 5 year, which also reduces the duration of diarrhoea and may prevent future episodes of other causes of acute watery diarrhoea. For children below 6 months of age, add zinc 10mg daily for 2 weeks. For children from 6 months to 12 years, add zinc 20mg daily for 2 weeks. Breastfeeding should also be promoted.

### **Prevention and control**

A multifaceted approach is key to control cholera, and to reduce deaths. A combination of surveillance, water sanitation and hygiene, social mobilization, treatment, and oral cholera vaccines are used.

Provision of safe water, proper sanitation, and food safety are critical for preventing occurrence of cholera. Health education aims at communities adopting preventive behavior for averting contamination. Prevention and preparedness of cholera require a coordinated multidisciplinary approach.

Main tools for cholera control are:

1. Proper and timely case management in cholera treatment centers.
2. Specific training for proper case management, including avoidance of nosocomial infections;
3. Sufficient pre-positioned medical supplies for case management (e.g. diarrhoeal disease kits);
4. Improved access to water, effective sanitation, proper waste management and vector control;
5. Hygiene and food safety practices;
6. Improved communication and public information.
7. Cholera outbreak: Act before it's too late.

# SEVERE ACUTE RESPIRATORY INFECTION

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## Introduction

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### Influenza Like illness (ILI)

- ILI surveillance is a syndromic approach surveillance system. It is not a illness by itself rather it is a group of several illnesses that have a similar initial presentation while cases are been seen in the outpatient clinics and ambulatory settings.
- Evidence based studies have shown that ILI illnesses data closely correlates with the laboratory based data from Influenza surveillance programs and also helps in the early detection of any impending epidemic. Yearly, adults and children can average one to three and three to six ILI, respectively in USA.

### Severe acute Respiratory Infection (SARI)

- Also, is a syndromic presentation like ILI, however with some more complications like involvement of lower respiratory tract, pneumonia, acute respiratory distress syndrome etc. requiring admission to the hospital facility.

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## Surveillance for Human AI ILI / SARI

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### Objectives of an influenza surveillance system

- Detect unusual or unexpected viral respiratory outbreaks.
- Determine the epidemiologic characteristics of influenza and other viral respiratory diseases (caused by, for example, Adenovirus, Para-influenza, and Respiratory syncytial Virus).
- Monitor influenza viruses and make recommendations for annual vaccine composition, determine the concordance between the vaccine and currently circulating strains; detect, in a timely manner, the appearance of new subtypes.
- Estimate the burden of ILI and SARI in humans.
- Guide the development of policies and guidelines for influenza prevention and control.
- Build the foundation of future studies on the impact of disease prevention and control interventions.

### Sentinel surveillance for human Influenza: Achieved through:

- Outpatient clinic-based Influenza like illness (ILI cases) or
- Admitted cases of severe acute respiratory illness (SARI cases)

A simple passive surveillance system to tract influenza episodes in the population with an objective to be able to detect any unusual activity as well as to keep tract of types of organisms causing respiratory illness in the communities.

**Enhanced surveillance for human influenza A/H5:** It involves active and passive approaches to find influenza cases with history of exposure through contact tracing in the area where case

patients reside or where bird /animal outbreaks of Influenza A/H5 are occurring. It can include measures such as telephone hotlines, media, radio or other emergency networks as needed for getting reports about suspect cases in the community.

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### **Recommended case definition**

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#### **Influenza Like illness (ILI):**

An acute respiratory tract infection with

- measured temperature of  $\geq 38^{\circ}\text{C}$
- cough
- with onset lasting less than 10 days

#### **Severe acute Respiratory Infection (SARI):**

- An acute respiratory tract infection with
- history of fever or measured fever of  $\geq 38^{\circ}\text{C}$ ;
- and cough;
- with onset within the last 10 days and
- requiring hospitalization.

#### **Influenza viruses**

Influenza viruses are the commonest cause of SARI/ILI. Different influenza virus subtypes can infect humans- avian [A(H5N1), A(H7N9), and A(H9N2), and swine (A(H1N1), A(H1N2) and A(H3N2)]. Human infections are primarily acquired through direct contact with infected animals or contaminated environments. Infection due to influenza virus ranges from mild upper respiratory tract symptoms (fever and cough) to rapid progression to severe pneumonia, septic shock and acute respiratory failure. Varying degree of extra pulmonary involvement- conjunctivitis, encephalitis and gastrointestinal symptoms may present depending upon viral serotypes.

There are 4 types of influenza viruses- A, B, C and D

- Influenza A viruses infect humans and many different animals. Emergence of new virus from animal with ability to infect people, and potential to sustain human to human transmission has caused pandemics in the past.
- Influenza B viruses circulate in humans and can cause seasonal epidemics.
- Influenza C viruses can infect humans and pigs but the infection is usually mild.
- Influenza D viruses primarily affect cattle and human infection is not known.

In 1997, human infections with A(H5N1) were reported from Hong Kong. Since 2003, this avian virus has spread across many countries causing millions of poultry infections, several hundred human cases and many human deaths.

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### **Incubation period**

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2-5 days A(H5N1) and 1-10 days for A(H7N9)

The disease due to avian influenza A(H5N1 and H7N9) has aggressive clinical course. Common initial symptoms are high fever ( $\geq 38^{\circ}\text{C}$ ) and cough with symptoms of lower respiratory tract involvement- dyspnea and chest pain. Sore throat and coryza are less common. Gastrointestinal and neurological symptoms have been reported. Complications include severe pneumonia, acute respiratory distress syndrome, septic shock, multi-organ failure and secondary bacterial infections. Case fatality rate is high.

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## Other information

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### Suspected case of Human Avian Influenza (HAI)

- A person presenting with unexplained acute lower respiratory illness with fever ( $>38^{\circ}\text{C}$ ) and cough, shortness of breath or difficulty breathing and
- One or more of the following epidemiological linkage or exposures within the 14 days prior to onset of the symptoms:
  - ☞ **Close contact** ( $< 1\text{ m}$ ) with a person who is a suspected, probable, or confirmed **H5N1**
  - ☞ **Exposure** to poultry or wild birds or animals or their remains or to environments contaminated by their faeces in an area where **H5N1** infections in animals or humans have been suspected or confirmed in the last month
  - ☞ **Consumption** of raw or undercooked poultry products in an area where **H5N1** infections in animals or humans have been suspected or confirmed in the last month
  - ☞ **Travel to:** an area where **H5N1** infections in animals or humans have been suspected or confirmed in the last one month
  - ☞ **Handling samples** (animal or human) suspected of containing **H5N1** virus in a laboratory or other setting

### Person under Investigation (PUI) for HAI

- A person whom public health authorities have decided to investigate for possible HAI A /H5 infection Or
- A case with SARI like symptoms
- And has one of the following histories of exposure:
  - ☞ Belongs to one of the “high risk categories”
  - ☞ Had close contact with (in the 14 days prior to onset of the symptoms):
  - ☞ Sick/dead poultry or birds; or
  - ☞ Direct contact (within 1 meter) with hospitalized patients who have (or died of) severe respiratory illness.

### High Risk Groups

- Children playing with or taking care of infected poultry and/or asymptomatic infected ducks
- Poultry handlers in live animal markets / wet markets
- Cullers without using proper PPE precautions
- Persons involved in defeathering and preparing of sick birds in wet markets / backyard poultry / kitchens

- People consuming undercooked poultry products
- Hospital functionaries managing human cases of AI without using proper PPE precautions
- Veterinarians exposed to avian influenza infected poultry
- Human or animal laboratory personnel or other staff who handle animal or human samples from persons / patients suspected of or known to contain H5N1 virus in a laboratory or field setting

### **Probable case for HAI**

- **Probable Case Definition 1:** A person meeting the criteria for a suspected case AND meets one of the following additional criteria:
  - ☞ Infiltrates or evidence of an acute pneumonia on chest radiograph plus evidence of respiratory failure (hypoxemia, severe tachypnoea) or
  - ☞ Positive laboratory confirmation of influenza A infection but insufficient laboratory evidence for A (H5N1) infection
- Probable definition 2:
  - ☞ A person dying of an unexplained acute respiratory illness who is considered to be epidemiologically linked by time, place, and exposure to a probable or confirmed H5N1 case

### **Confirmed case of HAI**

- A person meeting the criteria for a suspected or probable case AND meets one of the following positive results at a laboratory whose H5N1 test results are accepted by WHO as confirmatory:
- Isolation of a HAI A (H5N1) virus
- Positive H5 PCR results from tests using two different PCR targets, e.g. primers specific for influenza A and H5 HA
- A fourfold or greater rise in neutralization antibody titre for H5N1 based on testing of an acute serum specimen and a convalescent serum specimen
- A micro-neutralization antibody titre for H5N1 of 1:80 or greater in a single serum specimen collected on Day 14 or later after symptom onset and a positive result using a different serological assay

### **Diagnosis**

Samples- nasal and pharyngeal secretions

1. Rapid influenza diagnostic tests (RIDTs) have lower sensitivity compared to PCR
2. RT-PCR is confirmatory

### **Treatment**

1. Antiviral drugs, notably neuraminidase inhibitor (oseltamivir, zanamivir), can reduce the duration of viral replication and improve prospects of survival. And should be prescribed as



soon as suspected or confirmed. Treatment is recommended for 5 days but can be extended until there is satisfactory clinical improvement.

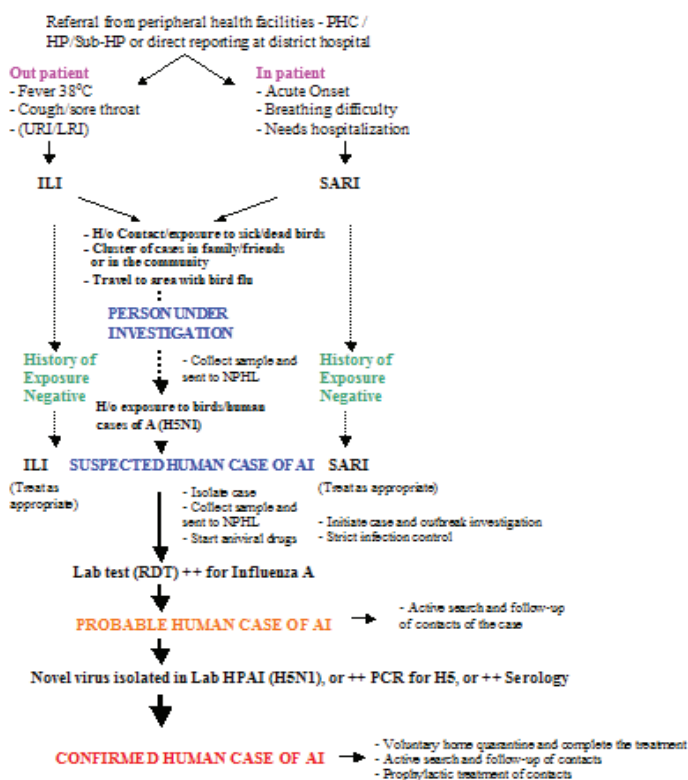
2. Supportive treatment with oxygen and intravenous fluids
3. Antibacterial agents if pneumonia
4. Management of complications

### Preventive measures

1. Use of personal protective equipment
2. Regular hand washing with proper drying of the hands
3. Good respiratory hygiene – covering mouth and nose when coughing or sneezing, using tissues and disposing of them correctly
4. Early self-isolation of those feeling unwell, feverish and having other symptoms of influenza
5. Avoiding close contact with sick people
6. Avoiding touching one’s eyes, nose or mouth

Health care workers performing aerosol generating procedures should use airborne precautions.

Clinical presentation and schematic flow chart for ILI/SARI/suspected case of human AI at the sentinel site and follow up



## **WHO Case Definition**

- Clinical: Fever, cough, diarrhoea and shortness of breath
- Epidemiological: Related to source of infection, e.g., contact/exposure to source of infection, consumption of infected food, and travel to locations where infection exists or handling materials that may be infected.
- Laboratory: Related to information from the laboratory investigations
- WHO case definitions may be sufficient in terms of providing operational case definitions for an outbreak investigation. It should be noted that as more data are made available regarding clinical, laboratory and epidemiological features, the 'status' or 'case definition category' may change with respect to (specific *time, person and place* components). Use of good clinical judgement to the process of modifying such 'set' definitions to the local situation may be generally advised to avoid missing any potential cases.
- In clinical situations requiring decisions on laboratory testing and management of patients with suspected H5N1 infection, any such decisions should be primarily based on clinical judgement and not on strict adherence to the case definitions.

## **Reporting procedure of Weekly SARI cases and immediate reporting of PUI / Suspected / Probable case of Human AI**

- SARI cases are to be reported weekly to the VBRDC on EWARS 3 form
- Cases of human AI (PUI / suspected case or probable case of human AI ) should be immediately reported to HO/ Health Directorate / EDCD on EWARS –2 form.
- Health staff should also be vigilant about any report or instance of any unusual death of domestic fowls and or wild birds in the community. In such cases they should contact the local livestock department officials and also inform the same to the Health office.

*Note: Please refer to the latest national guidelines (if available) for update of each disease.*

## ANNEX 3: OPERATIONAL DEFINITIONS

**Active surveillance:** Routine surveillance where reports are sought dynamically from participants in the surveillance system on a regular basis (e.g. telephoning each participant monthly to ask about new cases)

**Agent:** A factor, such as a microorganism, chemical substance, or form of radiation, whose presence, excessive presence, or (in deficiency diseases) relative absences is essential for the occurrence of a disease.

**Biologic transmission:** The indirect vector-borne transmission of an infectious agent in which the agent undergoes biologic changes within the vector before being transmitted to a new host.

**Carrier:** A person or animal without apparent disease who harbors a specific infectious agent and is in apparent throughout its course (known as asymptomatic carrier), or during the incubation period, convalescence, and post convalescence of an individual with a clinically recognizable diseases. The carrier state may be of short or long duration (transient carrier or chronic carrier).

**Case:** In epidemiology, a countable instance in the population or study group of a particular disease, health disorder, or condition under investigation. Sometimes, an individual with the particular disease, or an individual who meets the case definition of the particular disease.

**Case definition:** A set of diagnostic criteria that must be fulfilled to be regarded as a case of a particular disease or health-related condition. Case definitions can be based on clinical criteria, laboratory criteria or combination of the two.

**Case classification:** Gradations in the likelihood of being a case (e. g. suspected/probable./confirmed). This particularly useful where early reporting of cases is important (e. g. Ebola haemorrhagic fever) and where there are difficulties in making definite diagnoses (e.g. specialized laboratory tests required).

**Case-based surveillance:** The surveillance of a disease by collecting specific data on each case (e.g. collecting details on each case of Acute flaccid Paralysis in polio surveillance)

**Common source outbreak:** An outbreak that results from a group of persons being exposed to a common noxious influence, such as an infectious agent or toxin. If the group is exposed over a relatively brief period of time, so that all cases occur within one incubation period, then the common source outbreak is further classified as a "*point source outbreak*". In some common source outbreaks, persons may be exposed over a period of days, weeks or longer, with the exposure being either *intermittent* or *continuos*.

**Contact:** An individual who has had contact with a source of an infection, a person so exposed or a case, in a way that is considered to have cause significant exposure and therefore risk of infection.

**Contagious:** capable of being transmitted from one person to another by contact or close

proximity.

**Direct transmission:** the immediate transfer of an agent from a reservoir to a susceptible host by direct contact or droplet spread.

**Droplet nuclei:** The residue of dried droplets that may remain suspended in the air for long periods, may be blown over great distances, and are easily inhaled into the lungs and exhaled.

**Droplet spread:** The direct transmission of an infectious agent from a reservoir to a susceptible host by spray with relatively large, short-ranged aerosols produced by sneezing, coughing or talking.

**Endemic disease:** The constant presence of a disease within a given geographic area or population group.

**Epidemic:** The occurrence of cases of an illness clearly in excess of expectancy in a given area or among a specific group of people over a particular period of time. This is often referred to as an outbreak (more neutral).

**Epidemic period:** A time period when the number of cases of disease reported is greater than expected.

**EWARS:** The organized mechanism to detect/inform as early as possible any abnormal occurrence or any divergence from the usual or normally observed frequency or phenomenon.

**Feedback:** The regular process of sending analyses and surveillance reports on the surveillance data back through all levels of the surveillance system so that all participants can be informed of trends and performance.

**Health event:** Any event relating to the health of an individual (e.g the occurrence of a specific disease or syndrome, the administration of a vaccine or an admission to hospital).

**Health Information System:** A combination of health statistics from various sources, used to derive information about health status, health care, provision and use of services, and impact on health.

**Host:** A person or other living organism that can be infected by an infectious agent under natural conditions.

**Host factor:** An intrinsic factor (age, race, behaviors, etc.) which influences and individual's exposure, susceptibility, or response to a causative agent.

**Immunity, Active:** Resistance developed in response to stimulus by an antigen (infecting agent or vaccine) and usually characterized by the presence of antibody produced by the host.

**Immunity, passive:** Immunity conferred by an antibody produced in another host and acquired naturally by an infant from its mother, or artificially by administration of an antibody-containing preparation (antiserum or immune globulin).

**Incidence:** The number of persons who fall ill with a certain disease during a defined time period

**Incubation period:** a period of sub-clinical or in apparent pathologic changes following exposure, ending with the onset of symptoms of infectious disease.

**Indirect transmission:** The transmission of an agent carried from a reservoir to a susceptible host by suspended air particles or by animate (vector) or inanimate (vehicle) intermediaries.

**Infectious disease:** An illness due to a specific infectious agent or its toxic products that arises through transmission of that agent or its products from an infected person, animal, or reservoir to a susceptible host, either directly or indirectly through an intermediate plant or animal host, vector, or inanimate environment.

**Laboratory surveillance:** surveillance where the starting point is the identification or isolation of a particular organism in a laboratory. (e.g. surveillance of salmonellosis).

**Latency period:** A period of sub-clinical or inapparent pathological changes following exposure, ending with the onset of symptoms of a chronic disease.

**Morbidity:** Any departure, subjective or objective, from a state of physiological or psychological wellbeing.

**Mortality rate:** A measure of frequency of occurrence of death in a defined population during a specified interval of time.

**Notifiable disease:** A disease that must be reported to the authorities by law or ministerial decree.

**Outbreak:** The occurrence of two or more linked cases of a communicable disease. Synonymous with epidemic. Sometimes the preferred word, as it may escape sensationalism associated with the word epidemic. Alternatively, a localized as opposed to generalized epidemic.

**Pandemic:** an epidemic occurring over a very wide area (several countries or continents) and usually affecting a large proportion of the population.

**Passive surveillance:** Routine surveillance where reports are awaited and no attempt made actively seek reports from the participants in the system.

**Pathogenicity:** The proportion of persons infected, after exposure to a causative agent, who then develop clinical disease.

**Reporting completeness:** Proportion of all expected reports that were actually received (usually state as "% completeness as of a certain date").

**Reporting timeliness:** Proportion of all expected reports that were received by a certain due date.

**Reporting system:** The specific process by which diseases or health events are reported. This will depend on the importance of the disease and the type of surveillance.

**Reservoir:** The habitat in which an infectious agent normally lives, grows and multiplies; reservoirs include human reservoirs, animal reservoirs and environmental reservoirs.

**Risk:** The probability that an event will occur, e.g. that an individual will become ill or die within a stated period of time or age.

**Risk factor:** an aspect of personal behavior or lifestyle, an environmental exposure, or an inborn or inherited characteristic that is associated with an increased occurrence of disease or other health-related event or condition.

**Routine surveillance:** the regular systematic collection of specified data in order to monitor a disease or health event.

**Sentinel surveillance:** A surveillance system in which a pre-arranged sample of reporting sources, agrees to report all cases of one or more notifiable conditions. The sample should be representative of the total population at risk.

**Surveillance:** The systematic collection, analysis, interpretation and dissemination of health data on an ongoing basis to those who need to know, to gain knowledge of the pattern of disease occurrence and potential in a community, in order that action may be taken to control and prevent disease in that community.

**Transmission of infection:** Any mode or mechanism by which an infectious agent is spread through the environment or to another person.

**Vector:** An animate intermediary in the indirect transmission of an agent that carries the agent from a reservoir to a susceptible host.

**Vehicle:** An inanimate intermediary in the indirect transmission of an agent that carries the agent from a reservoir to a susceptible host.

**Zero reporting:** The reporting of zero cases when no case have been detected by the participant. This allows the next level of the system to be sure that the participant has not sent data has been lost or has forgotten to report.

**Zoonoses:** An infectious disease that is transmissible under normal conditions from animals to humans.

# ANNEX 4: COLLECTION, STORAGE AND TRANSPORT OF HUMAN SPECIMENS

## Collection of Human Specimens

### 1.1 For serological diagnosis

Venous blood specimens should be collected from suspected JE cases as early as possible in the acute phase, immediately after admission to the hospital or attendance at the clinic. A second, convalescent specimen should be collected later on, at the time of discharge from the hospital, if that comes first.

Five ml of blood is collected aseptically. The blood should be kept at room temperature for about 15 minutes to enable it to clot. Then at 4<sup>o</sup> C the clot is allowed to retract. The serum is separated from the clot and is transferred to a tightly stopped sterile container.

The container is sealed with adhesive tape; adhesive tape should also be used for a label, and the patient's name, identification number and date should be written clearly in pencil or indelible ink or typewritten.

Place serum in a refrigerator for storage prior to transportation to the laboratory.

Alternatively, blood can be collected in capillary tubes or on filter paper strips properly labeled. The blood soaked filter paper strips need to be dried in air, before they are sealed in an envelope. CSF specimens should be collected aseptically and placed in labeled containers.

### 1.2 For Virus Isolation

CSF specimens collected during the early acute phase labeled and inoculated into cells, such as AP61 cells at the bedside. If bedside inoculation is not possible; the specimen must be frozen on dry ice and transported to a laboratory immediately.

Brain tissue obtained from patients dying during the first two weeks of illness is the best source for the isolation of virus. Small pieces of brain tissue collected at autopsy should be obtained from different parts of the brain- cerebral cortex, cerebellum, basal nuclei and brain stem. If a full post mortem is not possible, small pieces of cerebral tissue may be obtained with the aid of a trephine. If even this procedure is not permitted, small pieces of brain tissue can be obtained by biopsy, using a Vim-Silverman needle inserted via the nose through the cribriform plate of the ethmoid bone.

The brain tissue(s) thus obtained should be immersed in 2 ml of transport medium available, 10% glycerol saline (pH 7.4) may be used. Alternatively, nutrient broth medium with antibiotics can be used. The container used should be moderately thick glass and should preferably be screw capped.

## **2. Storage and transport**

Specimen should be placed in a refrigerator at 4°C as soon as possible after collection. Do not freeze the specimens. They should be dispatched at the earliest possible opportunity in a large thermos or in an icebox to the central or referral laboratory on wet ice. They can either be air freighted or sent by road through as special courier. The courier should drain the water and replenish ice as and when required during the journey.

Specimen for virus isolation attempts should ideally be transported in sealed containers in dry ice or liquid nitrogen. In most places, however, such facilities are not available.



## ANNEX 5: LIST OF SENTINEL SITES

Existing sentinel sites

| SN | Province | Site Code | Health facility                                                    |
|----|----------|-----------|--------------------------------------------------------------------|
| 1  | 1        | 101       | Mechi Zonal Hospital, Jhapa                                        |
| 2  |          | 102       | Koshi Hospital, Morang                                             |
| 3  |          | 103       | District Hospital, Sunsari                                         |
| 4  |          | 104       | BPKIHS, Dharan, Sunsari                                            |
| 5  |          | 105       | District Hospital, Dhankuta                                        |
| 6  |          | 131       | District Hospital, Sankhuwasabha                                   |
| 7  |          | 132       | AMDA Hospital, Jhapa                                               |
| 8  |          | 136       | District Hospital, Illam                                           |
| 9  |          | 138       | District Hospital, Solukhumbu (Phaplu Hospital)                    |
| 10 |          | 234       | District Hospital, Taplejung                                       |
| 11 |          | 235       | District Hospital, Panchthar                                       |
| 12 |          | 236       | District Hospital, Terhathum                                       |
| 13 |          | 237       | District Hospital, Bhojpur                                         |
| 14 |          | 238       | District Hospital, Khotang                                         |
| 15 |          | 239       | Rumjatar Hospital, Okhaldhunga                                     |
| 16 |          | 240       | District Hospital, Udaypur                                         |
| 17 | 2        | 106       | Sagarmatha Zonal Hospital, Saptari                                 |
| 18 |          | 107       | Ramkumar Umasankar Hospital, Lahan                                 |
| 19 |          | 108       | District Hospital, Siraha                                          |
| 20 |          | 109       | Janakpur Zonal Hospital, Dhanusha                                  |
| 21 |          | 110       | District Hospital, Rautahat                                        |
| 22 |          | 111       | District Hospital, Bara                                            |
| 23 |          | 112       | Narayani Sub Regional Hospital, Parsa                              |
| 24 |          | 128       | District Hospital, Mahottari                                       |
| 25 |          | 134       | District Hospital, Sarlahi                                         |
| 26 | 3        | 113       | District Hospital, Makwanpur                                       |
| 27 |          | 114       | Bharatpur Hospital, Chitwan                                        |
| 28 |          | 115       | Kanti Children Hospital, Kathmandu                                 |
| 29 |          | 116       | Sukraraj Tropical and Infectious Disease Hospital, Teku, Kathmandu |
| 30 |          | 130       | District Hospital, Rasuwa                                          |
| 31 |          | 133       | District Hospital, Chautara                                        |

| SN | Province | Site Code | Health facility                                   |
|----|----------|-----------|---------------------------------------------------|
| 32 |          | 135       | District Hospital, Sindhuli                       |
| 33 |          | 137       | Dhulikhel Hospital, Kavre                         |
| 34 |          | 202       | District Hospital, Dhading                        |
| 35 |          | 203       | District Hospital, Ramechhap                      |
| 36 |          | 204       | Bhaktapur Hospital, Bhaktapur                     |
| 37 |          | 205       | Patan Academy of Health Sciences (PAHS), Lalitpur |
| 38 |          | 207       | Trishuli Hospital, Nuwakot                        |
| 39 |          | 208       | Charikot PHC, Dolakha                             |
| 40 |          | 209       | Jiri Hospital, Dolakha                            |
| 41 |          | Gandaki   | 201                                               |
| 42 | 206      |           | District Hospital, Gorkha                         |
| 43 | 210      |           | District Hospital, Syangja                        |
| 44 | 211      |           | District Hospital, Tanahun                        |
| 45 | 212      |           | Pokhara Academy of Health Sciences, Kaski         |
| 46 | 213      |           | District Hospital, Myagdi                         |
| 47 | 215      |           | Dhaulagiri Zonal Hospital, Baglung                |
| 48 | 216      |           | District Hospital, Parbat                         |
| 49 | 218      |           | District Hospital, Manang                         |
| 50 | 219      |           | District Hospital, Mustang                        |
| 51 | 5        | 117       | United Mission Hospital, Palpa                    |
| 52 |          | 118       | Prithvi Chandra Hospital, Nawalparasi             |
| 53 |          | 119       | Prithvi Bir Hospital, Kapilvastu                  |
| 54 |          | 120       | Lumbini Provincial Hospital, Rupandehi            |
| 55 |          | 121       | Rapti Sub Regional Hospital, Dang                 |
| 56 |          | 123       | Bheri Hospital, Banke                             |
| 57 |          | 127       | District Hospital, Bardiya                        |
| 58 |          | 214       | District Hospital, Gulmi                          |
| 59 |          | 217       | District Hospital, Argakhanchi                    |
| 60 |          | 220       | District Hospital, Pyuthan                        |
| 61 |          | 221       | District Hospital, Rolpa                          |
| 62 | Karnali  | 122       | Provincial Hospital, Surkhet                      |
| 63 |          | 139       | District Hospital, Dolpa                          |
| 64 |          | 140       | District Hospital, Humla                          |
| 65 |          | 222       | District Hospital, Rukum                          |
| 66 |          | 223       | District Hospital, Salyan                         |
| 67 |          | 224       | District Hospital, Jajarkot                       |

| SN | Province         | Site Code | Health facility                                  |
|----|------------------|-----------|--------------------------------------------------|
| 68 |                  | 225       | District Hospital, Kalikot                       |
| 69 |                  | 226       | Karnali Academy of Health Sciences (KAHS), Jumla |
| 70 |                  | 227       | District Hospital, Mugu                          |
| 71 |                  | 228       | District Hospital, Dailekh                       |
| 72 | Sudur<br>Paschim | 124       | Seti Zonal Hospital, Kailali                     |
| 73 |                  | 125       | Mahakali Zonal Hospital, Kanchanpur              |
| 74 |                  | 126       | District Hospital, Doti                          |
| 75 |                  | 129       | Dadheldhura Hospital, Dadeldhura                 |
| 76 |                  | 229       | District Hospital, Achaam                        |
| 77 |                  | 230       | District Hospital, Baitadi                       |
| 78 |                  | 231       | District Hospital, Darchula                      |
| 79 |                  | 232       | District Hospital, Bajura                        |
| 80 |                  | 233       | District Hospital, Bajhang                       |
| 81 |                  | 301       | Bayalpata Hospital (Nyaya Health), Achham        |
| 82 |                  | 302       | Tikapur Hospital, Kailai                         |

Newly decided sentinel sites (in 2019)

| SN | Province                                                           | Health facility                                                 |                                                                |
|----|--------------------------------------------------------------------|-----------------------------------------------------------------|----------------------------------------------------------------|
| 1  | 1                                                                  | Nobel Medical College, Biratnagar, Morang                       |                                                                |
| 2  |                                                                    | United Mission to Nepal, Okhaldunga                             |                                                                |
| 3  | 2                                                                  | Janaki Medical College, Janakpur                                |                                                                |
| 4  |                                                                    | National Medical College, Birgunj, Parsa                        |                                                                |
| 5  | 3                                                                  | Armed Police Force (APF) Hospital, Balambu, Kathmandu           |                                                                |
| 6  |                                                                    | Birendra Army Hospital, Chhauni, Kathmandu                      |                                                                |
| 7  |                                                                    | Chitwan Medical College, Bharatpur, Chitwan                     |                                                                |
| 8  |                                                                    | Civil Service Hospital, Minbhawan, Kathmandu                    |                                                                |
| 9  |                                                                    | CIWEC Hospital, Lazimpat, Kathmandu                             |                                                                |
| 10 |                                                                    | College of Medical Science, Bharatpur                           |                                                                |
| 11 |                                                                    | Grande International Hospital, Tokha, Kathmandu                 |                                                                |
| 12 |                                                                    | HAMS Hospital, Dhumbarahi, Kathmandu                            |                                                                |
| 13 |                                                                    | Kathmandu Medical College, Sinamangal, Kathmandu                |                                                                |
| 14 |                                                                    | Kathmandu Model Hospital, Bagbazar, Kathmandu                   |                                                                |
| 15 |                                                                    | KIST Medical College, Lalitpur                                  |                                                                |
| 16 |                                                                    | Manmohan Memorial Community Hospital, Thamel, Kathmandu         |                                                                |
| 17 |                                                                    | NAMS (Bir Hospital), Kathmandu                                  |                                                                |
| 18 |                                                                    | Nepal Medici Hospital, Lalitpur                                 |                                                                |
| 19 |                                                                    | Nepal Police Hospital, Maharajgunj, Kathmandu                   |                                                                |
| 20 |                                                                    | Nepal Medical College, Jorpati, Kathmandu                       |                                                                |
| 21 |                                                                    | Norvic International Hospital, Thapathali, Kathmandu            |                                                                |
| 22 |                                                                    | Om Hospital & Research Center, Chabahil, Kathmandu              |                                                                |
| 23 |                                                                    | Sumeru Hospital, Lalitpur                                       |                                                                |
| 24 |                                                                    | Teaching Hospital (Tribhuvan University) Maharajgunj, Kathmandu |                                                                |
| 25 |                                                                    | Vayodha Hospital, Balkhu, Kathmandu                             |                                                                |
| 26 |                                                                    | Gandaki                                                         | Madhya Bindu District Hospital, Danda, Nawalparasi East        |
| 27 |                                                                    |                                                                 | Gandaki Medical College, Pokhara, Kaski                        |
| 28 |                                                                    |                                                                 | Manipal Teaching Hospital, Pokhara, Kaski                      |
| 29 |                                                                    | 5                                                               | Siddhartha Children and Women Hospital (AMDA Hospital), Butwal |
| 30 | Crimson Hospital, Manigram, Rupandehi                              |                                                                 |                                                                |
| 31 | Devdaha Medical College, Devdaha, Rupandehi                        |                                                                 |                                                                |
| 32 | District Hospital, Rukum East                                      |                                                                 |                                                                |
| 33 | Lumbini Medical College and Teaching Hospital, Prabhash, Palpa     |                                                                 |                                                                |
| 34 | Nepalgunj Medical College and Teaching Hospital, Kohalpur, Banke   |                                                                 |                                                                |
| 35 | Universal College of Medical Science (UCMS), Bhairahawa, Rupandehi |                                                                 |                                                                |
| 36 | Karnali                                                            | Chourjahari Hospital, Chourjahari, Rukum                        |                                                                |

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